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Research and Practice

Editor
Prof. Dr. Nizami DURAN

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FOREWORD

This book is a very valuable work in terms of covering the data obtained as a result of various scientific observations and experiments in the field of medicine and health. In the book, the researchers shared many of their scientific results at the point of producing solutions to scientific problems. Researches describing health problems are based on scientific studies and observations. The experience of scientists is needed at the point of their solutions. Since this book contains the experiences and observations of many scientists working in the field, I believe that it will be a very important resource for readers. Scientific progress can only be achieved by announcing the studies in the related field of science on various platforms, discussing the problems and sharing the experiences. In this respect, every finding in this book has been deemed invaluable in terms of sharing the experiences of scientists.

I would like to express my heartfelt thanks to all my colleagues who contributed to the preparation of this book.

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CONTENTS

CHAPTER 1

COMPARATIVE ANATOMY OF THE HEART (HUMAN, QUADRUPEDAL MAMMALS AND AVIAN)

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1. An Historical Overview of Comparative Anatomy of Heart

Comparative anatomy is a branch of anatomy that examines the similarities and differences of anatomical structures among species, and although it is important in the fields of veterinary medicine and anthropology, it has gained more importance with the increase in experimental animal disease models in the last decades. The heart is the most important organ of the body that has been wondered since ancient times. The Greek philosopher Aristotle described the heart as the most important organ of the body, the first to form, based on his observations on chick embryos. According to Aristotle (384-3222 BC), it was the seat of intelligence, movement and sensation - a warm, dry organ. Moreover, Aristotle described it as a three-chambered organ that was the center of vitality in the body. More interestingly, other organs surrounding it (such as the brain and lungs) served to cool the heart (1).

Anatomy is one of the oldest branches of medicine. There are both human and animal studies dating back to the 3rd century BC. For example, Arsitole (384-322 BC) worked on the comparative anatomy of human and animal anatomy and made valuable researches on the anatomy and physiology of animals living in Erasistratos, who is considered almost his contemporary. However, it was Galen who studied anatomy emphatically in the real sense.

Galen (129-216AD) tried to explain the functions of organs and tissues, especially with his experiments on dogs. His most famous book is De Anaatomicis Administrationibus (On Anatomical Procedures). This work was the most notable early anatomy book that uses animals in its research to try to understand the normal structure and function of the body). When this work was rediscovered in the 16th century, it rekindled interest in anatomy and scientific methods. Besides, the Renaissance was a period of discovery in science as in every field, and it is also an important period in which the foundations of our current knowledge of human and animal anatomy were laid. The arguably the most important anatomist of this period is Andreas Vesalius (1514-1564). Later, Anatomy came into focus with Gabriele Falloppio (1523-1562 AD), who is credited with the discovery of the Fallopian tubes, as well as Matteo Realdo Colombo (1510-1559 AD), who described the pulmonary circulation and the atrial and ventricular cavities. During this period, animal studies in the field of medicine became widespread. Because, both church-believers and scientists such as Descartes argued that animals could not reason or feel pain and were automatons, therefore only humans were conscious, had minds and souls, could learn, and could have language (2,3).

William Harvey's famous work De Motu Cordis, commonly called Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus (Eng, 'An Anatomical Exercise on the Movement of the Heart and Blood to His Living Beings'), was first published in 1628. In this book, he argued that there may be small and large blood circulation in the body, and it was accepted as a turning point in the history of physiology and anatomy. In this period, As a result of dissection studies on humans and animals, important heart structures such as the eustachian valve (Bartolomeo Eustachio), the Thebesian valve and Thebesian veins (Thebesius), and the sinus of Valsalva (Antonio Maria Valsalva) were also identified. In the post-Renaissance stage, there was a severe shortage of the human body available for dissection. Often, the bodies were procured by grave robbers. In addition, the bodies of those who were executed for traitors and ordinary crimes were illegally and secretly provided by the investigators. After than, concrete findings were tried to be obtained by looking at the animal equivalent of the discovered structure. Thus, the foundations of copmarative anatomy began to be laid. Later, in the early 19th century, the first organized opposition to animal research occurred. This was pioneered by the Cruelty to Animals Act, passed in England in 1876. With this law, which passed the parliament, a series of measures were introduced to limit the indiscriminate use of animals. This was followed by the Laboratory Animal Welfare Act of 1966, which was amended in the United States in 1970, 1976, and 1985. These laws started a new era for animal research

by making it mandatory for laboratory animals to be made in experimental medicine in a controlled and appropriate laboratory. However, the need for animal research is still great; for this reason, animals are used and will continue to be used in research in many fields including cardiovascular device, drug and vaccine trials. The field of anatomy will probably remain one of the most important in this process. To diagnose and treat a pathological cases, normal structure and function must be known. This is umdoubtedly the basis for determining what is abnormal (2). Still, Historically, animal research has been fundamental to most of the understanding of the functioning of the human body in general, and much of the progress made in medicine was initially made possible by animal research.

Functionally, the heart has a major impact on most organs in the body. Looking at the historical process, detailed information linking human and mammalian models of cardiovascular system is still lacking. Therefore, it is vital to pay attention to the similarity of the human cardiovascular system in animal models to be used. Especially in drug or vaccine development, it is absolutely necessary to investigate the effects on experimental animals before starting the initial phase period. In addition, before an invasive device (a class III medical device) can be tested in humans, it is a legal requirement to demonstrate that the device works in the desired and appropriate manner on animals. Because the device will behave in humans similar to its function determined in animal models. However, it requires that the animal model chosen for significant testing be similar to that of humans in terms of anatomy and physiology. Although a lot of research was done in dogs and pigs in the 1970s and 1980s, it was later realized that dogs are more resistant to ischemia and reperfusion than humans due to the coronary artery anastomosis structure in their hearts. For this reason, the studies of most drugs that were tested by looking at the results in the dog had to be reviewed. Later, it was determined that pig or sheep hearts are closer to human hearts. Meanwhile, Job Janszoon van Meekeren (1682'), a Dutch surgeon, was reported as the first successful Xenotransplantation when the skull of a Russian soldier was repaired with a piece of dog bone. Although conservative church officials had ordered removal of the canine graft on the head, it was too late and the graft had healed too well to separate from the bone. Later, Alexis Carrel created a stream of organs, the first xenotransplant to suture blood vessels in anastomoses. Today, heart valves are replaced with cow and pig valves. In recent times, there are intense studies to replace non-functioning organs with animal organs (2).

2. General Characteristics of the Heart

Almost most mammalian and avian hearts, including humans heart anatomical structures and function are same However, the sizes, shapes, and positions of the

hearts may vary between species, depending on their position on ground and the structures of the thoracic cavities.

2.1. Heart Shape

The heart, which is the center of the circulatory system, is a hollow musculoskeletal organ in all mammals (4-6) and in birds (7,8) with a yellowish color in case of reddish overlying adipose tissue. It has a wide base called the basis cordis and a narrow top called the apex cordis (4-8). In addition, the hearts of most quadrupedal mammals have an oval heart with a

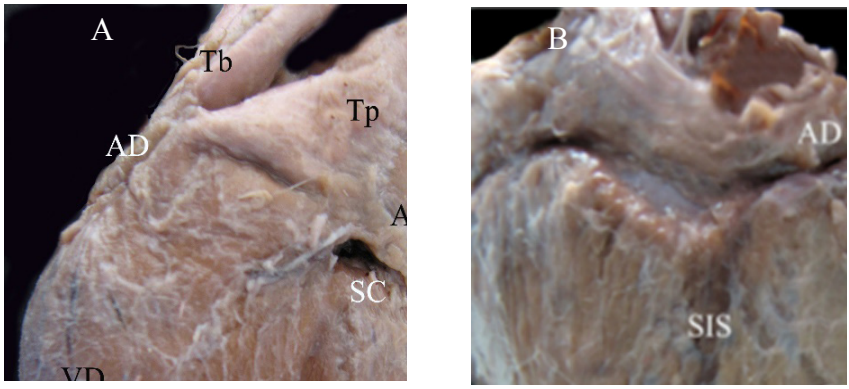

Figure 1. Genaral Anatomy of the Heart (A: anterior , B: posterior)

AO- Aorta, AC- Apex cordis, AD- Atrium dextrum, AS- Atrium sinistrum, Pr- Pericardium fibrosum, SIS- Sulcus interventricularis subsinuosus,Tb- Tr. barchiocephalicus, Tp- Truncus pulmonalis, VD- Ventriculus dexter, VS- Ventriculus sinister, SC- Sulcus coronarius, SIP- Sulcus interventricularis paraconalis

nearly blunt apex, as in humans. The human heart (5,6) is in the form of a trapezoid or oval cone, and in avian (8,9) it is in the form of a smooth cone (Figure1). Moreover, the heart takes a more conical shape in deep-chested mammalian breeds (9). Also, there are two important diameters that give us an idea of the heart shape. Two diameters, dexter-sinister (transversal diameter) and cranio-caudal (sagittal diameter) have been defined in the heart (4,10,11). Dexter-sinister diameter is the distance between the most protruding right and left sides of the heart, and the cranio-caudal diameter is the distance between the two planes passing through the most protruding parts of the cranial and caudal edges of the heart (12). By looking at these diameters, it can give information about the heart shape.

2.2. Weight of heart

The weight of the heart varies according to ecological factors, the work done, animal species characteristics and body temperature (24,25).

Physiological hypertrophic heart occurs in individuals doing sports and animals used for sports purposes, such as horses and dogs (Table 1).

However, due to high basal metabolism, high body temperature and active motility, the ratio of the average heart weight to body weight in Avian (Table 2) is much higher than in mammals (8,22,25,26).

Table 1: Heart weight in mammalian species

Mammal species Avearag Heart Weight (Gr)		Ratio of heart weight to body weight (%)	References
Human	300-350	0,5-0,6	6
Horse	4000	0,7	14
Donkey	3700	1-0.7	15
cattle	2500	0,4-0,5	16
Sheep	220-240	0,51	10
Goat	220- 240	0,51	10
Sheep	160.93	0,31	17
Goat	148.75	0,33	17
Mandate	-	0,42	18
Dog	48- 301	0,64-0,78	4
Cat	18,4	0,55	19
Cat	12,6	0,49	11
Rabbit	6,6	0,32	11
Monkey	45	0,55	20
Dolphin	252,7	0,05	21

It is generally accepted that adult sheep and adult pigs have smaller heart weight to body weight ratios than adult dogs. The ratio of heart weight to body weight for adult dogs (6.95:7 g/kg) is for pigs (2.89:2.5 g/kg) and sheep (3.13:3 g/kg). The normal ratio of adult human heart weight to body weight has been reported as 5 g/kg, which is quite similar to that of young pigs.

2.3. Location of the heart

In humans (5) including mammals (9) and avian (8), the heart is located in the thoracic cavity, just above the diaphragm, between the two lungs. The heart is located in the mediastinum medius in all species. The heart is surrounded by the sternum and cartilage ribs anteriorly (ventrally), both lung lobes laterally, and the organ and columna vertebralis located in the mediastinum posterius posteriorly (dorsal) (Table 3). In addition, there are diaphragms inferiorly (cavudal) and veins entering and exiting the heart superiorly

(Cranial). Similar to humans, most quadrupedal mammals have a distinctly left-sided heart. In addition, the heart tends to have a more ventrally oblique long heart axis. Meanwhile, in birds, the sternum has a different organization and shape from mammals in order to facilitate flight (Figure 2,3,4). For this reason, most birds have a large part of the heart embedded in the sternum cavity. On the other hand, the heart, which is reported to be partially shifted to the right of the median line in birds, tends from craniodorsal to caudoventral (5,8,27). Although there is a similarity in shape between the hearts of birds and mammals, the in birds organs of the cavum abdominalis and the cavum thoracis have taken a position facilitates to flight. Unlike mammals, birds do not have a fully formed diaphragma, so the abdominal and thoracic cavities are united, so it was called cavum cardioabdominalis. In birds, the heart is located in the dorsal half of the body cavity completely separated from the walls of the thoracic cavity by the lungs.

Table 2: Heart weight in some bird species

Bird Species	Avearag Heart Weight (Gr.)	Ratio of heart weight to body weight (%)	References
Budgerigar	038 – 0.83	1.45 - 1.19	13
Parrot	1.94 – 1.24	1.18 –1.62	13
Hawk	4.85 – 9.62	0.49 – 1	13
Swan	10.3	1.12	22
Mallard	13.6	0.98	22
Mudbird	3.05	1.02	22
Spoonbill Duck	6.38	1.03	22
Minute Hand	3.67	0.82	22
Fisherman	4.17 – 15.2	0.87 – 0.92	22
Seagull	4.16	0.81	22
Woodcock	1.16	1.54	22
Noob	8.36	0.88	22
Owl	2.4	0.92	22
Crow	8.1	1.1	22
Bush Warbler	0.16	1.25	22
Pigeon	3.06	1.28	22
Sparrow	0.91	1.43	22
Finch	0.35	1.84	22
Freckle Bird		0.41	23
Wild Rooster		0.78	23
Stork		1.15	23
Jade Swallow		1.45	23
Sea Tern		1.59	23
Chicken		0.6-0.67	23
Turkey		0.5	8
Goose		0.8	8

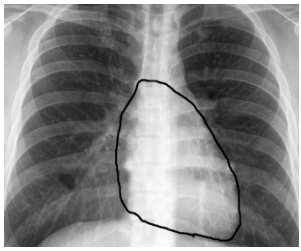

Figure 2. General location of the heart in human

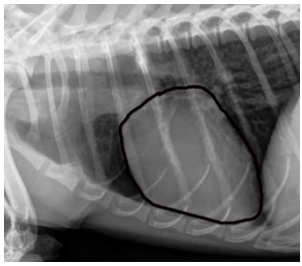

Figure 3. General location of the quadruped mammals

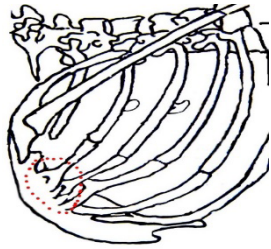

Figure 4. General location of the heart in birds

On the other hand, unlike mammals, in birds the heart is found in the dorsal half of the body cavity completely separated from the walls of the thoracic cavity by the lungs. Basis cordis, laterally the sacropleural membrane, is in contact with the last part of the trachea, medially with the proventriculus (8,28). The apex of the heart extends between the right and left lobes of the liver. The cranial half of the heart enters between the sternum and the saccus pulmonalis, which is the air sac (29).

Accordingly, dorsally, the basis of the heart is in contact with the lung, the ventral face (facies sternalis) is in contact with the sternum, the dorsal (facies hepatica) and letary face is surrounded by the liver, and even the left side of the heart is in contact with the proventriculus (8). Meanwhile, Wagner and Kiberger (30) reported that the right and left lobes of the liver are in close contact with the heart in their study with ultrasound in the ostrich, which should be considered in ultrasonic examination. In addition, the heart has a close relationship with the air sacs

3. Structure of the Heart

3.1. Pericardium

In humans, mammals and birds, the heart is contained in a fibrous sac called the cavum pericard. Pericard attaches to the places where the vessels entering and leaving the heart exit the heart. Although the basic structure of the pericardium is the same, it differs slightly between species. Basically, as the heart size increases, the pericardial wall thickness increases. However, this situation is different in humans, as humans have a much thicker pericardium than animals with similar heart sizes (32). Specifically, the pericardial thickness of human heart is 1 to 3.5 mm sheep hearts 0.32 ±0.01 mm; pig hearts 0.20 _+ 0.01 mm;

dog hearts 0.19 ± 0.01 mm) (33) Pericardium consists of two layers, the outer pericardium fibrosum and the inner pericardium serosum. In avain mammalian and human, Pericardium serosum consists of two layers, the lamina visceralis on the side facing the heart and the lamina visceralis (epicardium) attached to the Pericardium fibrosum. The space between these two laminae is called the cavum pericardium. Inside this cavity is a fluid called liquour pericardii. The amount of this fluid varies according to the size of the heart. For example, it is 20-30 ml in humans and dogs (34).

3.2. Endocardium

The free face of the heart, consisting of endothelial cells, is smooth and shiny (10). The endocardium, which is mainly composed of endothelial cells, controls myocardial function. It forms the basis of the much more voluminous myocardium, the muscle tissue responsible for the contraction of the heart.

Table 3. Surface projections of the heart

Species	Intercostale space - References
Human	2-5 (35)
Monkey	5.-8. (36,37)
Equide	2.-6. (9), 3.- 6. (4,19) , 2.- 5. (4)
Cattle	3.-5. (38), 3.-6. (38)
Sheep	2.-5. (17,39,40), 2.-6. (4)
Goat	2.-5.- 2.-6. (4) , 3.-6. (17,40)
Pig	3.-6. (4,15) , 2.-5. (9)
Dog	3.-6. (41), 3.-7. (9,14,15,23)
Cat	2.-6. (9,42)
Bird	2.-5. (8)
Ostrich	3.-5. (43)

3.3. Myocardium

It is the involuntary, striated muscle that forms the main tissue of the heart wall. The heart muscle (myocardium) lies between the outer layer of the heart wall (pericardium) and the inner layer (endocardium), forming a thick middle layer with blood supplied through the coronary circulation. It consists of individual heart muscle cells that are interconnected. It is surrounded by intercalated discs and collagen fibres and other substances that make up the extracellular matrix. It is composed of muscle fibres arranged in a complex arrangement. The muscle layer of the ventricles is much stronger than the muscle layer of the atria (10).

3.4. Connections of the pericardium and the heart

The ligaments responsible for fixing the heart are formed by the pericardium fibrosum. In humans, the part of the pericardium adjacent to the sternum is called the pars sternocostalis. The ligament connecting the pericardium to the sternum is the sternopericardiaca. The part of the pericardium adjacent to the diaphragm is called the pars diaphragmatica. Here it attaches to the diaphragm

via the ligamentum phrenicopercardiale. Its pericardium is connected to the vertebrae via the ligamentum spericardiovertebralis. The heart is attached to the diaphragm with the ligamentum phrenicopericardiacum in Sus and carnivores (4). In ruminants, eguide (39), and aves (8) it is attached to the sternum via the ligamentum sternopericardiacum. In addition (23), reported that pericardium fibrosum adhered to the wall of the air sacs in poultry.

3.5. Annulus fibrosus

These structures are fibrous rings surrounding the ostium atrioventriculare dextrum, ostium atrioventriculare sinistrum, ostium aortae, and ostium trunci pulmonalis at the base of the ventricles.

Annulus fibrosus separates the muscle layer of the atria from the muscle layer of the ventricles (5,9,10,15). Anulus fibrosus is present in all species and It has important function such as maintain the position of the heart in the Pericardium, creating the origo and insertio of the cusps on the heart valves, prevent excessive dilatation of valves and cavities, to form the main attachment point of the heart muscle, preventing electrophysiological continuity between the atrium/ ventricle myocardium (except the conduction system of the heart). This structure, which is a continuation of the anaulus fibrosus called the interval septum or membranous septum, has been determined to be absent in sheep, although it varies on the basis of species. In addition, while the segment of this ring is found at the base of the posterior (mural) leaflet, this situation may not be found in sheep in some dog breeds. Moreover, large species such as cows and horse have an ossicle called ossa cordis embedded in the myocadium and supporting the heart (44).

4. External View Of The Heart

Notable structures on the outer surface of the conical heart are the grooves for the passage of coronary arteries and veins, as well as the borders of the heart.

4.1. Faces of the heart

The shape of the heart is a flattened, inverted, irregular cone in mammals. It has an upper wide part called the basi cordis, where the origin and diranege of vessels, and an end called the apex cordis. In the horse and donkey, it is in the shape of a full cone. In ruminants and pigs, the apex cordis is more pointed than that of horse and donkey. Carnivores usually have a plump cone and a blunt apex cordis. Meanwhile, Human, sheep and pig have a blunt apex cordis. The position of the heart in the thoracic cavity determines the faces of the heart. Unlike humans, quadruped mammals have two faces in the heart because their chest is flattened from the sides; facies diaphragmatica (facies atrialis), and the

other is facies sternalis (facies auricularis) (5). In humans, the thorax is flattened in the posteroanterior direction, the heart is trapezoidal and includes the also two faces called as Facies Pulmonalis Dexter and Facies Pulmonalis Sinister. In birds, the heart has two faces: facies sternalis (facies ventrocranialis), facies hepatica (facies dorsocranialis) (29), in other words, they are called as facies atrialis (dorsal face), facies auricularis (ventral face) (8). In addition to these faces, the basis cordis was called facies pulmonalis (29). In the birds heart, the facies ventrocranialis is the form of a relatively smooth cone, the dorsocranialis is relatively flat (8). It right and left margins are partially rounded (29). Rigdon and Frölich (1970) stated that the right side of the heart (facies atrialis) of ducks is concave, while the left side (facies ventrocranialis) is convex (28).

In all mammals, including humans, the outer surface of the heart contains two edges called margo ventriculus dexter and margo ventriculus sinister, and three grooves, sulcus coronarius, sulcus interventricularis paraconalis, sulcus interventricularis subsinuosus, which contain the coronar vessels (4,5,45). In human, sulcus the interventricularis paraconalis is called the sulcus interventricularis anterior and the sulcus interventricularis subsinuosus as the sulcus interventricularis posterior.

4.2. Margo ventriculus dexter (right, cranial edge): it located cranially. it is convex and parallel to the sternum (5,15)

4.3. Margo ventriculus sinister (left, caudal edge): it is the concave edge (5,15)

4.4. Sulcus coronarius: In birds, humans and mammals, it marks the boundary between atria and ventricles.While the groove surrounds the heart, it is interrupted only by the truncus pulmonalis (4,5,8)

4.5. Sulcus interventricularis paraconalis: it is prominently found on the outer surface of the heart in humans, Avian and mammals and located in the facies auricularis of the heart. It defines the border between ventriculus. It starts from the sulcus coronarius and proceeds to the apex of the heart (4,8,10,29,46,47). In birds (8,46,47), unlike mammals (4,10), the sulcus

Table 4: Sulcus coronarius length in some quadruped mammals

Species	Sulcus coronarius length (cm), References
Cow	42-51 (4)
Bull	46-51 (4)
Calf	31,2-32,7 (4)
Cattle	38 (48)
Sheep	19.1 (17)
Goats	19 (17)
Dogs	16-26.8 (4)

interventricularis paraconalis is very shallow. Tıpırdamaz (17) reported in his study that the length of sulcus interventricularis paraconalis is 9.58 cm in sheep and 9.14 cm in goats.

4.6. Sulcus interventricularis subsinuosus: it is found in humans, mammals, and birds, and is located in Facies attrialis. It begins in Sulcus coronarius and progresses to the apex cordis (4,8,46,47). It is a shallower groove than Sulcus interventricularis paraconalis (15). Tipırdamaz (17) determined that the length of sulcus interventricularis subsinuosus is 5.66 cm in sheep and 5.75 cm in goats (17). In birds (28) and mammals (4-6,15), it finds a notch called incisura apex cordis at the junction of the sulcus interventricularis paraconalis and sulcus interventricularis subsinuosus, close to the apex cordis. However, Linsday and Smith (46) reported the absence of incisura apex cordis in poultry. Apart from these grooves, sulcus intermedius is present in cattle (9,48), sheep (39,40), Angora goat (40), and sometimes pig (4,49). Meanwhile, Tipırdamaz (17) determined that this groove is 7.17 cm long in sheep and 6.33 cm in goats.

5. Inside the Heart

The inside of the heart, which looks like a cone when viewed from the outside in all warm-blooded animals, is actually; It is divided into four compartments called the atrium sinistrum, atrium dextrum, ventriculus sinister, and ventriculus dexter. Atrium sinistrum and atrium dextrum are separated from each other by septum interatriale, ventriculus sinister and ventriculus dexter by septum interventriculare (Figure 5). Although the septum interatriale is a strong structure in mammals (4,5,10), it is weak in poultry (8).

5.1. Atriums

The right and left atria of the hearts of adult mammals and poultry are separated by the interatrial septum. They form the basis cordis of the heart. The sole is where all the major veins are located. Although there are differences in stance among species, it is generally upwards of ventriculs.

5.2. Atrium dextrum

The atrium dextrum is located dorsal (superior) of the ventriculus dexter, and right and anterior to the left atrium. In mammals, birds and also human the Atrium dextrum cavity is mainly diraneged the v. cava caudalis/ (inferior in humans),

the sinus coronarius and cava cranialis (superior in humans). V. cava caudalis is much larger in birds compared to mammals and opens with an oval hole at the base of the atrium dextrum (8,50). The length of this main vein between the heart and liver in poultry is much shorter than in mammals. V. cava cranialis is a single vessel in equide, ruminant, carnivore (4,10) and human (5,51). Interestingly, it is found in rabbit (52), rodent (53-55) also and Avian (8,9,23,29,56-58) as two veins called v. cava cranialis dexter and v. cava cranialis sinister. These vessels open into the sinus venarum cavorum of the atrium dextrum via the ostium venae cava cranialis sinister, ostium venae cava cranialis dexter and ostium v. cava caudalis (Figure 6). Sinus coronarius is the main collector of Vv.coronaria and empties blood into the sinus venorum cavorum cavity of the atrium dextrum (5,9,10,15,23). Sinus coronarius can be found in humans (5,59) (and domestic mammals (4, 45), rodents (53-55), whales (60) exists. On the other hand, some reserchers has been reported that sinus coronarius is absent in rabbits (Figure 6) (52,61,62), some equine such as donkeys (63), horse specimens (64), and also beavers (65). Although some authors (8,46,47) reported its absence in birds, Mark et al (66) mention the presence of sinus coronarius in chicken and quail

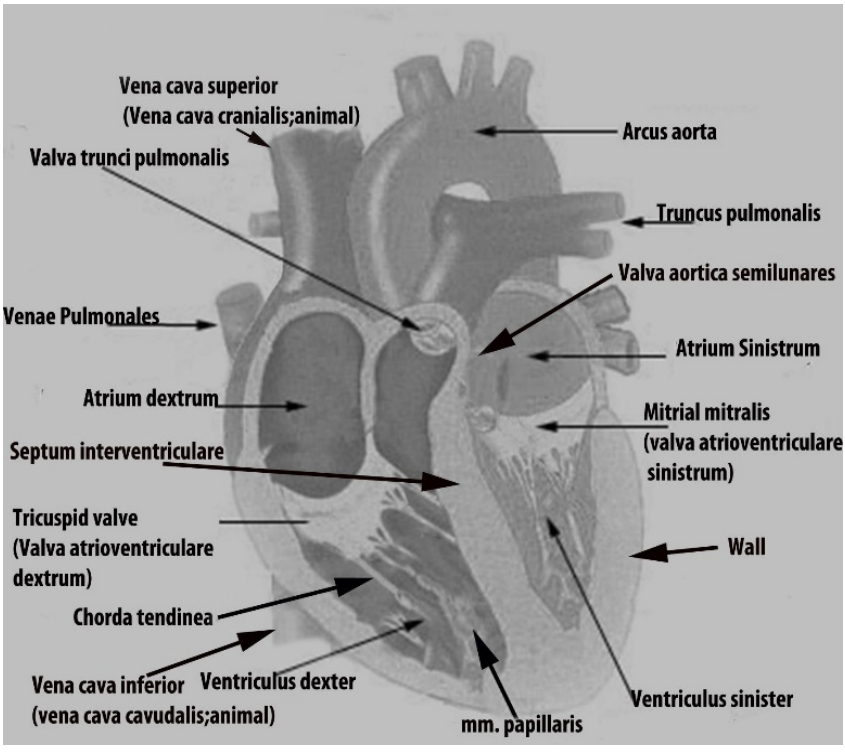

Figure 5. Genaral Anatomy of the Heart

hearts. It opens into the atrium dextrum via the ostium sinus coronarius. Between the ostium venae cava cranialis and the ostium vena cava caudalis, there is a projection called the tuberculum intervenosum (9,10,17,38,42). Calislar (40) reported that this formation was higher in Karaman sheep heart compared to that of Angora goat. However, Tuberculum intervenosum is not very prominent in humans (5). On the side of the septum interatriale, which separates the atriums from each other, facing the atrium dextrum, there is a light colored, round hollow area called fossa ovalis as a result of the closure of the foramen ovale in intrauterine life (4,67-69). On the face of the atrium sinistrum, there is a relief called valvula foraminis ovalis (4) . The foremen ovale is in the form of a sieve (8) or a few holes (28) in embryonal life in birds. Then it closes through a tight membrane of the foremen ovale and turns into fossa ovalis (70). Furthermore, compared to Humans, the fossa ovalis is located more posteriorly (caudally) in dogs and sheep, but deeper and higher in the pig heart. Sinus venosus is a common structure in mammalian hearts. It is only prominently found in the embryonic heart between the two vena cavae. In adults, the Sinus venosus is included in the right atrium and is important for the presence of a sinoatrial node in mammals.

5.3. Atrium sinistrum

The atrium sinistrum is located on the left and posterior margin of the heart, above the ventriculus sinister. All species have a cavity called the ear (auricular sinistra; left auricular appendix). It is slightly narrowed at the ground where it joins the main atrium cavity; it is longer, narrower, and more curved than the right, and the margins are more deeply indented. It is directed forward and to the right and overlaps the root of the pulmonary artery. In all mammals and birds, there are muscle protrusions called mm. pectinati, located on the inner surface of the Auricula sinistra (12,38). In addition, although there is little difference between species, auricula sinistra is more voluminous than auricula dextra (10,23,38) and the free edge of auricula sinistra is more notched than auricula dextra (5,12,23,38). In birds (8,28) and mammals (4,9,10,15,23) the size of atrium dextrum is wider than that the atrium sinistrum , and the wall thickness is atrium sinistrum.The presence of an arc-shaped muscle ridge on the roof of the atrium sinistrum and atrium dextrum has been reported (8). This slice-shaped structure was named arcus tranversus sinister and arcus transversus dexter (71). It has been stated that mm.pectinati originates from these structures (7,8,28). Atrium sinistrum in all mammals and humans, including poultry, contains ostia venarum pulmonalium, which is the opening hole of vv. pulmonales(15). The presence of camera pumonalis, which is characterized as an enlargement of the atrium sinistrum and formed by the fusion of vv.

pulmonales with the atrium sinistrum just before entering the atrium sinistrum, has been reported in birds (8,71). However, the presence of camera pulmonales is not mentioned in the study in Ducks (28). In birds, after vv. pulmonales unite, it can be opened into the atrium sinistrum with a single hole, or it can be opened into the atrium sinistrum as separate holes (71). The number of vv.pulmonales is 7-8 in equides (72) , 5 in cattle (38) and 2-3 in angora goats (40). Moreover Tipırdamaz (17) determined that it was 5-6 in Akkarman sheep and goats. Although Ghoshal (19) and Miller et al (41) reported that it was 5-6 in cats and dogs, Crouch and Lackey (73) stated that there was 4 in cats. Meanwhile Tecirlioğlu et al reported (12) that there was 5 in Buffalo (12). Moreover its number are 4-5 in beaver (65), 4 in the rabbit (53), 4 in humans (5). Nickel et al. (8), Tipırdamaz (29) and Yıldız and Gültekin (74) shown that 2 in birds. However, Chiasson (56) stated that there was found 4 vena pulmonales in pigeons and also Rigdon and Frölich (28) reported that ducks had 2 veins. Moreover, there is no valve in the opening of the veins. The presence of muscle structures extending to the openings of the atrium sinistrum of the vessels instead of the valves has been known (23).

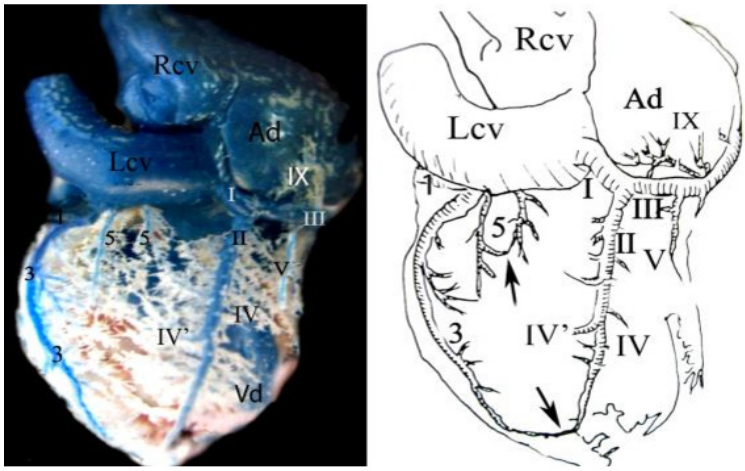

Figure 6. Vena cava cranialis dexter an sinister in rabbit (corrosion casting):
Lcv: The left cranial vena cava, Rcv: The left cranial vena cava Ad: Atrium dextrum, I v.cordis magna (sinus coronaries not formed) (52)

5.4. Ventriculus

The left and right ventricles in both human and winged and mammalian species contain basically the same structure and components. They are structurally very similar to the human heart and are called ventirculus dexter and ventriculus sinister. The ventricles act as the main output pumping elements of the heart. Therefore, the wall thicknesses are much thicker than the atriums (Figure 5,7).

5.5. Ventriculus dexter

In birds (8,56) and mammals (9,10), including humans (5,6), the ventriculus dexter is larger in volume than the ventriculus sinister, but its wall thickness is thinner than that of the atrium. The ventriculus dexter reaches the junction of the lower 1/3 of the heart length and the middle 1/3 in humans, dogs, pigs, and poultry. Bisaillon (65) reported that the ventriculus dexter reached as far as the apex cordis in seven of nine beaver hearts. Tr. pulmonalis ventriculus takes its origin from the ostium trunci pulmonalis located at the base of the dexter (8,10,15,29). The diameter of the pulmonalis is measured as 0.81 cm in sheep, 0.94 cm in goats (17), and approximately 2.5-4 cm in dogs and humans (41).

The valves in the ostium trunci pulmonalis are similar in structure and function in large mammals, some birds, and humans. There are 3 valves in the ostium trunci pulmonalis in the bird, called valvula semilunaris dextra, valvula semilunaris sinistra, valvula seminularis dorsalis (7,8,71). In mammals (4,10,15,75) there are three valves called valvula semilunaris dextra, valvula semilunaris sinistra and valvula semilunaris anterior (intermedia). However, Farnandez et al. (76) reported that 140 of 206 hamsters had tricuspid, 45 had bicuspid, and 9 had quadricuspid. In a similar study, Cardo et al. (77) reported that 37 of 247 adult hamsters had bicuspids. The valve in Ostium trunci pulmonalis in mammals including humans and wings is in the shape of a crescent moon and there are formations called noduli valvulorum semilinarium on it (4,10,15). In addition, there is a strong muscle protrusion crista supraventricularis between the conus arteriosus and the ostium atrioventricularis (4).

There is ostium atrioventriculare dextrum, which is oval in mammals (4,10) and luna in birds (8,9,29), which is located on the floor of the atrium dextrum and allows the blood to pass to the ventriculus dexter. Moreover, the human ostium atrioventriculare dextrum is similar in structure, shape, and function to other mammals.

Most mammals and humans have three valves that surround this ostium. However, rabbits have 2 valves. In addition, since the junction of the valve anterosuperior leaflet and the inferior leaflets is wide, it gives an appearance with 2 cusps in dogs. Although there are small differences, there are 3 mm.papillaris accompanying these valves. Chordae tendineae originating from mm.papillaris subarteriosus, mm.papillares parvi and mm.papilares magnus located in the ventirculus dexter attach to the three-cuspid valva atrioventricularis dextra (valva tricusurpidalis) located in the ostium atrioventriculare dextrum (4,10,38,65). However, McClure et al. (42) reported that the valva atrioventricularis dextra in cats consists of two valves, cuspis parietalis and cuspis angularis.

In birds, the ostium atrioventriculare dextrum contains a single valve (8,23,56,74). Interestingly, unlike mammals, the valve is muscular rather than membranous, and also the valve (8,23,29,57,78) is supported by a muscular projection from the outer wall of the ventriculus dexter towards the lumen (8).

The chordea tendea are ray-like and fibrous structures that connect the valves to the mm.papillaris (4,10). The number of chordea tendea, which has a very thin thickness in mammals, varies between 6-10 (16). Chordae tendineae can either come out of mm.papillares as a single thread or divide into many branches after their emergence and adhere to the valvula (4,8,10). There are different and controversial opinions on poultry. e.g; In their study on chickens, Cayre et al. (79) reported that the ostium atrioventriculare dextrum contains a large valve and additionally a cover consisting of microleaflets, these small leaflets are attached to the septum with chordea tendineae, and even there are no prominent mm.papillares. However, Yildiz and Cavuşoğlu (74) in their study on 10 chicken materials, found that there is a single cuspid valve in the ostium atrioventriculare dextrum, mm. reported the absence of papillares and chordea tendineae.

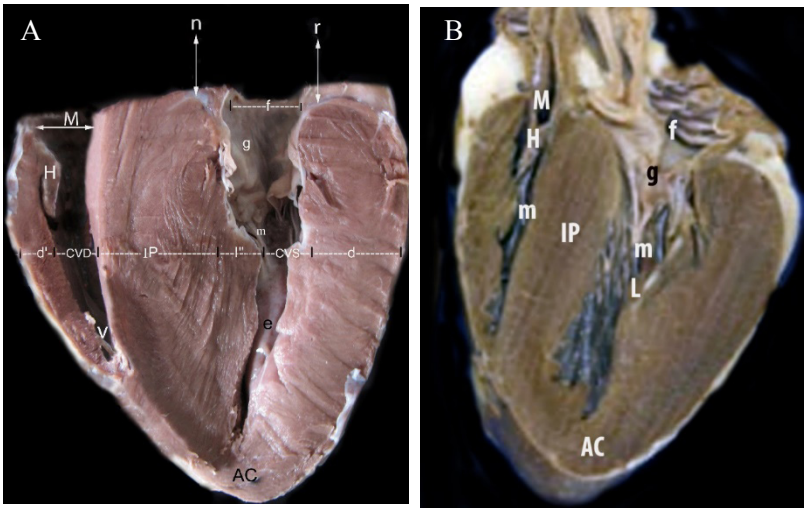

Figure 7. Vertical section of ventriculus in Birds (A) and Mammalian(B)

AC- apex cordis,CVD- Cavitas ventriculi dextri,CVS- Cavitas ventriculi sinistri,d- Wall of Atrium sinistrum, d'- Wall of Atrium dextrum,e- Trabucule septi marginalis, f- Ostium atrioventriculare sinistrum,g- Valvula atriventricularis sinistra, H- Valva atrioventricularis dextrum, IP- Semptum interventriculare, l'- Mm. Papillares, m- Chardea tendineae, M- Ostium atrioventriculare dextrum, n- Cartilago cardis, r- Anulus fibrosus, V- M. transversus

5.6. Ventriculus Sinister

In mammals, the ventriculus sinister is located to the left and behind the heart. Its outer wall has an oval, convex shape (4,9,10,41). In birds, it is in the shape of a very smooth cone and its cross section is round (29). In addition, the wall thickness of the ventriculus sinister is significantly thicker than that of the ventriculus dexter, as it pumps the blood to the whole body via the aorta in all avian, mammalian and human species (4,10,41). However, unlike mammals, the wall thickness of the ventriculus sinister in the bird is 3-4 times greater than that of the ventriculus dexter (8). Meanwhile, Straub et al. (2002) emphasized that the heart is thinner in the apex region on budgerigars, parrots and hawks, unlike other species (13). Apex cordis is formed by the ventriculus sinister in avian and many mammals such as sheep, dogs, including humans (4). But, Bisaillon (65), in his study on nine beaver hearts, reported that the apex cordis was formed by both ventricles in seven hearts. Fourthmore , the wall thickness of the ventriculus sinister is significantly thicker than the ventriculus dexter, as it pumps the blood to the whole body via the aorta in all avian, mammalian and human (4,10,41). However, unlike goats, sheep, pigs and rodents, the wall thickness of the ventriculus sinister in poultry is 3-4 times greater than that of the ventriculus dexter (8). Meanwhile, Straub et al. (2002) emphasized that unlike other species, the thickness of the ventriculus in budgerigars, parrots and hawks becomes thinner towards the apex (13).

Table 5: Thickness of ventriculus sinister and ventriculus dexter

Spiecens	Ventriculus Sinister (cm)	Ventriculus Dexter (cm)	References
Human	1,2	0,3-0,5	83
Horse	3,9	1,8	4
Mare	3,1	1,9	4
Donkey	20,25	6,73	83
Ox	27,3	6	12
Sheep	1,32	0,41	17
Goat	1,21	0,37	17
Dog	1,5-2,2	0,5-0,9	4
Cat	0,4	0,2	11
Rabbit	0,5	0.1	11
Pig	20.5	10.9	4

In humans (5) and domestic mammals (4,23), some bird such as ostrich (52) and pelicans (78) there are formations called trabeculae carneae, which serve to strengthen the walls during contraction and increase the force applied when the

heart is loaded, on the walls of both the ventirculus sinister and ventirculus dexter close to the apex (52,57). These formations are less common in the ventriculus sinister than in the ventriculus dexter. On the other hand, Bisaillon (65) found that these formations are more common in the ventriculus sinister than in the ventriculus dexter in the beaver. These structures are much more developed and coarse in animals than in humans. There is ostium atrioventriculare sinistrum, which functions the same in all warm-blooded species, providing blood passage from atrium sinistrum to ventriculus sinistere (4,29). In humans and most mammals, there is a valve with two cuspis (cuspis septalis, cuspis parietalis) called Mitrial or bicuspid valve at the valva atrioventricularis sinistra (valva mitralis, valva bicuspidalis) (9,10,23,38,80). However, some authors have reported that 4 cusps were found, two of which are the main cusps and two small commissural cusps, should be seen in humans (81). In addition, it may vary in rodents. For example, Icardo et al. (80) reported that there was two mitral valves in on mice. Moreover, Hill and Curran (82) reported that in guinea pigs, the ostium atriovnetriculare consisted of three cuspid valves.

In most birds, valva atrioventricularis sinistra; It consists of three cuspis called cuspis sinistra, cuspis dextra and cuspis dorsalis. In birds, one is located in a way that touches the septum, while the others are located on the outer wall of the ventriculus syncyter (8,74). However, Chiasson (56) reported that pigeons have one valve at the mouth of this hole. In all warm-blooded species, chordae tendineae emerge from the muscle bubbles called mm.papillaris subauricularis and mm.papillaris subatrialis found in Ventriculus sinister and attach to the cuspis (9,10,38). However, in Pigeons, a large number of wing-shaped flaps combine to form a single flap (56). It is reported that a long chordea tendineae protrudes on the edge of the structure forms this valve and adheres to the ventriculus sinister wall. In addition, Ventriculus sinister is stronger than ventriculus dexter in terms of its mm.papillaris and chordae tendineae (4,10,17,54,65,83) (Tablo 6).

Diameter of the aorta at its origin is reported that it is 1.2-1.9 cm in humans, 1.05 cm in sheep, 1.13 cm in goats (17) 0.2 cm in rats, 0.4 cm in rabbits, 0.5 cm in cats (11). All warm-blooded species have 3 valves at ostium aorta. The valva aorta is called valvula semilunaris sinistra, valvula semilunaris dextra and valvula semilunaris posterior in humans, in domestic mammals (4,10,17,38). However, in birds they are called valvula semilunaris sinistra, valvula semilunaris dextra ventralis, and valvula semilunaris dextra dorsalis. Meanwhile, Fernandez et al (76) reported that 136 of 206 hamsters had ostium aorta, tricuspid and the rest had bicuspid in hamsters.

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CHAPTER 2

SCIMITAR SYNDROME

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1. Introduction

Scimitar syndrome is a rare condition occurring in 1 to 3 of 100,000 births (1). In scimitar syndrome, a combination of congenital heart and lung anomalies, there is typically an abnormal pulmonary vein from the right lung to the inferior vena cava. Associated findings classically include atrial septal defect, aortopulmonary collaterals, and both right pulmonary artery and right lung hypoplasia (2-4).

2. History

The first definition of scimitar syndrome was made in an autopsy by Cooper and Chassinat in 1836. The findings were later recognised by Dotter in 1949 in an asymptomatic living patient (1,5,6). However, the term "scimitar" was first used by Halasz et al. in 1956 to describe the appearance of the abnormal vessel (7). In 1960, Neil et al (8). referred to it as 'Turkish sword syndrome'. For a patient with findings now considered representative of the syndrome, a right lower lobectomy was performed by Drake and Lynch in 1950 (9), while Kirklin et al. redescribed the overall findings in 1956 (10).

3. Clinical examination

Symptoms are associated with left-to-right shunt from an abnormal vein, grade of pulmonary hypertension, parenchymal lung disease, and intracardiac lesions (11).

Patients with scimitar syndrome can be divided into three groups (12,13). Those with a diagnosis of other clinically significant congenital heart defects other than atrial septal defect and patent ductus arteriosus constitute the "infantile"

group. These patients present early in infancy and they also have additional cardiac pathologies that affect the course of the disease. Among patients without significant associated pathologies, those in the "isolated infantile" group often have significant pulmonary hypertension and present with respiratory distress, cyanosis, or heart failure before the age of 1 year (13). Adults have mild symptoms such as exercise intolerance and recurrent lung infections (1).

The small retrospective series and examinations to date confirm that "infantile" forms of the syndrome have a high incidence of symptoms with aortopulmonary collaterals, associated congenital heart defects, extracardiac anomalies, and pulmonary hypertension and these patients have a worse prognosis compared to patients diagnosed later in life (14).

Associated cardiac and extracardiac anomalies have been reported in one-third to three-quarters of patients (15). Cardiac anomalies include atrial and ventricular septal defects, functional univentricular hearts, double-outlet right ventricles, tetralogy, tricuspid atresia, and abnormal origin of the left coronary artery (14,16-22).

4. Methods of diagnosis

Small right lung, heart located to the right, or a shadow of an abnormal vein can be detected on chest X-ray. Right ventricular hypertrophy can be seen on electrocardiography. Echocardiography is diagnostic. Intracardiac lesions and localisation of the abnormal vein may attract attention (2).

On Doppler sonography, normal pulmonary venous flow is biphasic or triphasic, with one or two peaks in systole, one peak in diastole, and reverse flow in atrial contraction. However, flow in the abnormal pulmonary vein is monophasic and extends throughout the cardiac cycle with no atrial contraction and reverse flow. This feature can be better demonstrated by transoesophageal echocardiography (2,19,23-25). Shibuya et al (2). were able to map the abnormal venous connection with only colour Doppler in nine out of ten cases.

Contrast computed-tomography and/or three-dimensional magnetic resonance angiography now allow comprehensive assessment of the intracardiac anatomy, diameter, and orbit, as well as the drainage site of the scimitar vein and its relationship to the right lung hilum. These methods can be used safely to replace traditional angiography for a definitive diagnosis (18,26,27,29,30).

Angiography may be indicated in suspected cases of embolisation of the aortopulmonary collateral arteries or for therapeutic intervention in the presence of stenosis of the scimitar vein (1,13,14,16,17,31,32). Ventilation/perfusion scans are recommended as a routine. Routine bronchoscopy and bronchography are also recommended by some researchers for pre- and postoperative evaluation (33,34).

Fig 1: A chestradiography of a patient with scimitar syndrome showing a left-side anomalous pulmonary vein (Panel A), which was confirmed by magnetic resonance imaging (Panel B).

5. Surgical treatment

5.1. Surgical anatomy

The scimitar vein typically drains the entire right lung, but sometimes it can drain only the lower or middle lobe (34). It can be seen anterior or posterior to the right lung hilus. It is not always wide and curved like a scimitar; instead, it may be straight, slender, or multiple. It is usually connected to the inferior caval vein (35-38). When connecting to the inferior caval vein, the connection site is usually subdiaphragmatic, but it may be close to the supradiaphragmatic or inferior cavoatrial junction (39). It has been reported that the vein is stenotic in one-fifth of these patients as a harbinger of poor prognosis (40).

A left-sided abnormal vein has also been identified (12,42-44). For example, in 2005, Juraszek et al (41). identified an isolated case where all the left pulmonary veins converged under the left atrium and then drained subdiaphragmatically into the right inferior caval vein (42). Such left-sided connections are less frequently obstructive but may cause resistant pulmonary hypertension (43). Pulmonary arterial hypertension may occur in one-third of all cases (1,13,14,16,17).

An abnormal artery from the descending thoracic or abdominal aorta typically perfuses the lower or middle lobes but may rarely perfuse the entire right lung (45-47). Left lung hyperfusion has been reported in three-quarters of cases upon pulmonary scintigraphy (34). Tracheobronchial abnormalities in the form of sequestration, diverticula, stenosis, or atretic bands may occur. No cases with a normal bronchogram were reported (34). In their series of 32 patients, Najm et al. reported the incidence of pulmonary sequestration in only two-fifths of them. However, bronchial sequestration is rarely present (33,41). There have been 14 patients reported with horseshoe lungs, with the two lungs fused in the posteroinferior segments posterior to the heart and anterior to the oesophagus. The right pulmonary artery and right bronchus usually cross the midline to supply part of the left lung (1,13,35,48-50).

5.2. Surgical indications and techniques

Management of this syndrome, including indications, timing, and type of intervention, remains unclear (1,13,14,16,17,35,36,51). In infancy, medical therapy is indicated to balance heart failure prior to surgical repair unless

pulmonary hypertension develops. However, pulmonary hypertension must be dealt with prior to surgery, either by medical intervention or by reducing the pulmonary blood flow by coil embolisation of the aortopulmonary collateral arteries (1,13,14,16,17,52). According to some authors, cardiac arrest is not used in the cardiopulmonary bypass and repair procedure (53). In general, surgical repair is recommended for all symptomatic patients and for asymptomatic patients with pulmonary-to-systemic flow ratios greater than 1.5:1 or lower pulmonary-to-systemic flow ratios. Clinically treated pulmonary hypertension is greater than 1.5:1 in cases of scimitar vein stenosis or concomitant cardiac lesions (32,35). Indications for surgery in adults are still debated, as many adults with this syndrome lead normal lives without surgical treatment. However, the general consensus is that surgery is indicated for symptomatic patients and when the pulmonary-to-systemic flow ratio is greater than 1.5 in asymptomatic patients. Diuretics, sodium potassium/ATPase inhibitors, β-agonists, ipratropium bromide, antibiotics, and cortisones are used on an individual basis.

The principles of surgical treatment entail the establishment of a new pathway for the vein through an existing or newly established interatrial communication without creating tension, kinking, or stenosis in the abnormal pulmonary vein. Concomitant anomalies are also treated simultaneously (1,13,14,16,17,52).

Since the surgical strategy depends on the configuration of the scimitar vein and the drainage site, accurate anatomical information must be obtained before surgery (2,19,38). Many types of surgical repair have been proposed for scimitar syndrome (40,53,55,56). and the choice of technique is largely dependent on the surgeon. Most repairs are designed to remove pulmonary venous blood from the systemic circulation system and return that blood to the left atrium (16,37).

The intracardiac repair re-implantation technique has been reported as the most commonly used reparative technique for many years. However, there is no consensus on the best surgical option. The former method involves creating a long intracardiac tunnel by turning the outlet of the scimitar vein toward the left atrium. Secondly, the scimitar vein is separated from the inferior vena cava and re-anatomised into the left atrium. The risk of postoperative venous stenosis is the same for both procedures but is higher in the infantile period than in adulthood. Some authors have reported balloon dilation to cope with postoperative vein obstruction (37), and right pneumectomy may be performed when patients continue to complain of severe respiratory symptoms.

When comparing direct vein re-implantation and interatrial repair among infantile patients, no significant difference was observed in the incidence of post-

repair stenosis, heart failure recurrence, or overall mortality, findings consistent with previous reports (16,17).

CONCLUSION

Scimitar syndrome involves congenital anomalous pulmonary venous return to the inferior vena cava. Two main forms have been identified: Infantile form presents with severe symptoms in neonatal period. It is asso ciated with other severe thoracic and cardiac anomalies; Adult form may have a benign course and may be picked up incidently. Optimal management remains controversial.

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CHAPTER 3

PRIMARY CARDIAC TUMORS AND SURGICAL APPROACH

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1. Introduction

Primary heart tumours are rare in children and occur in 0.027% to 0.08% of paediatric autopsies (1). It was reported that the incidence has increased in recent years (2). Most paediatric heart tumours are benign, and rhabdomyoma is the most common histologic type, followed by fibroma and teratoma (3). However, approximately 10% of paediatric heart tumours are malignant, and sarcomas constitute the most common primary cardiac malignancy in children. The presence of non-specific symptoms in patients complicates the diagnosis (1). Patients may be asymptomatic or apply with symptoms of arrhythmia, embolism, outflow obstruction, and congestive heart failure (2).

2. History

Primary heart tumours were first identified by Realdus Columbus in 1559 (4). Although cardiac tumours have been mentioned in several post-mortem studies, they were first diagnosed by Barnes et al. as the result of peripheral metastatic lymph node biopsy of a patient with primary cardiac sarcoma (5). The first successful surgical repair was operated by Claude S. Beck in 1936 in a patient with intrapericardial teratoma (6). Surgical resection with cardiopulmonary bypass was performed by Crafoord in 1954 in a patient with left atrial myxoma (7).

3. Clinical picture

The clinical manifestations of cardiac tumours range from asymptomatic presentations to life-threatening cardiac events. The clinical symptoms of

cardiac tumours are often non-specific and are usually related to the tumour size and location rather than the tumour type (8). Non-specific heart murmur, arrhythmia, respiratory problems, and congestive heart failure are the most common symptoms (8-11).

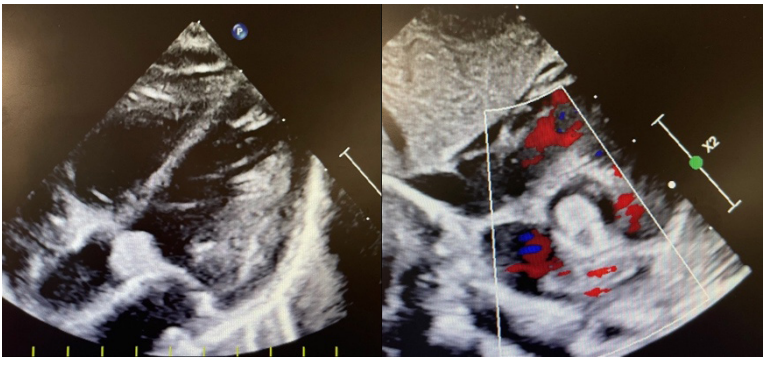
In the El Bardissi et al. series, 25% of tumour embolization was associated with aortic valve and left atrial tumours (12). Right atrial tumours can imitate congenital heart diseases, such as Ebstein's anomaly and tricuspid stenosis. They may cause right and left shunt and cyanosis due to increased right atrial pressure. Right heart failure symptoms can be seen due to obstruction or valve dysfunction in intracavitary lesions in the right ventricle (13,14). In cases in which the tumour extends into the left ventricular cavity, it can cause mitral regurgitation or inflow or outflow obstruction. In cases in which there is excessive infiltration of the tumour into the left ventricular myocardium, myocardial ischemia may occur due to heart failure and coronary compression (15).

4. Methods of diagnosis

Chest X-ray is abnormal in more than 80% of patients with cardiac tumours. Cardiomegaly, mediastinal enlargement, pleural effusion, congestive heart failure, and pulmonary oedema are the most common findings. Calcification can be seen in fibromas (13,16).

Electrocardiographic findings are infrequent and usually non-specific. AV block, atrial enlargement, ventricular hypertrophy, and ST segment changes may also be seen.

Echocardiography is the primary diagnostic tool in cardiac tumours. M-mode and two-way echocardiography is a safe and effective non-invasive test (10,17-20). It provides rapid information regarding tumour localization, extent, and characteristics. Obstruction and its hemodynamic significance can be examined via Doppler echocardiography. Antenatal fetal echocardiography facilitates early diagnosis in most centres (21).



5. Primary benign cardiac tumours

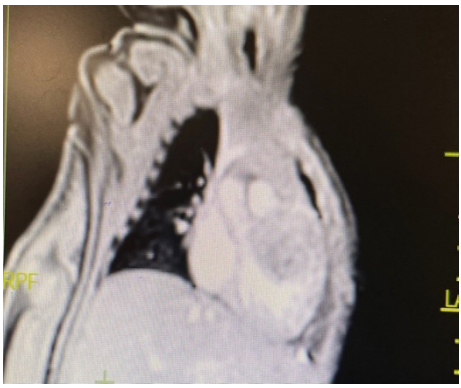
5.1. Rhabdomyoma

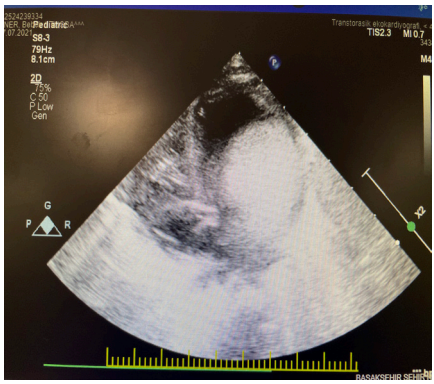
Cardiac rhabdomyoma is the most common paediatric heart tumour, and is highly associated with tuberous sclerosis (22). Approximately 80% of children with cardiac rhabdomyoma have a clinical, radiological, or family history of tuberous sclerosis.[8] Conversely, more than 50% of patients with tuberous sclerosis have cardiac hamartoma (23). A retrospective study with 33 infants and children recruited from three paediatric cardiology centres showed that 30 of the patients (90.9%) were associated with tuberous sclerosis (24).

The clinical image of cardiac rhabdomyomas is diverse. In some, the tumour may cause stillbirth or perinatal death (25,26). In others, the clinical picture is dominated by cardiomegaly, congestive heart failure, or cardiac arrhythmias, and sudden and unexpected death has been reported (27). Its clinical significance is largely determined by tumour size, whether they are single or multiple, and whether they have expanded into a chamber space. The vast majority are multiple, but this is not always immediately apparent.[25] They are frequently found in the interventricular septum or the free wall of the heart (28).

The pathological features of cardiac rhabdomyomas are evident. Their gross appearance consists of limited, but not encapsulated, lesions that can range in size from millimetres to several centimetres. They can enlarge at odd rates, with intracavitary appendages that almost completely destroy the cardiac chambers. Microscopically, the tumour consists of oddly swollen myocytes, usually with a centrally located cytoplasmic mass and a nearly 'empty' cytoplasm with a nucleus. The term 'spider cell' began to be used for this architectural arrangement. Immunohistochemical and electromicroscopic studies can confirm the myogenic nature of the cells involved.

Practically, any intracavitary mass occurring in an infant is suggestive of a cardiac rhabdomyoma, given the fact that myxomas are extremely rare in this age group. This is clinically important; since once cardiac rhabdomyoma has been diagnosed, surgical intervention is no longer indicated unless clinical signs from the heart are present. In fact, spontaneous regression of these tumours is well known. For this reason, instead of operating in the absence of any signs or symptoms, there is an opinion to wait and see whether the tumour will regress or not (29-31).





5.2. Fibroma

Cardiac fibromas appear to be the second most common tumour type in infants and children. Most cardiac fibromas are usually discovered in children before 1 year of age, but the upper range of onset extends into late adulthood. About 3% of patients with Gorlin syndrome have a cardiac fibroma. Gorlin syndrome is caused by germline mutations in the PTC gene, which maps to chromosome 9q22.3 and is homologous to the Drosophila patched (PTC) gene (32).

Fibromas are usually single lesions and often cause symptoms that require surgical resection (4,33). Clinical signs and symptoms are largely dependent on the location and size of the tumour. The leading sign is cardiomegaly, but symptoms may include heart failure, arrhythmias, sudden death, cyanosis, and chest pain.[4] Rarely, a cardiac fibroma may grow to enormous size while the patient is asymptomatic (34).

The most common site of cardiac fibroma is the ventricular septum. However, the free walls of the left and right ventricles are other common sites. Atrial fibromas are extremely rare. Cardiac fibromas can cause a variety of symptoms, including obstruction of blood flow, affected valve function, and arrhythmias that can result in syncope and sudden death (4)

The pathology of cardiac fibromas is usually clear. These tumours generally appear as solid, firm, and whitish lesions that are clearly separated from the surrounding myocardium. Rarely, there may be extensive dissemination among the pre-existing myocardium to such an extent that resection cannot be performed (35).

Cardiac fibromas show structural similarities to proliferative fibrous lesions known as fibromatosis. This has led to the concept that both are the same disease processes (36). The term ‘cardiac fibromatosis’ was therefore proposed.

These considerations are clinically important, as they raise the question of whether surgical intervention should be performed in an asymptomatic presentation. Partial resection of a histologically confirmed fibroma located in the interventricular septum in an approximately 6-month-old infant showed no further growth 14-months post-procedure (37). In another case report, subtotal resection of a cardiac fibroma originating from the lower free wall of the left ventricle was performed in a 22-month-old infant. It was revealed that the child was asymptomatic 7 years after surgery and was in good condition. Therefore, it can be argued that in a symptomatic patient for whom surgical intervention is deemed necessary, there are no indications for complete removal of the cardiac fibroma when the procedure compromises postoperative cardiac function (38).

5.3. Angioma

Angioma is a relatively rare tumour in infants and children (9) The clinical presentation is largely dependent on the location and size of the lesions. They can occur anywhere in the heart, but they are usually seen in the epicardium, where they can produce hemopericardium (39). An intramyocardial location can cause myocardial dysfunction with congestive heart failure or imitate valvular heart disease (40). A strange case was documented in a 15-year-old girl who presented with signs and symptoms of pulmonary outflow tract obstruction and inoperable right ventricular haemangioma (41). In addition, an intramural placement may cause atrioventricular block (42). Cardiac angiomas usually present as localised lesions. However, they can sometimes present as an angiomatosis with extensive and diffuse involvement of a large part of the heart.

The biological behaviour of cardiac angiomas is similar to that seen in angiomas in general. They usually have limited growth potential and survive unless surgically removed, although spontaneous involution has been documented (43).

The rough appearance of a cardiac angioma is usually dominated by the aggregation of smaller and larger vascular spaces. Microscopically, common variants, capillary, and cavernous types do not pose a diagnostic problem. Although extremely rare in the paediatric age group, careful investigation should be performed for signs of malignancy such as prominent cellular pleiomorphism, high mitotic count, and tumour necrosis (44).

5.4. Teratoma

Although rare, there is a clear preference for infants and children, as expected. Teratomas are usually located intrapericardially and attached to the aortic root

and pulmonary trunk. However, the heart wall may be involved and sometimes the tumour may present as an intracardiac mass. Clinical signs and symptoms are related to the locality. Cardiac enlargement is the predominant feature and is often accompanied by signs and symptoms of cardiac compression. Teratomas can grow rapidly and come to involve the anterior mediastinum. To date, excision has yielded positive results, even in cases of subtotal resection. Once a teratoma has been diagnosed, it is clinically important that careful investigation be undertaken to exclude the possibility of malignancy.

Gross pathology is usually a lobulated, often multilocular cyst with fluid-filled spaces of varying size mixed with solid areas. Microscopically, teratomas contain elements derived from all three germ layers and diagnosis is usually not problematic (29).

5.5. Myxoma

Although myxoma is the most common primary heart tumour in adults, myxomas are rare in the paediatric age group. Four myxomas were found in infants and children younger than 16 years of age in a meta-analysis, and all were in children older than 1 year of age. The relevant clinical connotation is that intracavitary enlargement of a very young cardiac mass should promptly suggest a cardiac rhabdomyoma rather than a myxoma option (45).

The importance of cardiac myxomas for the paediatric age group relates specifically to a condition known as myxoma syndrome. This syndrome was described by Carney et al. with a complex of myxoma, spotty pigmentation, and excessive endocrine activity. Based on a family study, an autosomal dominant mode of inheritance was considered likely (46). The syndrome is also known as ‘family endocrine myxolentiginosis’, which describes its main components (47). Indeed, the syndrome occurs in a variable complex of mucocutaneous, visceral, and endocrine disorders that are not all present in a single patient. Lesions to be considered in these cases are cardiac myxomas (with a strong proliferative tendency), cutaneous myxomas (single or multiple), breast myxoid fibroadenomas (single or multiple), spotty mucocutaneous pigmentation (including lentigines and blue nevi and their combinations), primary pigmented nodular adrenocortical disease (including patients symptomatic with Cushing’s syndrome), testicular tumours (characteristically Sertoli cell tumours, usually bilateral and multicentric), and tumours that secrete pituitary growth hormone (may cause acromegaly or gigantism) (44,46).

The clinical significance of this syndrome is that the recurrence rate of cardiac myxomas is much higher than in patients with 'sporadic' cardiac myxomas (21% vs. 1%) (48). In addition, recurrences tend to grow more rapidly and show more pronounced local invasiveness. Multicentre onset is also expressed by the fact that, in these patients, recurrences can grow in more than one heart chamber at the same time. Therefore, the previously discussed features should warn against the possibility of myxoma syndrome, and some features may be well present in the paediatric age group (49,50).

5.6. Cardiac lipoma

It has been reported that cardiac lipoma constitutes 5% of resected primary cardiac tumours (51). Cardiac lipoma includes solitary lipoma and infiltrative lipoma. Solitary lipoma is a complete capsule and has a clear border with surrounding cardiac tissues, while infiltrative lipoma lacks a clear border and shows extensive growth. Cardiac lipoma tumours can enter the heart chamber or pericardial space, causing blood flow obstruction or valve dysfunction. Severe cardiac lipoma can invade the cardiac conduction system, causing cardiac arrhythmia and sudden death. The data collection herein included three cases of paediatric cardiac lipoma with clinical manifestations of dyspnoea, oedema, and pericardial effusion. These patients subsequently underwent surgical treatment, and all have recovered since. If patients with cardiac lipomas experience clinical symptoms, tumour resection should be performed as soon as possible. Partial tumour resection can significantly improve the quality of life of young patients in cases in which the tumour cannot be completely removed due to tumour infiltration, the tumour is located in the vena cava, or patients have right ventricular outflow tract obstruction (52,53).

5.7. Cardiac papillary fibroelastoma

Cardiac papillary fibroelastoma, the most common heart valve tumour, and mainly involves the aortic valve, followed by the mitral valve (54). The most common clinical symptoms are fatigue, fever, chest tightness, and embolism. The probability of thrombosis is higher than myxoma, as the tumour is often located in areas subject to high pressure. This type of heart tumour typically appears as sea anemone-like undulating movement on echocardiography (55). Patients with cardiac papillary fibroelastoma located on the left side of the heart have important clinical symptoms that may put them at risk for embolism. Therefore,

surgical resection and valve replacement constitute the first recommended treatment method (54).

6. Primary malignant cardiac tumours

Primary malignant cardiac tumours are extremely rare and constitute less than 10% of primary cardiac tumours (10,56-59). The most common types are angiosarcomas, rhabdomyosarcoma, leiomyosarcoma, and fibrosarcomas. Rhabdomyosarcoma is more common, especially in the neonatal period (60).

Malignant cardiac tumours often remain asymptomatic for a long time (21). One-third of patients have metastases upon diagnosis (61). Symptoms are varied., and dyspnoea, atypical chest pain, and congestive heart failure may occur. Pericardial effusion is common (21,61). On echocardiography, sarcomas are solitary tumours that extend into homogeneous intramural and cardiac circles.

The outcome of malignant cardiac tumours is bad and life expectancy in untreated patients is less than 1 year (62). Even if surgical resection is performed, the average life expectancy is 2 years (61,63-65).

7. Spontaneous tumour regression

Spontaneous regression of rhabdomyomas is well documented and has been reported to be more common in younger patients and those with smaller tumours (66,67). Beghetti et al. found partial or complete spontaneous regression in 54% of 44 patients analysed (8). Farooki et al. (29) analysed five patients with cardiac rhabdomyoma associated with tuberous sclerosis, showing a regression rate of 0.9 to 6 mm per month. There have also been studies in which half of the patients with non-surgical rhabdomyomas showed partial or complete spontaneous regression. The remaining patients did not show any change in tumour size. Only 4 of 24 patients with rhabdomyoma required surgical intervention due to hemodynamically significant left ventricular outflow tract obstruction. Because of this spontaneous regression of rhabdomyomas, a non-surgical treatment is recommended.[58]

8. Surgical treatment indications and general principles

Since some cardiac tumours can potentially regress, surgical treatment is usually indicated when symptoms are present (68). The majority of studies have recommend surgery only in symptomatic patients with hemodynamic or respiratory distress or at risk for significant systemic embolization (9,10,67,69). The majority of tumours in the paediatric age group are benign.[57] Tumour growth is slow, has low invasiveness, and it is not the neoplastic potential of these tumours that should be considered rather than their mechanical conformation

(37). In most patients, the indication for surgery is mediastinal compression or intracardiac obstruction (58).

Surgical resection is usually tailored to the patient's characteristics. In most cases, especially when the mass is intracardiac, cardiopulmonary bypass and aortic cross clamping are required. Gentle manipulation of the heart is recommended to avoid cardiac mass fragmentation and embolization (i.e. myxomas). As the surgical approach (i.e. transatrial, transventricular, transaortic) depends on the mass position, accurate preoperative diagnosis of the localization is of great importance. Appropriate surgical exposure of the mass is essential to achieve a radical resection and preserve the integrity of the surrounding heart structures, particularly the coronary vessels that may travel close to the mass. Partial volume removal has proven effective in most benign histotypes when a more complete resection has damaged surrounding tissues. Finally, associated procedures such as atrial patch closure after myxoma resection and right ventricular patch reconstruction after fibroma resection may be necessary (68).

9. Conclusion

Primary cardiac tumors are rare at all ages and even less common in infants and children. Most of the tumors reported are benign. Rhabdomyoma is the most common tumor type. Regarding other tumor types, most authors recommend surgery only for symptomatic patients with hemodynamic or respiratory compromise or significant risk of systemic embolization

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CHAPTER 4

UNEXPECTED DEATH IN SLEEP: BRUGADA SYNDROME

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1. General aspects:

Brugada syndrome (BS) is an arrhythmia disease that can predispose to ventricular fibrillation (VF) and sudden cardiac death (SCD) in young adults without structural heart disease. It was first identified in 1992 by the brothers Pedro and Josep Brugada as an important cause of sudden cardiac death (1). Young adults without structural heart disease, accompanied by a distinctive ST segment elevation pattern in the surface ECG right chest leads (V1-V3) and right bundle branch block presenting with SCD was the typical presentation of the disease. The diagnostic criteria of Brugada syndrome were determined in 2002 and then algorithms were prepared about the diagnosis of the disease, risk classification and appropriate treatment approaches in 2005 (2).

Ventricular arrhythmias due to BS (mostly polymorphic ventricular tachycardia [VT]), syncope and SCD usually occur between the 3rd and 4th decades. The mean age at diagnosis or SCD is 40 ± 22 (2, 3). It is difficult to estimate its prevalence in the general population, as the ECG pattern in BS is highly dynamic and often hidden/covert (4). Its prevalence is around 1-5 /10,000 and it is responsible for 20% of SCD cases in individuals without cardiac problems and 4-12% of all SCD cases worldwide. While its frequency is observed much lower in Western countries; in Southeast Asia, especially in Thailand and the Philippines, it is the most important cause of death in men <40 years old, excluding accidents. Because of the most SCD events are during sleep, the syndrome is often referred to as "Sudden Unexpected Nocturnal Death Syndrome (SUNDS)" in these endemic countries (5, 6, 7).

Genetic transmission is autosomal dominant in BS. The first identified gene for this disease is SCN5A, which encodes the alpha subunit of voltage-

dependent cardiac sodium channels (5, 8). These mutations, most of which are missense mutations with loss of function in the Na channel, are present in 18% to 30% of Brugada Syndrome cases (4). From later periods until today, mutations such as GPD1-L that regulate the functions of Na channels and loss or gain of function mutations detected in different ion channels (such as Ito, L-type Ca channels, K channels) continue to be defined (6, 8). Although there is no defined genetic defect transmitted by the sex chromosome and the mutation frequency is evenly distributed between the sexes, the disease phenotype is observed 8 to 10 times more in men than in women (5, 6, 7).

2. Clinical Manifestation and diagnosis:

The presentation of one-third of BS patients is with symptoms as syncope, seizure, agonal breathing or aborted SCD, most of which occur at rest or while sleeping. In most cases the underlying arrhythmia is polymorphic ventricular tachycardia or ventricular fibrillation. The other two-thirds of BS patients are diagnosed without symptoms. Most of these asymptomatic patients are spotted during familial screening (9).

Before the expert consensus statement in 2013, the diagnostic criteria were including both symptoms and the specific ECG pattern. But after 2013, it was proposed to make the BS diagnosis with only the specific ECG pattern called Type-I either in spontaneous ECG or in the ECG of provocation tests with sodium channel blockers, in at least one of two right precordial leads. Presence of the symptoms is no more required. The Type-I ECG pattern is defined as a >0.2 mV of coved ST-segment elevation in one right precordial lead, with a negative T wave in the end. There are more ECG patterns other than Type-I but they are not enough for the diagnosis. Although the other BS ECG patterns are merely not sufficient, they are useful for clinicians to decide to the need for a sodium channel blocker test, which can reveal a Type-1 ECG pattern. Besides the standard electrode positions, the diagnostic ECG can be taken in superior position in which the electrodes are positioned in the second intercostal space. This positioning provides an increased sensitivity (5).

Despite its sufficiency for diagnose, the Type-I ECG pattern can sometimes be seen in other medical conditions such as right ventricular ischaemia, acute pericarditis, acute pulmonary embolism, compression of the right heart and metabolic disturbances. Apart from diseases, some drugs can also cause Type-I ECG pattern (6, 10). Clinicians must be aware of such conditions and evaluate the patients from this perspective to avoid misdiagnoses.

While unmasking of the Type-I ECG pattern by some drugs can sometimes lead misdiagnoses, this situation is also an advantage for BS diagnose. Class I antiarrhythmic drugs such as Ajmaline and flecainide are used to diagnose concealed forms of BS by unmasking the Type-I ECG pattern in patients with high clinical suspicion but without certain ECG findings (6).

3. Risk Stratification:

After the challenging diagnose of BS, the most challenging part of the disease management starts: The risk stratification. Since the main treatment choice is implantable cardioverter defibrillator (ICD) and this therapy itself brings some risks in long term follow up, it is important to make risk stratification and to decide which patients are at high risk of malignant arrhythmias and SCD. There are many variables that are thought to be valuable in the risk stratification but among those just spontaneous Type-I ECG pattern and symptoms like surviving from SCD or syncope are indisputable (11, 12).

In SCD survivor BS patients, it has been shown that the risk of recurrence is %10 per year in the first 4 years. Also syncope is shown to be associated with %1.5 of annual risk for VF which is four times higher than the risk in asymptomatic patients (9). At this point, it becomes very important to distinguish the vasovagal/neuromediated syncope since this patient group has not been shown at high risk of developing malignant arrhythmias (13).

Spontaneous ECG pattern in BS patients is another reliable risk factor that increases the risk of SCD %0.81-2.3 yearly (9). On the other hand, the variable nature of the ECG pattern in BS makes it essential to make a long term ECG evaluation. Holter monitoring is a good option in patients with high probability of having BS but without spontaneous ECG pattern (14).

Apart from the symptoms and spontaneous ECG pattern, male sex is another risk factor. Despite the autosomal dominant transmission of the disease, probably due to incomplete penetrance and variable expressivity, the spontaneous ECG pattern is three times and the SCD risk is eight times more in male patients (15, 16).

The risk is also associated with age. In children and elderly patients (>60 years) the SCD risk significantly decreases. Although the risk decreases, the mortality is not negligible so that attention is needed to detect BS even in these age groups (16, 17).

Many gene groups have been shown to be related with BS. Among those the SCN5A gene is recommended to be analyzed just for documentation, not for

prognosis or treatment modification for now by the current guidelines, since the association with prognosis is not proven by large studies (9).

Atrial fibrillation (AF) has been shown to be more frequent in BS patients. %30 of BS patients develops AF and that is associated with poor prognosis (18). Likewise there are other ECG markers that are thought to be related with disease prognosis such as fragmented QRS complexes (19), QRS duration (20), late potential (21), aVR sign (22) and Tpeak-Tend interval duration (23) but their influence on prognosis has not been proven by large cohort studies.

Several large prospective studies have promising results that supports the use of electrophysiological study (EPS) in risk stratification of BS patents (24). However that is recently controversial, so that guidelines recommend ICD implantation as IIb even if ventricular arrhythmias are provoked in EPS (5).

4. Management:

The mainstay of BS treatment is ICD implantation. It has been shown to be effective to prevent SCD. After making the risk stratification by given variables, patients may be categorized into three groups. The low risk group is asymptomatic patients without spontaneous but with drug induced ECG pattern. In this group ICD implantation is not indicated. High risk group is the symptomatic patients with spontaneous ECG pattern. In high risk group ICD is indicated. Decision of ICD implantation is more difficult in intermediate risk group. Intermediate risk group includes the asymptomatic patients with spontaneous ECG pattern. In this group the cumulative risk of VF is %12 at 10 years (25). Considering the risk of ICD implantation, it is better to evaluate the patient in terms of other risk factors. And final decision should be made with patients after they are informed in detail.

EPS has growing importance in management of BS day by day both in terms of arrhythmia induction for risk stratification and also ablation of arrhythmias especially for the patients in electrical storm (26). Recently the ablation of arrhythmic electrophysiological substrate (AES), the region generally located in right ventricle anterior wall and outflow tract, has been shown to resolve the ECG abnormalities and even prevent arrhythmic events in BS (27).

Long term drug treatment for BS is quite limited. In some studies it has been shown that quinidine has benefits for arrhythmia management. But the limited data available and the wide range of side effects of quinidine restricted its widely use (28).

Life style modification is another important point in BS. Patient should be advised to avoid excessive alcohol intake and decrease physical activity. Fever

that can also provoke arrhythmias must be aggressively treated. The list of drugs that may induce arrhythmias should be given to all patients. And familial screening should be performed to identify other family members at risk (6).

5. Conclusion

BS is a rare but is an important disease in terms of its impact on mortality. The diagnosis, risk stratification and management is challenging because of the limited data. But there is a trend of growing knowledge and new technics day by day.

The main risk factors for SCD are known as spontaneous ECG pattern and symptoms of the patient. But new data suggests many other variables that may be useful in risk stratification of patients in the future.

Although ICD is the only proven therapy of choice in BS for now, EPS has a promising role for both risk stratification and treatment. For saving more lives, more data and further studies are needed.

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CHAPTER 5

CURRENT USE OF NOVEL CARDIAC BIOMARKERS IN ACUTE OR CHRONIC CARDIOVASCULAR DISEASES

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1. Introduction

Cardiovascular diseases are the major cause of death all over the world. In 2019, 17.9 million deaths, which represent 32% of all global deaths, were based on cardiovascular diseases (1).

As cardiovascular diseases become very common because of the aging of the world population, advances in cardiac biomarker research and screening methods for early detection came into prominence. Biomarkers serve a wide range of purposes in disease progression assessment and in therapeutic approaches.

In this book chapter, we aimed to evaluate the current use of novel cardiac biomarkers (microRNAs, Galectin-3, Soluble Suppression of Tumorigenesis-2, Growth Differentiation Factor 15, Adrenomedullin, LL-37, F-2 Isoprostanes, Choline) and their association with acute or chronic cardiovascular diseases.

2. MicroRNAs

MicroRNAs, which are composed of 22 nucleotides, are essential in cardiac development and in the formation of heart tissue (2). Deletion of Dicer1, a gene

involved in miRNA processing, results in heart failure and cardiac malformations in mice (2). MicroRNA-1, muscle specific miRNA, negatively changes cardiomyocyte growth by adjusting expression of calmodulin (3). In addition to miRNA-1, miRNA-133 has also a role in the regulation of cardiomyocyte proliferation by repressing cyclin D2 and serum response factor (Srf) (3).

Various microRNA studies showed that different microRNAs have a pathogenic role leading to heart failure caused by hypertrophy, apoptosis and hypoxia (4,5). Because of their stability in plasma and their proven relation in the onset and outcome of heart failure, the discovery of circulating miRNAs can be used as novel biomarkers in cardiovascular diseases (2).

According to 21 research articles published between 2008 and 2015, miR-1 plasma levels were increased in patients who were affected from acute myocardial infarction (6,7) MiR-195 levels were up-regulated in both dilated cardiomyopathy left ventricle tissues and heart failure myocardial biopsy (8,9). Moreover, miR-30a serum levels were elevated in reduced ejection fraction heart failure (10,11). Hu et al. showed that miR-210 improves heart function by contributing angiogenesis and inhibiting apoptosis so that it can improve cardiac function in a murine model of myocardial infarction. Hu et al. proposed the use of miR-210 as a newly discovered therapeutic approach when planning a treatment in ischemic heart disease (12).

Some studies emphasize the utility in differential diagnosis of miRNAs. Tijsen et al. reported that miR-423-5p levels are differently expressed between non-heart failure caused dyspneic patients and heart failure caused dyspneic patients. In addition to its cardiovascular diagnostic properties, it can be used as a differential diagnosis tool too. (5)

3. Galectin-3

Galectins (known as “S-type lectins”) are a subfamily of soluble proteins that typically bind β-galactoside using its carbohydrate recognition domain (CRD) with high specificity. The CRD has a known role in the pathogenic way of heart failure (13). In addition, Galectin-3 is dominant in cardiac fibrosis, inflammation and fibrosis (13) .

3.1. Expression of Galectin-3

Galectin-3 is expressed in vascular smooth muscle cells, macrophages, eosinophils, neutrophils, and mast cells (14,15) In the tissue level, galectin-3 is

most abundantly found in lung, spleen, stomach, colon, adrenal gland, uterus, and ovary. (14)

3.2. Some Cohort Studies

In the Framingham Offspring Cohort (mean age 59 years; 53% women), Gal-3 is found associated with risk of incident heart failure (hazard ratio [HR]: 1.28 per 1 SD increase in log Gal-3; 95% confidence interval [CI]: 1.14 to 1.43; p <0.0001) (16). According to Bernardo Study (1393 participants) Galectin-3 is found as an independent predictor of cardiovascular death (HR 1.24, 1.05-1.47) after adjusting for N-terminal pro B-type natriuretic peptide (17). Moreover, in "Prevention of Renal and Vascular End-Stage Disease" study, serial measurement of Galectin 3 levels (5958 subjects with the median duration of follow-up 8.3 years) were strongly associated with an up-regulated risk of onset heart failure, cardiovascular mortality, new-onset atrial fibrillation compared to subjects of control group with non-increased Galectin-3 levels (18).

3.3. Galectin-3 and Other Systemic Diseases

Besides its probability of use in determining cardiovascular diseases, Galectin-3 can be used as a predictor in other systemic diseases. Nishi et al. showed that Galectin-3 levels were specifically elevated in bronchoalveolar lavage fluid from patients with idiopathic pulmonary fibrosis and interstitial pneumonia associated with collagen vascular disease (CVD-IP) (19). In addition to that, Mueller et al. reported that an increased Galectin-3 levels were associated with pneumonia, renal diseases and sepsis (20) .

3.4. Galectin-3 and Statin Therapy

In addition to its diagnostic function, Galectin-3 can be used also in a prognostic way. A study by Gullestad et al. hypothesized that a decreased galectin-3 levels may show that the patients ,who had chronic heart failure and left ventricular systolic dysfunction due to ischaemic heart disease, benefited from statin therapy (21).

4. Soluble Suppression of Tumorigenesis-2 (sST2)

Soluble suppression of tumorigenesis-2 (sST2), which is produced mostly by alveolar cells and vessel wall cells and leastly by cardiac fibroblasts and cardiomyocytes, is released after vascular congestion and before fibrotic stimuli (22). Because of its role in the fibrosis and inflammation process, various studies

have been made to expose the features of sST2 biomarker and to consider its contribution to heart failure management.

In the assessment of chronic heart failure, we are using mostly high-sensitivity troponin T, N-terminal pro-B-type natriuretic peptide and soluble suppression of tumorigenesis-2 (sST2) (23). Aimo et al. evaluated a study about the influence of age on the mentioned biomarkers. They found that soluble ST2 is less influenced by age compared to NT-proBNP or hs-TnT (23).

4.1. Association of sST2 and Atherosclerosis

According to a meta-analysis in which 7 studies with 6372 patients, sST2 is shown as a predictor of cardiovascular death in chronic heart failure outpatients. (24) In the view of molecular level, a study with 316 patients was made to report the association of sST2 with platelet activation. This study showed that sST2 has an association with soluble P-selectin and monocyte TF expression in atherosclerosis (25). According to another study driven by Ates et al., sST2 is evaluated as an risk factor for subclinical atherosclerosis because of increased carotid intima-media thickness (26).

4.2. Association of sST2 and Right Ventricular Dysfunction

A retrospective single-centre cohort study which is made with 48 chronic hemodialysis patients (mean age: 74) showed that increased sST2 levels are independently associated with right ventricular dysfunction (27). Coldea et. al. reported that there is a strong correlation between circulating sST2 levels and RV ejection fraction ($r = -0.799$; $p < 0.001$), tricuspid annular plane systolic excursion, ($r = -0.773$; $p < 0.001$) and increased pulmonary artery systolic pressure ($r = 0.603$; $p < 0.001$) (28).

5. Growth Differentiation Factor 15 (GDF-15)

Growth differentiation factor 15 (GDF-15) is a growth-factor beta cytokine that is mainly expressed in response to inflammation, oxidative stress, hypoxia, telomere erosion and oncogene activation (29,30). After GDF-15 is produced as a precursor protein, N-terminal propeptide from mature GDF-15 protein is released in the process of proteolytic cleavage (29).

5.1. GDF-15 And Coronary Artery Disease

Circulating GDF-15 levels are independently associated with age, diabetes, smoking status, hs-CRP and renal dysfunction in patients with coronary artery

disease (29). A study made with 2081 patients who have acute chest pain reported that GDF-15 can be used as a new biomarker of mortality in patients with non-ST- elevation acute coronary syndrome (31).

5.2. GDF-15 And Coagulopathies

An elevated GDF-15 levels which were measured within 24 h after symptom onset, had a strong association with non-CABG (coronary artery bypass graft) related life- threatening coagulopathies. In the case of atrial fibrillation, GDF-15 is a leading risk factor for bleeding, stroke and death (32). Wallentin et al. also emphasized that the measurement of circulating GDF-15 levels, HAS-BLED score (a score which asses 1 year- risk of bleeding for people having an anticoagulant therapy for atrial fibrillation) and other biomarkers have statistically significant independent prognostic value on major bleeding; the c index was 0.664 without and increased significantly to 0.682 (P<0.0001) with GDF-15 (32).

6. Adrenomedullin

Adrenomedullin, which is initially isolated from pheochromocytoma by Kitamura et al. in 1993, is a vasodilatory peptide hormone synthesized by endothelial and vascular smooth muscle (33). When there is a malfunction or overproduction of adrenomedullin, vascular leakage and pulmonary oedema can be seen. As Adrenomedullin receptors occupy a major place in the body, cardiovascular and pulmonary tissues have the highest density of binding sites (33).

Nishikimi et al. proposed that circulating adrenomedullin levels are proportional with the severity of the heart failure (34). They also found that plasma adrenomedullin level has a positive association with ANP, BNP and norepinephrine levels whereas it has a negative correlation with left ventricular ejection fraction (34).

6.1. Adrenomedullin and Myocardial Infarction

According to a study with 15 patients admitted within 6 hours of acute myocardial infarction, plasma levels of adrenomedullin are increased, especially in patients affected from acute myocardial with a history of infarction congestive heart failure (35). Adrenomedullin levels have strong association with right atrial pressure, pulmonary capillary wedge pressure, pulmonary arterial pressure and heart rate in the beginning of the acute myocardial infarction (35).

7. LL-37

LL-37 is an antimicrobial peptide in Cathelicidin family. The peptide found in human body and functions in various mechanisms of homeostasis. Lately, its role as a biomarker in cardiovascular diseases has been investigated.

7.1. LL-37 in Myocardial Infarction

An association was established between decreased levels of LL-37 and acute ST-segment elevation myocardial infarction (STEMI) by previous research. (36)

7.2. LL-37 in Atherosclerosis

Innate immune system includes antimicrobial peptides. As LL-37 is produced in atherosclerotic lesions, its mechanism of action as an immune modulator has been discussed toward chemokine expression and activation of adhesion molecules. (37)

LL-37 in atherosclerotic lesions may have a role as a mediator of vascular smooth muscle cell death induced by immune cells. (38)

7.3. LL-37 in Heart Failure

As one of the leading causes of hospitalization among elderly, heart failure found to be related to decreased levels of LL-37, which is a human analog of cathelicidin-related antimicrobial peptide. (39)

8. F-2 Isoprostanes

Isoprostanes are in vivo formed prostaglandin-like structures which derived from the free radical mediated peroxidation of arachidonic acid.(40) Their use of measuring oxidative stress is very important and can be measured with use of urine specimens.

8.1. F-2 Isoprostanes in Atherosclerosis

F-2 Isoprostanes are thought to be indicators of oxidative stress. Since increased oxidative stress can be related to atherosclerotic diseases, the relationship between F-2 Isoprostanes levels and existence of atherosclerotic disease was worth investigating.

Previous research indicated that urinary 8-iso-prostaglandin F2 alpha is an independent and sensitive biomarker of coronary heart disease.(41)

8.2. F-2 Isoprostanes and Smoking

Lipid peroxidation products as F-2 Isoprostanes are found to be increased among smokers; this relation may indicate the effect of smoking toward oxidative damage and further coronary heart diseases. (42)

8.3. F-2 Isoprostanes as Vasoconstrictors

The compound has a role of vasoconstrictor; this effect of 8-iso-prostaglandin F2 alpha acts through interaction with vascular thromboxane and endoperoxide receptors. (43)

9. Choline

Whole blood choline level is an important indicator of cardiovascular pathologies. Choline measurement may be useful in patients with suspected cardiovascular diseases when negative troponin levels were obtained. (44)

9.1. Choline in Acute Coronary Syndrome

Choline levels are increased in the presence of acute coronary syndrome such as unstable angina and myocardial infarction. (45)

Increase of choline levels in acute coronary syndrome can be induced by several mechanisms such as factors related to unstable atherosclerotic plaques and factors related to ischemia and reperfusion. (45)

9.2. High Choline Levels

Other than acute coronary syndrome, some other situations where choline levels increase are end-stage renal disease and cerebral ischemia with presence of carotid plaques. (45)

10. Conclusion

Diagnostic and prognostic tools for cardiovascular diseases carry an important role toward patients' health. Since laboratory biomarkers are one of the most reliable indicators of patients' health; research in the area is significant. Newly discovered biomarkers may help clinicians to diagnose the acute situations earlier so the intervention can be applied earlier as well. Prognostic values of these novel biomarkers can be improved by evaluations in clinical studies and be implemented in routine use. In this chapter, some of these novel biomarkers that may be useful in clinical evaluation and management in cardiovascular diseases were discussed.

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CHAPTER 6

STOMA IN SURGERY APPLICATIONS

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1. Introduction

Stoma is a Greek word meaning opening of the mouth. However, in the medical literature, the stoma consists of various parts of a hollow organ. Mouth to the abdominal wall for reasons it means (1,2,3).

- **Stoma**: It means opening or mouth.
- **Temporary stomas**: Situation requiring stoma shut down after
- **Permanent stomas**: remain for life (4,5)

Today, 3 types of ileostomy are used

a) End ileostomy (Brooke ileostomy)
b) Loop ileostomy
c) Continent (Kock) ileostomy (6,7,8)

2. Stoma Types

a) Gastrostomy
b) Ileostomy
c) Colostomy
d) Urostomy

Gastrostomy, non-orally fed provide nutrition to patients to the abdominal wall of the stomach mouthing. Percutaneous Endoscopic also called gastrostomy (PEG). Jejunostomy is the abdominal wall of the jejunum.mouthing. Percutaneous Endoscopic also called jejunostomy (PEJ) (4,8).

2.1. Reasons for Opening an Ileostomy

Usually opens to the bottom right, for various reasons, large intestine and the rectum is completely removed by surgery or ileostomy in cases where it

is disabled opens. Can be temporary or permanent, as in colostomy, as with ileostomy, stool output cannot be controlled in ileostomy, stool is liquid, burning and is too much (2,10).

- Surgery of the large intestine and rectum cases where it is completely removed or disabled (blockages, cancers, injuries, etc.) (11,12)
- Ulcerative colitis
- Crohn's disease
- Familial adenomatous polyposis (AAP/FAP)
- Congenital anomalies
- Traumas

*2.2. **Conditions to be considered in the patient with ileostomy***

- Patient fluid and electrolyte imbalances should be followed in terms of
- It should be followed in terms of dehydration.
- The bag should be emptied frequently and the output amount should be measured
- The patient's intake of copious amounts of fluid must be provided (13-15)

*2.3. **Reasons for Colostomy Opening***

- Colon cancer
- Crohn's disease
- Colon obstruction
- Traumas
- Intestinal ischemia
- Fecal incontinence
- Hirschsprung's disease (16)

*2.4. **Colostomy***

Usually opens on the lower left side of the abdomen, the main function of the colostomy; bowel expulsion of its contents through the stoma to provide. Because the colostomy does not have a sphincter muscle as in the anus, the individual with a colostomy cannot control their bowel movements and stool evacuation. More gas formation in the large intestine filter bag for individuals with they must use colostomy (17,18).

2.4.1. ***Temporary Colostomy***

- Large bowel obstruction
- Bowel injury
- Congenital anomalies
- For anastomosis healing (19)

2.4.2. ***Permanent Colostomies***

- Cases of removal of the anus
- Miles operation

3. Stoma care

- Changing the stoma bag
- Skin Care
- Nutrition
- Smell
- Gas extraction
- Bathing and dressing
- Recreation and Sports activities
- Return to work and social life
- Going on vacation
- Sexual life
- Pregnancy
- Drug use (21-26)

3.1. ***Choosing the right material***

- Adapter
- Bag
- Scissors
- Paste, Skin barrier, Powder
- Gauze
- Warm water
- Garbage bag
- Stoma measurement ruler

3.2. Stoma Bag And Adapter Systems

- One-piece bottom drain system
- One-piece bottom closed system

- Double-piece (bag adapter separate) from the bottom drainable system
- Two-piece bottom closed system Stoma Bag And Adapte (23,24)

3.2.1. Pre-cut adapter

There are forms cut in different sizes especially the elderly, who cannot adjust the adapter diameter recommended for patients. soft/hard ones available.

3.2.2. Cuttable adapters

Cuttable adapter to individual stoma diameter are systems.

3.2.3. The paste form

This form is around the stoma, stoma padding in the surrounding abdominal folds used as a substance.

3.2.4. *Evaluation of the Stoma*

a) Stoma color, moisture; It should be bright pink in color and moist. dark or black If the blood flow is blocked, the circulation is not sufficient, and if the stoma is pale in color, the individual may be anemic must be known.
b) Stoma diameter; Diameter within 4-6 weeks after surgery shrinks. For this reason, attention should be paid to the measurement of stoma diameter and the diameter of the adapter should be suitable for the stoma.
c) Stoma height; Most stomas are round and 1.5-2.5 cm from the skin is in height.
d) Stoma shape; May be round, oval, irregular
e) Stoma location;
   In ileostomies → Right lower quadrant
   In colostomies → Left lower quadrant
   Transfers colostomies → Above the umbilicus

Parastomal skin can be soft or hard. Adapter When choosing flexible for hard skin, for soft skin hard adapter must be used (24-28).

4. Stoma Complications

1. Ischemia and necrosis
2. Stomal Retraction
3. Stoma stenosis

4. Peristomal dermatitis
5. Parastomal hernia
6. Bowel obstruction
7. Stomal prolapse
8. Bleeding

(29-35)

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CHAPTER 7

AN ALGORITHM FOR APPROACH TOWARDS RUPTURED ANEURYSMAL SUBARACHNOID HEMORRHAGE PATIENTS

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1. INTRODUCTION

1.1. Definition

Subarachnoid hemorrhage (SAH) was defined by Sacco et al. in 2013 as hemorrhage between the brain or spinal piamater and the arachnoid membrane, i.e., the subarachnoid space. SAH is a destructive and complex cerebrovascular disease that affects the functions and perfusion of the brain (1,2).

1.2. Epidemiology:

Hippocrates reported 2400 years ago that certain neurological findings occur after a spontaneous hemorrhage. He defined cerebrovascular angiographic vasospasm. In the18th century,Morgagni and Buimi identified that aneurysms cause SAH. Egas Moniz started the use of cerebral angiography in 1927. Dott performed the first internal carotid artery aneurysm clipping in 1931. In 1951, Ecker and Riemenschneider defined angiographic vasospasm, and in 1980, the Fisher classification was made. Bederson 1998; Cai 2012; Suzuki 2010 employed digital subtraction angiography (DSA), magnetic resonance angiography and synchrotron radiation angiography (1,3).

1.3. Etiology and frequency:

A subarachnoid hemorrhage may occur in two ways. The first is post-traumatic and the second is nontraumatic, i.e., spontaneous SAH. The incidence of SAH varies between 2 to 32 per 100,000, and is less frequent in the Far East than the Northern European countries (4,5). SAH is usually observed around 40-50 years of age, peaking at 55. The risk is high particularly in premenopausal women. Approximately 15% of the cases are traumatic whereas85% are nontraumatic. 90% of nontraumatic aneurysms are aneurysm-related hemorrhages whereas in 10%, the angiogram is negative, thus they are non-aneurysmal. The incidence of aneurysm is 2-3% with an annual rupture risk of 0.7-4%. The mortality rate in these patients is approximately 32-35% in the U.S. whereas in poorer countries, this rate may increase up to 50%. In aneurysmal SAH, the mortality rate rises up to 40-60%. Some of these patients die before access to a hospital or receiving a diagnosis (4).

1.4. Pathophysiology:

In the early stage following the hemorrhage, firstly the patient's intracranial pressure increases. Cerebral perfusion pressure is disrupted, cerebral blood flow is disrupted and usually decreased, cerebral autoregulation is disrupted, and excitotoxicity and extensive ionic imbalance (potassium, sodium, calcium, etc.), oxidative stress, inflammation, apoptosis, autophagy, necrosis and cerebral edema occur (6,7).

At the late stage, cerebral vascular spasm, microvascular spasm and dysfunction in the blood vessels of the brain, microthrombosis and diffuse cortical ischemia develop (8).

2. IMAGING AND DIAGNOSIS

Cranial Computed Tomography (CCT): In head traumas and brain hemorrhages, firstly a regularcranial computed tomography is performed.

CT angiography: It is an examination method performed by administering contrast media to the patient during imaging, and the imaging is done simultaneously by using iodinated contrast media. Sometimes 3D images are also formed with the assistance of the CTA program. This methodis advantageous mainly forits short duration and non-invasive nature (9), (Figures 1, 2).

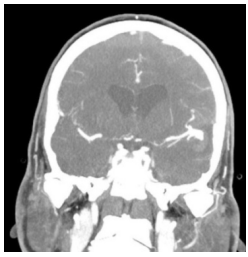

Figure 1a

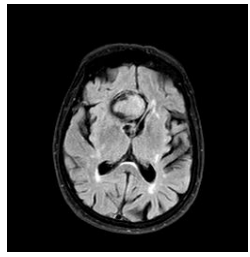

Figure 1b

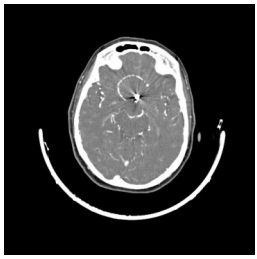

Figure 1c

Figure 1: a. Left middle cerebral artery aneurysm; b and c. MRI and CT angiography of a giant aneurysm having a calcified wall and thrombosed lumen post-treatment.

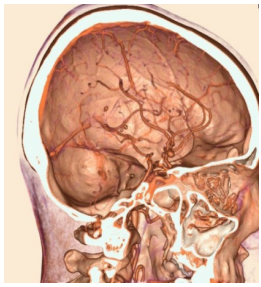

Figure 2a

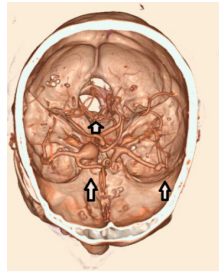

Figure 2b

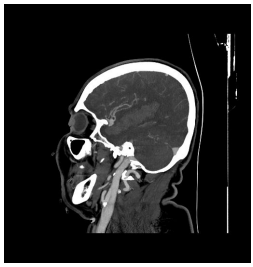

Figure 2c

Figure 2: a. CT Angiography of an Anterior communicating Artery Aneurysm; b. Aneurysms at the right ICA supraclinoid segment, left MCA M2 segment and right PICA; c. Aneurysm and intraparenchymal hematoma at the level of left MCA trifurcation.

Magnetic Resonance Angiography: This method takes advantage of the different contrast characteristics of mobile protons versus stationary protonsin magnetic resonance imaging. MR angiography can be performed with or without contrast, and the non-contrast MR angiography method has two types, namely TOF MR angiography and phase-contrast MR angiography (10) (Figure 3). MR angiography imaging combines routine MR imaging techniques and angiography which is an intravenous imaging method, thereby providing detailed information about the blood vessels. MRA does not involve the radiation of catheter angiography and CT angiography. Further, unlike DSA, it does not require catheter placement (11).

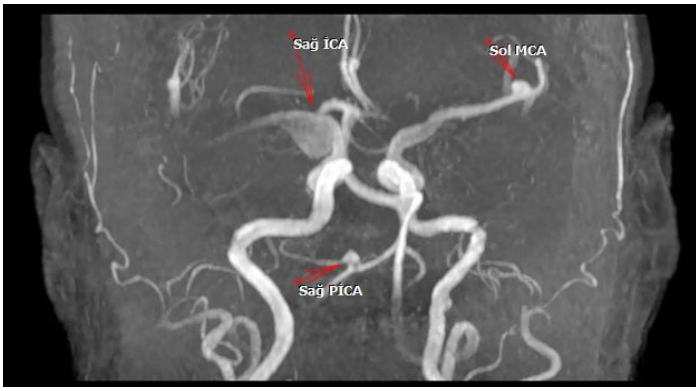

Figure 3. MR angiography.

DSA: Also identified as digital subtraction angiography, this method requires a specific angiography unit and a specifically trained team. Insertion may be done through various areas, e.g., by femoral, radial or, in the old times, direct carotid access. Firstly, a guide is inserted into the vein followed by a special guiding catheter and many other special catheters to reach the desired area, thereby performing the necessary operations. This method enables aneurysm coiling, stent implantation or aneurysm diagnosis (12,13).

3. CLASSIFICATIONS:

Fisher:

Group	Computed tomography bleeding
Grade 1	None
Grade 2	Diffuse hemorrhage thinner than 1 mm
Grade 3	Vertical layers or localized clots thicker than 1 mm
Grade 4	Intracerebral or intraverticular hemorrhage

Hunt-Hess:

Grade 0	Unruptured aneurysm, no neurological deficit
Grade 1	Asymptomatic or minimal headache with slight nuchal rigidity
Grade 1a	No acute meningeal or brain reaction but with fixed neurological deficit
Grade 2	Cranial nerve palsy (3,4), severe headache, nuchal rigidity
Grade 3	Drowsy, confused, or mild focal deficit
Grade 4	Stupor, moderate hemiparesis, early decerebrate rigidity
Grade 5	Deep coma, decerebrate rigidity, moribund

WFNS:

WFNS grade	GCS score	Motor deficit
Grade 1	15	Without deficit
Grade 2	14-13	Without deficit
Grade 3	14-13	With deficit
Grade 4	7-12	With or without deficit
Grade 5	3-6	With or without deficit

The main classifications used in the follow-up and treatment of SAH are the Fisher, Hunt-Hess and WFNS classifications (6,13-15)

4. EMERGENCY AND TREATMENT APPROACHES

4.1. Cases in which endovascular coiling is preferred:

Posterior circulation aneurysms, basilar type aneurysms, intracavernous and internal carotid aneurysms, older patients,

4.2. Cases in which surgery is preferred:

Middle cerebral artery aneurysms, fusiform aneurysms, giant aneurysms, wide-necked aneurysms, artery bifurcation aneurysms, ruptured aneurysms and younger patients are preferred for surgical treatment (16).

The main principles of treatment are as follows:

1. It is necessary to meet the patient at the emergency unit and stabilize the vital signs. The treatment requirements include giving the patient a CCT and a neurological examination, taking note of the Fisher, GKS and WFNS grades, immediate evaluation by a radiologist of the CCT report of those

patients diagnosed with SAH, and admission into intensive care in order to arrange treatment (17).

2. Initiation of medical treatment:
   a. An isotonic or balanced fluid is administered depending on the conditionof the patient in terms of hypertension, diabetes or additional diseases (110-125cc/h).
3. Analgesic treatment (Metamizole amp 3x1, Paracetamol vial or tablet 3x500-1000 mg) is initiated. The painkiller may be changed according to the patient's condition. The patient should absolutely be sedatized (for sedation, 2-10 mg x3-4 dose/day Diazepam may be administered depending on the patient's agitation level).
4. For the aim of reducing or preventing spasms, nimodipine in vial should be initiated at 5-10 cc/hour and continuedat BP 140/90, 130-80 mmHg, if it can be obtained and is considered for clinical use. It should be continued for a total of 21 days as of the day of the bleeding,in the form of infusion during the intensive care period and as Nimodipine 6x2 tb during hospitalization and post-discharge. However, certain discussions in the literature point to disagreements among clinics about the use of nimodipine. Some clinics consider that nimodipine is not useful, and might even be harmful. (18,19).
5. Dexamethasone ampoule is initiated at 4x4-8 mg and gradually stopped based on the severity of the brain edema. Mannitol is arranged according to the amount of bleeding and the patient's consciousness and brain edema. If mannitol is to be used, it is recommended to start at 1 mg/kg. In case of lack of sufficient urination following the administration of mannitol, a complete furosemide ampoule or half of it is administered subsequently. As for antiepileptic drug administration, if the patient has previously been on antiepileptic medication, it should be continued in the same manner, and if not, an epanutin loading dose of 17 mg/kg is administered within 1 hour, followed by a maintenance treatment of epanutin at 5mg/kg, 2-3x100 mg (15,18).
6. During CCT angiography imaging, due care should be taken to make sure that the test is performed by trained personnel and released in 3D imaging form. It should be ensured that the test is reported by the radiologist as soon as possible.
7. If the radiologist has reported an aneurysm or if an aneurysm is obvious in the imaging, the report on aneurysm is confirmed upon consultation with the radiologist. In this case, the patient's physician may decide for surgery

or the patient may be referred to DSA imaging. If no aneurysm could be detected, it is recommended that the patient is given a DSA imaging by an experienced physician. In case DSA is reported and an aneurysm is obvious, the patient's physician may decide for surgery (20,21).

8. If no aneurysm is detected in neither CCT angiography nor DSA, medical treatment is performed and during the follow-up period, the patient undergoes a CCT angiography at 3-month intervals, and another DSA after 20-30 days. It is reported in the literature that DSA may give negative results at a rate of approximately 15-16% (11,22).
9. If an aneurysm has been detected, the patient undergoes open or endovascular repairdepending on the location of the aneurysm, the experience of the physician and the preference of the patient. Recent publications report cases in which either intervention is superior or less successful (16).
10. The patient's relatives should be informed on the fact that mortality rate in such patients is high (at a rate of 10-20% or one fifth), they belongin a disease group that is at high risk for re-rupture, and hydrocephalus and neurological deficits may develop. The treatment is planned in order to address the main objective of 3H therapy (hypertension, hypervolemia and hemodilution) (23-25).

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CHAPTER 8

ANTIOXIDANT TREATMENT IN MALE INFERTILITY

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Introduction

Infertility is a worldwide health problem and is defined as the absence of a clinical pregnancy after 12 months of regular unprotected sexual intercourse (1). The incidence of infertility worldwide is reported to be approximately 8-12%. Infertility may be associated with female infertility, male infertility, female and male or a combination of unexplained factors. Male infertility accounts for almost half of all infertility cases and covers approximately 7% of the male population. More than 15% of married couples face various fertility problems resulting in infertility, and approximately 50% of these couples have male-induced factors (2). Male infertility has been reported to be caused by hormonal imbalances, genetic problems, anatomical problems, physical causes, environmental, psychological or behavioral factors. In addition, advanced male age can affect sperm quality and lead to male infertility. As a result, the causes of male infertility are multifaceted. Evaluation and management of male infertility during infertility treatment is extremely important for couples.

1. Effects of Oxidants on Testis and Spermatogenesis

Male factor is frequently encountered with semen pathologies. Diet, lifestyle, environmental factors, drugs, toxic substances occur as a result of their negative effects on semen (3). It is known that by shifting the oxidant-antioxidant balance to the oxidative stress direction, the reactive oxygen species (ROS) produced in the testicle cause disturbances in semen parameters with a negative effect on spermatogenesis, resulting in idiopathic infertility (4).

Oxidative stress, together with rising ROS levels, can cause damage to cells, tissues and organs (5). The spermatozoa membrane contains high amounts of unsaturated fatty acids that can be oxidized as a result of lipid peroxidation. In addition, its cytoplasm contains enzymes that can neutralize a very small amount of ROS. Therefore, spermatozoa are sensitive to the harmful effects of ROS. As a result of inducing lipids in the cell membrane with oxidative stress, increased permeability with loss of membrane integrity may lead to inactivation of cellular enzymes, structural DNA damage and cell apoptosis. This causes the formation of sperms with decreased number and activity and decreased motility and impaired morphology (6-8). Excessive ROS production causes sperm dysfunction through lipid peroxidation, loss of motility, and DNA damage. Thus, it can initiate many pathological processes in the male reproductive system.

2. Effect of Nutrients on Infertility

Various studies have shown that dietary nutritional contents affect sperm quality, morphology, motility and number (9). It is known that healthy nutrition has positive effects on fertility and positively affects sperm parameters. Unhealthy eating habits, smoking and alcohol use, excessive consumption of saturated fatty acids, trans fats and sodium, and less consumption of vegetables and fruits are more common in infertile men. In the semen of subfertile men, ROS levels were found to be higher and seminal antioxidant levels were lower.

3. Antioxidants Used in Male Infertility

3.1. Arginine

It is a semi-essential amino acid that can be taken with many animal and vegetable nutrients. Since it is the precursor of nitric oxide synthesis, it is involved in endothelial function and is seen in the pathophysiology of many vascular diseases. Improvement in sperm parameters is reported in men with daily use of 1-15 gr. (10,11).

3.2. Zinc

It is an essential micro-mineral with 2-4 mg in the body, mostly in the prostate gland. Repair of DNA damage is involved in testicular development and spermatogenesis. There is an improvement in semen parameters with 400 mg of zinc daily (12-13).

3.3. Selenium

Intracellular antioxidant is a trace element that reduces glutathione peroxidase (GPX-4) and increases antioxidant capacity. In some studies, it was observed that the level of antioxidants, especially selenium and zinc, was very low in semen samples taken from infertile men (14). An increase in sperm motility has been reported with the use of 100 mcg daily (15).

3.4. Coenzyme Q10 (ubiquinone)

In the inner mitochondrial membrane, it plays a role in oxidative phosphorylation by establishing a bond between flavoproteins and cytochrome. improvement in the respiratory chain of the mitochondria with the increase of CoQ10 in seminal fluid and spermatozoa for 6 months, an increase in antioxidant capacity and consequently an increase in sperm parameters, especially in advanced mobility, an increase in fertilization with the use of spontaneous pregnancy and treatment methods that help reproduction (16). An increase in sperm count and motility has been reported after the use of CoQ10 for 6 months at 300 mg/day. While serum inhibin B levels increased, there was also an increase in Sertoli cell function (16).

3.5. Carnitine and L-carnitine

It is naturally abundant in epididymal fluid and is 2000 times higher than plasma in epididymis. L-carnitine is involved in energy metabolism by transporting active long chain fatty acids (acyl CoA) into the cell. L-carnitine is transported into the sperm cell in the epididymis, takes part in the transition of fatty acids from the cytosol to the mitochondria, and initiates sperm motility in the form of L-acetyl-carnitine (LAC). In controlled studies, an increase in sperm motility and a decrease in ROS levels have been reported (17-18). Improvement in sperm motility and morphology is reported with the use of 1-2 grams daily.

3.6. Glutathione

It is released in my epididymis and acts as an antioxidant by preventing lipid peroxidation. With the use of 600 mcg daily, improvement in sperm motility and improvement in morphology have been reported (19).

3.7. Vitamin E

It is a fat-soluble antioxidant. Although the recommended dose in infertile men is 15 mg/day, an increase in sperm motility and an improvement in morphology have been shown (20).

3.8. Vitamin A

Ascorbic acid is taken with diet and cannot be synthesized in the body. It has strong antioxidant properties and acts on NADPH-glutathione pathways. The recommended daily dose is 75 mg/day (21). With daily doses of 200-1000 mg, a high concentration in seminal fluid is reached in 4 weeks. An increase in sperm motility, improvement in morphology, and an increase in post-treatment pregnancy rates have been reported.

3.8. Vitamin C

Collagen synthesis, hormone production and antioxidant effects are known. In ascorbate deficiency, degeneration is observed in the germinal epithelium of the testicle. Ascorbic acids increase the effectiveness of gonadotropin treatments. It is recommended to use 90 mg daily. A decrease in sperm DNA damage, an increase in sperm motility, and an increase in pregnancy rates have been reported with the combined use of vitamins C and E for 2 months (22).

3.9. Myo-inositol

It has been shown to increase sperm motility and improve sperm mitochondrial function in patients with oligo-astheno-teratozoospermia (23).

3.10. Alpha-lipoic acid

It acts as a coenzyme for pyruvate dehydrogenase and a-ketoglutarate dehydrogenase in mitochondria. It is reduced to dihydrolipoic acid (DHLA), which is stronger as an antioxidant in cells and tissues. It forms chelates with metals and prevents membrane lipid peroxidation and protein damage through interactions with glutathione (24). In their randomized controlled study, Haghighian et al. (25) found significant improvements in sperm motility and morphology in the treatment group given 600 mg/day ALA for 12 weeks.

3.11. Combined Antioxidant Use

Studies have shown that the side effects of prolonged overuse of a single antioxidant agent may increase, and the controlled use of combined antioxidant agents has been recommended. In the literature, it has been emphasized that antioxidant complex treatments have a curative effect on spermatogenesis by reducing ROS-induced sperm damage (26). An increase in pregnancy rates has been reported with vitamin and antioxidant supplements (27). Table 1 summarizes

the effect of various antioxidants on sperm parameters and pregnancy rates (27). Table 2 summarizes the effect of various antioxidants on pregnancy rates with assisted reproduction treatment methods. In a meta-analysis of seventeen randomized controlled trials (n=1665), the effect of various antioxidant treatments (vitamin C and E, zinc, folic acid, selenium, carnitine, N-acetyl cysteine, carotenoid) on sperm parameters and pregnancy rates was investigated (28). A statistically significant difference was found in pregnancy rates with the use of antioxidants. As a result of 48 randomized controlled trials using various antioxidant drugs on 4179 subfertile men published in 2014 using the Cochrane database (29), it was observed that antioxidant treatment consisting of L-carnitine, Co-Q10, Zn, vitamin E and vitamin C significantly increased pregnancy (AVG.: 3.43) and live birth rates (AVG.: 4.21) in subfertile men when used before ICSI.

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Table 1. The effect of various antioxidant treatments on sperm parameters and pregnancy rateS

Daily dose	Duration/ month	Healing semen parameters	Oxidative stress measurement	Pregnancy
Vitamin E 300 mg	6	Motility	Decrease in MDA	17% increase in pregnancy
Vitamin E 300 mg	3	–	–	Good bonding to the zone
Vitamin C 1000 mg	1	Motility-morphology	–	–
Vitamin E 1000 mg	2	–	–	–
Vit E 1gr + Vit C 1gr	2	–	DNA damage is reduced	–
Vitamin E 10 mg + Vitamin C 5 mg+ Zn 200 mg	3	–	Decrease in MDA	–
CoQ10 300 mg	6	Number and motility	–	–
Sn 100 mcg + Vitamin A 1gr + Vitamin C 10 mg + Vitamin E 15 mg	3	Motility	–	11%
Sn 200 mcg + NAC 600 mg	6	Number, motility, morphology	–	–
Glutathione 600 mg	2	Morphology and motility	–	–
L-carnitine 2 g	2	–	Decrease in MDA	–
NAC 600mg	3	Number	–	–
NAC 600mg	3	Motility	–	–
Vitamin E 400 mg+ Sn 225 mcg	3	Motility	Decrease in MDA	–
Vitamin C 30 mg + Vitamin E 5 mg + beta-glucogan 20 mg + papaya 50 mg + lactoferrin 97 mg	3	Motility morphology	–	–
Vitamins C and E, Sn, Lycopene, folate, Zn	3	–	–	22%

Table 2. The effect of various antioxidant treatments on pregnancy rates with assisted reproduction treatment methods

Authors	Method	Treatment	Results
Greco (2005) (50)	Initial ICSI negative TUNNEL >15%	Vit C 1gr 2months Vit E1gr	Reduction of DNA damage: 76% Pregnancy with ICSI: 48%
Greco (2005) (51)	TUNNEL > 15%	Vit C 1gr 2months Vit E1gr	DNA damage reduction : 22%--9%
Menezo (2007) (52)	Initial ICSI negative DFI >15%	Vit C 400 mg 2months Vit E 400 mg Zinc, Selenium, Beta-carotene	DNA damage reduction: 32%--26%
Dattilo (2014) (53)	Recurrent pregnancy loss and DFI high	Vit E 400 mg 3months Zinc, Vit B	70% spontaneous pregnancy

CHAPTER 9

INTRAVITREAL INJECTIONS IN EYE DISEASE

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1. Introduction

Intravitreal injection can be defined as the injection of an agent into the vitreous to treat a clinical condition (infection, vascular diseases, retinopathies, etc.).Air injection into the vitreous for retinal detachment repair was reported for the first time by Ohm in 1911 (1).Later, in the 1940s, the interest in antibiotic injections and intravitreal injections for the treatment of endophthalmitis increased with experiments (2).The United States Food and Drug Administration (FDA) officially approved fomivirsen intravitreal for use in 1998 (3).Since then, many Anti-Vascular Endothelial Factors (VEGF)molecules such as pegaptanib, ranibizumab, bevacizumab, aflibercept, and molecules such as etriamcinolone, dexamethason implant, ocriplasmin have been approved and introduced for use by ophthalmologists (4-6).

With the intravitreal injection method, physicians can achieve a greater therapeutic effect in the intended target tissue. However, the method also offers the opportunity for treatment with a lower risk of systemic side effects. Because of these advantages, intravitreal injections are attractive options for the treatment of many ocular disorders.

More than 4 million injections were performed in the United States of America (USA) in 2013 alone (7).The existence of many studies in the literature on intravitreal injections increases the use of this method among ophthalmologists. With these literature studies, new indications for medical

agents in use are determined. In addition, with the developing current techniques and nano technology methods, the pharmaceutical industry offers many new molecules to the use of ophthalmologists every day. Considering all these, it is thought that intravitreal injections will take a large place in the practice of ophthalmology today and in the future.

2. Molecules Used and Their Indications

2.1 Anti VEGF

Subretinal neovascularization and pathological ocular angiogenesis are one of the most important causes of irreversible progressive deterioration of central vision. Central vision loss is a clinical condition that can seriously affect the quality of life and comfort. Choroid neovascular membranes (CNVM) occurring in age-related macular degeneration (AMD) are among the leading causes of irreversible blindness in individuals aged 50 and over in high-income countries (8).Similarly, diabetic macular edema (DME), macular edema (ME) due to retinal vein occlusion (RVO), and CNVM secondary to degenerative myopia are among the important causes of low vision and blindness worldwide (9-11). Inhibition of VEGF, which plays an important role in the pathophysiological cascade of the mentioned clinical conditions, is an effective treatment method. In this sense, anti-VEGFs are FDA approved molecules in routine use in cases of DME, RVO-ME, CNVM in degenerative myopia and AMD-CNVM.Apart from these areas of use, they can also be used in clinical conditions such as Retinal Angiomatous Proliferation, Polypoidal Choroidal Vasculopathy (PCV), Premature Retinopathy, Central Serous Choroid Retinopathy, Cystoid Macular Edema, Hereditary Retinal Dystrophies and Neovascular Glaucoma.

Pegaptanip, the first intravitreal anti-VEGF molecule to be used, is not in use today. There are three anti-VEGF molecules currently available for use by ophthalmologists. These molecules are bevacizumab (Avastin®; Genentech Inc., San Francisco, CA, USA), ranibizumab (Lucentis®; Novartis, Basel, Switzerland) and aflibercept (Eylea®; Bayer, Leverkusen, Germany). Bevacizumab is a humanized recombinant monoclonal antibody that causes inhibition by binding all isoforms of VEGF-A. It was approved by the FDA in 2004 for colorectal CA. Its efficacy and safety have been shown in short-term studies and although it is an off-label use, it is included in intravitreal injection use. Similarly, Ranibizumab is a humanized recombinant monoclonal antibody fragment that causes inhibition by binding all isoforms of VEGF-A. It received FDA approval in 2006. Theoretically, it easily penetrates all layers of

the retina due to its small molecular weight. Aflibercept, on the other hand, is a human recombinant fusion protein that binds with higher affinity to all isoforms of VEGF-A, PIGF and VEGF-B than Ranibizumab and Bevacizumab, and has a long-lasting effect. It was obtained by binding of extracellular fragments of VEGFR1 and VEGFR2 to the Fc portion of human IgG1 antibody. It was approved by the FDA in November 2011. Besides these, brolicuzumab, a new generation anti-VEGF that binds all isoforms of VEGF-A and causes inhibition binds to VEGF-A with higher affinity than bevacizumab while it has similar affinity compared toranibuzumab and aflibercept (12).However, although there are studies (13,14) showing that the penetration of brolicuzumab into the tissue is faster and that more active metabolites are given per dose, the molecule is still very new and studies on it are very limited. It is not yet a VEGF antibody in routine use.

2.2. Steroids

Steroids are potent edema solvents that have been in use in medicine for many years and continue to be used for many indications. In this sense, although it is used in cases of ME, which is among the anti-VEGF indications, it is also used in the intravitreal injection method in cases of middle, posterior and pan uveitis addition to the anterior uveitis. Despite the increased variety of drugs used in the treatment of uveitis and their easy accessibility, recent studies have shown by Optic Coherence Tomography that 44% of uveitis patients develop ME (15).Intravitreal injections of steroids in this sense involve the administration of triamcinolonacetoid or dexamethasone into the vitreous by direct injection methods. In direct intravitreal use, increased intraocular pressure (IOP) and cataract should be kept in mind as undesirable side effects.

Slow-release intravitreal implants are also available to prolong the short duration and potential of steroids and to avoid the risks of repeated injections. Slow release dexamethasone implant (Ozurdex, Allergan Inc., Irvine, CA) is a potent cytokine inhibitor derived from human pericyte cells. Although it is a high potency molecule, it is thought to have less side effects such as IOP increase and cataracts (16).

2.3. Antibiotics

Endophthalmitis is an intraocular infection that affects the anterior chamber and vitreous. Although it is mostly exogenous (90%), this exogenous nature is usually associated with surgery lesser part (5-10%) is formed as a result

of the colonization of hematogenous microorganisms (17).Current treatment components of endophtalmia treatment are vitrectomy and intravitreal antibiotic injection (18).Intravitreal antibiotic treatment used in the treatment of endophthalmitis is applied immediately after vitrectomy and is repeated 48 hours later in case of clinical unresponsiveness. Frequently preferred antibiotics are vancomycin combined with ceftazidime or amikacin (19).Although the evidence is inconsistent with each other, steroids are usually added to this intravitreal antibiotic treatment (18).The role of steroids in this treatment is to increase antibiotic penetration by restoring the blood-retina barrier.

2.4. Ocriplasmin-Chemical Gas

With aging, the vitreous becomes liquefied, and the posterior vitreous cortex is separated from the inner limiting membrane with the weakening of the vitreoretinal ligaments. The conditions in which this separation does not occur completely and causes traction in the macula and low vision are called vitreomacular traction syndrome (20).While this separation occurs spontaneously in 11% to 40% of patients with VMT syndrome; intervention is required for the remaining majority. For many years, vitrectomy was the only option for this separation to occur. Later, pharmacological vitreolysis became another treatment option for VMT.The molecule used for pharmacological vitreolysis is ocriplasmin. Ocriplasmin is a 27 kDa recombinant selective serine protease subunit of human plasmin.Some side effects have been reported after ocriplasmin applications, and it is known to be a costly treatment method (21).Recent studies have shown a success rate of 41% for ocriplasmin in VMT syndrome (22).Low efficiency and high cost limited their use.

Today, intravitreal gas injection method is used as a more up-to-date treatment method for VMT.Gases used for this purpose include octafluoropropane (C3F8), sulfur hexafluoride (SF6), and hexafluoroethane (C2F6) (23-25). There are many recent publications and studies on the effects of intravitreal air injection on VMT (26).In this sense, the air seems to be an advantageous treatment method due to its easier resorption, low potential for side effects and low cost.

2.5. Tissue Plasminogen Activator (tPA)

It can be defined as gross hemorrhage between the sub-macularhemorrhage neurosensory retina and the retinal pigment epithelium. Among the causes are AMD, PCV, degenerative myopia, ocular histoplasmosis syndrome, macro-

aneurysms, and blunt traumas (27,28).As a treatment method in sub-macular hemorrhages, different methods such as vitrectomy, intravitreal injection of tPA, intravitreal gas injection and intravitreal injection of anti-VEGF can be applied separately or in combination.

tPA is a thrombolytic serine protease that activates plasminogen plasmin (29). This activation provides liquefaction of blood clots by breaking down the fibrin. Studies have shown that intravitreal injection of tPa alone removes the clot in as little as a week, and although it provides anatomical improvement in the retina, it is not very effective for retinal degeneration (30).Later, tPA was used as a component of the combined therapies mentioned above rather than being used alone.Chen et al. used intravitreal tPA and gas injection to remove the blood from the macula and provide its resorption with the method they defined in 1996 (31).In this method, sulfur hexafluoride (SF_6) or perfluoro propane ($C_3F8_)$ were used as gas.

2.6. Experimental molecules

Apart from these molecules mentioned above and actively used by ophthalmologists, many molecules that are still in the experimental stage are being investigated for many ophthalmic diseases. In this section, a few molecules that are in the experimental stage will be briefly discussed.

Irvine Gass syndrome is the cystoid ME that develops after cataract surgery and is thought to be involved in the pathogenesis of peri and post-operative inflammatory processes (32).Similarly, non-infectious uveitis is a clinical condition in which inflammatory cytokines are present in their pathophysiology (33).Adalimumab, on the other hand, is an anti-TNFαagent and studies on its use in the treatment of non-infectious uveitis and cystoid ME after cataract surgery are ongoing as it slows down the inflammatory processes (34,35).

The use of melphalan in the treatment of vitreous and subretinal insemination of retinoblastoma, a newborn and childhood ophthalmic tumor which occurs in advanced stages and affects the response and prognosis, is in the experimental stage and there are ongoing studies (36).Additionally, autologous bone marrow mesenchymal cells have been tested intravitreally in the treatment of retinitis pigmentosa, which is one of the important hereditary dystrophies causing permanent visual impairment (37).

3. Implementation

As mentioned above, many molecules are used for intravitreal injection in many indications. In this part of the book, the points to be considered before, during

and after the injections will be explained. These three main topics have been prepared by reviewing the current protocols and guidelines.

3.1. Pre-Injection Protocol

Considerations during patient evaluation before intravitreal injection include ocular hypertension/glaucoma, use of anticoagulants, previous ocular surgery, povidone-iodine allergy, blepharitis and extraocular infections, eyelid and adnexa anomalies. These points should be kept in mind while taking anamnesis from patients and performing biomicroscopic examinations.

3.1.1. Ocular Hypertension / Glaucoma

Although several retrospective studies showed an increased risk of ocular hypertension in patients receiving long-term, repeated anti-VEGF therapy (38), many studies showed that after repeated anti-VEGF injections, including patients with a pre-injection diagnosis of glaucoma (39), the injection was not a risk factor for the progression of pre-existing glaucoma or ocular hypertension (40,41).Moreover, in the analyses performed with the data obtained from random MARINA and ANCHOR studies, no relationship was found between the increases in IOP after injection and the number of injections (42).It should be noted that the primary goal in this patient group is the preservation of visual function. In accordance with the glaucoma and ocular hypertension treatment guidelines, these patient groups should be given intravitreal injection and the treatment of patients receiving intravitreal injection therapy should not be interrupted for this reason. If patients have optic nerve damage, they should be documented and monitored closely (43).In the case of acute IOP elevations, pre-injection prophylactic paracentesis is not recommended routinely. Although it is generally a safe procedure, the risk of endophthalmitis should be kept in mind, even if it is low (44).Keeping in mind that acute IOP elevation after injection is an important and irreversible threat to vision, paracentesis to soften the globe is left to the discretion of the physician (43).

3.1.2. Use of Anticoagulants

In a retrospective study of 1710 injections with CNVM due to AMD, it was shown that vitreous hemorrhage or subretinal hemorrhage occurred in 3 patients who received systemic anticoagulation and in 1 patient who did not use any anticoagulants, and the difference was not found to be statistically significant (45). In another retrospective study examining 220 patients with intravitreal

ranibizumab injection, diabetes and diabetes/hypertension association were considered risk factors for macular bleeding while anticoagulant use was not considered a risk factor (46). In the light of the information obtained from these studies, the use of anticoagulants does not constitute a contraindication for intravitreal injection.

3.1.3. Previous Ocular Surgery

The ocular conditions and the previous ocular surgeries of the patient scheduled for injection should be known, the requirements of these clinical situations should be followed, and intravitreal injection should be performed if there is an indication. At this point, the consideration should be to stay away from the incision area of □□ previous surgeries. Bleb and filtration surgeries should be kept in mind for previous glaucoma surgeries (43).No restrictions on immediate intravitreal injection have been reported after cataract surgery.

3.1.4. Povidone-Iodine Allergy

Although irritant effects are observed in patients in proportion to the duration of povidone-iodine exposure, true cases of povidone iodine allergy are very rare (47).Although no povidone-iodine-related anaphylaxis has been reported after intravitreal injections, some cases have been reported after open wound or mucosal applications (48).The history of systemic iodine allergy does not turn into povidone-iodine allergy. The use of povidone-iodine is an important component of the intravitreal injection preparation and its conjunctival bactericidal effect has been proven (49).Saline solutions can be used to prevent contact irritation and ocular surface problems.

3.1.5. Blepharitis and Extraocular Infections

Endophthalmitis is one of the most serious and feared complications of intravitreal injection. In a prospective observational study comparing 47 patients who developed endophthalmitis after anti-VEGF injection with 200 control cases, it was shown that blepharitis, which was present in 6.5% of cases, was a significant risk factor for endophthalmitis (50). In light of this information, unless the benefits of injection are considered to be clearly superior to the risk of endophthalmitis, injection should be delayed until the ongoing infection is treated (43).In cases involving the eyelid, adnexa, and ocular surface, the risk of endophthalmitis in a similar scope should be evaluated as potential and acted accordingly.

3.1.6. Antibiotic Prophylaxis

The use of eye drops containing antibiotics before injection is another controversial topic. Isenberg et al., in a study they conducted on this subject, thought that the combined use of povidone iodine and antibiotic before surgery had a synergistic effect and showed that 83% of the conjunctivae of the patients treated with this combination were sterile, while this rate was 40% for povidone iodine only and 31% for only antibiotics (51).However, there is no study showing that the use of prophylactic antibiotics prevents endophthalmitis. There was no use of prophylactic antibiotics in the studies included in most of the meta-analyses on this subject. The incidence of endophthalmitis was also very low in studies that did not use prophylactic antibiotics. As current guideline information, the use of prophylactic antibiotics before injection is not recommended (52).

4. Injection Protocol

In this section, topics such as the area of intravitreal injection, the use of gloves/ drapes, the use of masks, povidone-iodine application, pupil dilatation, and anesthesia will be addressed, and the points to be considered will be explained.

4.1. Clinical Setting

The frequency of endophthalmitis after intravitreal injection in the office and operating room was found to be extremely low. In a retrospective study performed after intravitreal anti-VEGF in the office procedure room and operating room, the endophthalmitis rates were 4/3.376 for the office environment while this rate was 0/8.873 for the operating room and the difference was not clinically significant (53).In this sense, it can be said that there was no difference between intravitreal injection in the office or operating room (43).

4.2. Bilateral Injection

Endophthalmitis cases after intravitreal injections are generally known to occur in series and through the contamination of the shared drug prepared. Considering the risk in this context, for patients who will receive bilateral injection in the same session, the injection for each eye should be evaluated as a separate procedure. The area for each eye should be cleaned separately, and drapes, gloves and consumables should be used separately (43).If possible, different drug groups should be considered for both eyes,or a different shared drug should be injected.

4.3. Gloves/Drapes

In a retrospective study of 15,895 intravitreal injections performed without gloves, the rate of endophthalmitis was reported to be 0.057% (54).Similarly, the rate of endophthalmitis was found to be 0.029% for an injection series of 10,254 cases without drape (55).These rates are similar to the rates of endophthalmitis occurring after intravitreal injections. Current guidelines state that sterile or non-sterile gloves can be used during injection, but there is not enough evidence for the use of drape (43).765 experts participated in a survey conducted among retina specialists and 58% stated that they used gloves, 58% of those who used gloves stated that they used sterile gloves, while only 12% stated that they used drapes (56).

4.4. Using Masks / Talking

Organisms frequently detected in the meta-analysis of endophthalmitis studies after intravitreal injections are streptococci, and this source of transmission is thought to be through oropharyngeal droplets (43).However, there are no controlled studies on the risk of infection with mask use and limited talking. In a study simulating intravitreal injection with agar plates placed in the perioral region, it was showed that the use of masks and limited talking significantly reduced bacterial growth (57).As a result, a mask should be used during injection and talking should be limited in the operation room.

4.5. Povidone Iodine Application

Although there is no study comparing the risk of endophthalmitis in cases with and without the use of povidone-iodine for intravitreal injections, studies conducted on this topic in relation to cataract surgeries show that there is a serious decrease in the risk of infection (58).Studies have shown that a 15-second time frame for 5% povidone iodine application time is insufficient while 30-second time frame is sufficient (49).Povidone-iodine should be applied not only to the conjunctiva, but also to the lid, lid edges and eyelashes. Prior to intravitreal injections, povidone-iodine must be applied to the lids and eyelashes due to its effectiveness, cost, and accessibility.

4.6. Pupil Dilatation

While some physicians are of the opinion that documenting visual acuity before injection is sufficient, some physicians think that it should be dilated as fundus

examination will be required due to the possibility of post-injection complications. Dilatation may be considered in terms of the appearance of the needle tip during injection, post-injection optic nerve perfusion, evaluation of retinal detachment as dilatation does not pose a significant risk for most patients. At this point, the choice of pupil dilatation is left up to the physician's discretion (43).

4.7. Anesthesia

As in all surgical applications, anesthesia should be applied before intravitreal injections. In this sense, pre-injection topical drops, drops applied to the applicator, subconjunctival injection and lidocaine gel can be considered. In studies conducted with the application of these different anesthesia methods, no significant difference was found between the pain scores of the patients (59). Boden et al. found in their study that the application of lidocaine gel created a barrier for povidone-iodine and reduced the sterility of the procedure (60).For this reason, if the choice of anesthesia is lidocaine gel, povidone-iodine should be used before and after the gel application.

4.8. Speculum Use

It is obvious that the eyelid and eyelashes should be away from the intervention area during the injection. In a retrospective analysis which is more than 37,000 intravitreal injections; no difference was found between manual eyelid retraction and the use of a sterile speculum in terms of endophthalmitis risk (61).While the use of a speculum allows the physician to use both hands and can provide a more controlled and consistent injection, the manual valve retraction may be more comfortable for the patient.

4.9. Area of Injection

There is a great deal of cumulative experience with intravitreal injection applications. The consensus is that the injection should be applied 3.5-4 mm behind the limbus, between the horizontal and vertical rectus muscles in the pars plana and perpendicular to the sclera. The quadrant of injection area should be decided by the physician by considering the position, previous surgery, and ocular special conditions. Although tunnel incision is defined as the injection technique, it is not preferred because of the difficulties of application, reflection, crystalline lens, or retinal damage.

4.10. Needle Length / Thickness

For FDA approved drugs (excluding Ozurdex and triamcinolonacetoid) the recommended needle thickness is 30-gauge and thinner needles. The needle length should be 18 mm or less. Although thinner needles are thought to have less vitreous reflux and lower pain scores, there is no proven study. However, fine needles have been shown to have a lower risk of IOP (62).

5. Post-Injection Protocol

In this section, areas to be focused on after intravitreal injections by taking into account the above-mentioned issues are addressed in this section.

5.1. Central Retinal Artery Perfusion

Immediate complications of the post-injection procedure should be excluded. Sudden pressure increase due to the volume of the molecule injected into the vitreous may cause a temporary cessation of perfusion of the central retinal artery. This may result in blurred vision and lack of light perception in the patient. Studies in primates on this topic have shown that the central retinal artery occlusion can be tolerated up to 97 minutes without causing any detectable damage to retinal tissues (63). Thus, it should be confirmed that reperfusion has been achieved before discharge, even if there is no alarming situation. In such cases, it should be confirmed that reperfusion is achieved by measuring IOP, evaluating the patient's vision or directly evaluating the artery by indirect ophthalmoscope, and discharge should be planned accordingly.

5.2. Intraocular Pressure

Bakri et al. showed that the IOP elevation is a common condition after 212 intravitreal injections in 161 patients, but approximately in 90% of the patients the values return to normal without any intervention (64).As can be expected, after corticosteroid injection, the expectation of increase in IOP is higher. Therefore, it should be remembered that IOP monitoring is an important step in patient management after injection.

5.3. Post-Injection Antibiotic Use

Prescribing antibiotics after intravitreal injections is more common than the use of prophylactic antibiotics. Jager et al. reported the use of antibiotics in 10 of 17 studies in their above-mentioned review, but unfortunately this practice

lacks supporting data. There is a common belief among ophthalmologists that it prevents the use of antibiotics after post injection. At this point, a planning should be made considering the spectrum of antibiotics and cross reactions. If antibiotics will be used after injection, it is recommended that the usage period should not exceed 72 hours. Another point for which evidence is lacking is the use of post-injection steroids, but it is not generally used or recommended.

5.4. Discharge

If the presence of vision is confirmed after injection and there are no specific symptoms related to injection, discharge can be planned. The patient should be informed about the symptoms that may arise in cases such as endophthalmitis, retinal detachment, and vitreous hemorrhage. These symptoms can be described as pain, discomfort, sensitivity to light, redness, and blurred vision, loss of some or all of the central or peripheral vision. There is no need to take any special precautions during discharge, but the patient should be reminded to avoid rubbing the eye.

5.5. Control/Follow-Up

The follow-up and control intervals of the patient after injection should be specific to the patient. This decision belongs to the physician with many variables such as the disease causing the injection indication, the severity of this disease, and the presence of additional disease in the patient.

6. Complications

6.1. Local Complications

Although it seems like a simple and non-traumatizing procedure, intravitreal injections are invasive procedures, and some unwanted complications may be seen after the procedure. The most devastating and feared of these complications is endophthalmitis. Although the incidence of endophthalmitis after intravitreal injections varies between different studies, it ranges between 0.19% and 1.6% (66).In recent studies; the incidence of endophthalmitis appears to be lower (67). Another complication, although less common, is rhegmatogenous retinal detachment. While some studies did not show a difference between the control groups and intravitreal injection groups in terms of detachment, there are studies showing retinal detachment, even if it was low. In this sense, the incidence of rhegmatogenous retinal detachment after intravitreal injection is between 0

and 0.67% (68).Subconjunctival hemorrhage is seen in approximately 10% of patients after injection which is often associated with anticoagulant use and does not require treatment. Although less common, choroidal and subretinal hemorrhages can also be seen after intravitreal injections. Information on IOP elevation has been mentioned above.

However, although they are very rare, a wide range of ocular complications can be seen. A few of these include posterior capsule rupture, contact with the crystalline lens, retinal artery / venous occlusion, anterior ischemic optic neuropathy, and 6th nerve paralysis.

6.2. Systemic Complications

Intravitreal injections are preferred because they allow for a higher number of active molecules to a specific location, as mentioned at the beginning. As general information, it is known that the rate of transition to systemic circulation is very low. Despite these low passage rates, intravitreal injections may have some systemic side effects. These systemic side effects can be listed as myocardial infarction, cerebrovascular events, and major bleeding. In this sense, data on systemic side effects should be evaluated more carefully since they may occur after a long period of up to 6 months after injection and are not associated with intravitreal injections. Most of the data and studies (in relation to the frequency of use) related to the topics covered under the sections of complications and systemic side effects are related to anti-VEGFs. In this sense, it should be kept in mind that each molecule injected into the vitreous may have other specific effects.

7. Conclusion

For the treatment of many ocular pathologies, intravitreal injections are one of the most powerful weapons that ophthalmologists have in current ophthalmologic treatments with their ease of application, the possibility of delivering higher doses of active ingredients, and lower expectation of side effects with less passage to the systemic circulation. In correlation with the advancement of the pharmaceutical industry and technologies, it is used in much wider indications and new active ingredients are offered to use every day. Intravitreal injections should be performed within the required indications and unnecessary injections should be avoided. Although it may seem like a simple application, it should not be forgotten that a sterile area such as the intraocular, is intervened, and it should be kept in mind that there are tissues including choroid and retina

that need to be treated very carefully. In line with this, the procedure should be planned carefully by following all protocols before, during and after injection. Despite full compliance with protocols, it should be known that both ocular and systemic side effects are always possible, and one should be prepared for complications that may occur and to manage these complications.

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CHAPTER 10

NEUROLOGICAL COMPLICATIONS OF COVID-19

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Introduction

Coronavirus disease-19 (COVID-19) which started in early December 2019 in Wuhan province of China, and caused infections from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have spread rapidly, causing a global pandemic around the world, and the World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020 that has resulted in millions of deaths (1, 2). By 14 October 2021, a total of 251,788,329 cases of COVID-19 and 5,077,907 deaths had been reported worldwide (3). COVID-19 is a virus which belong to coronaviruses family that are enveloped, positive-stranded RNA viruses that mainly cause respiratory and gastrointestinal tract infections (4). Of coronaviruses (divided into four genera: alpha, beta, delta, and gamma) betacoronaviruses causes human infections. SARS-CoV-2 is a coronavirus and is classified into the betacoronavirus 2b lineage.

The disease caused by SARS-CoV-2 is termed as COVID-19 consists of a variety of symptoms including fever, cough, and fatigue (5, 6). About 1 to 6 person who had COVID-19 disease may complications varying from mild to life threatining complications caused by condition known as cytokine release syndrome or a cytokine storm. This is when an infection triggers your immune system to flood your bloodstream with inflammatory proteins called cytokines.

These complications may affect different organ systems including; respiratory (acute respiratory failure, pneumonia, ARDS), gastrointestinal (acute liver injury), cardiovascular (acute cardiac injury), urinary system (acute kidney injury), secondary infections, septic shock, disseminated intravascular coagulation and neurological (smell and taste disturbances, headache, cerebrovascular diseases, iscemic/ hemoragic stroke, cerebral venous trombosis, syncope, ataxia and seizures) system (7-9).

In this chapter, we aimed to define the mecanism and the characteristics of neurological complications of COVID-19 syndrome.

1. Potential mechanism of COVID-19 mediated neurological complications

The clinical manifestations caused by COVID-19 depends on on the infection of the host cells; bronchial epithel and type II pneumocytes by the way of binding to cell surface receptors; angiotensin-converting enzyme 2 (ACE2), basigin (BSG; CD147), and neuropilin-1 (NRP-1) (10, 11). Hematogenous spread of COVID-19 viruses causes ACE2 as its entry receptor and TMPRSS2 cell protease for S protein priming (12). Infecting immune cells that express ACE2, such as monocytes, granulocytes, and lymphocytes may carry SARS-CoV-2 to the central nervous system, where it can infect the brain (13).

2. Types of neurological complicatıons of COVID-19

2.1. Smell and taste disturbances

Following the COVID-19 pandemic, patients with an incidence of 4.9–85.6% complained of olfactory dysfunction including; anosmia, hyposmia, phantosmia, and parosmia and decreased/loss of taste sensation. The onset of anosmia was abrupt in most of the patients with decreased/loss of taste sensation (14). It has been reported that there is a high rate of spontaneous recovery within 2 weeks of onset of symptoms and anosmia has been reported as the initial and early symptom of COVID-19 (15).

2.2. Headache

Headache is a common neurological complication of COVID-19 with a reported incidence of varying from 6.5 to 23%, and the mean of 8% in different studies and is one of the initial symptoms and early manifestation of the disease (16, 17). Also there are similar characteristics of COVID-19 headache and migraine attacks; it differs from migraine in as follows; higher intensity, rapid course, and resistance to usual analgesic medication during the disease course (18).

2.3. Cerebrovascular diseases

The exact mechanism of increased severity of COVID-19 in patients with cerebrovascular disease is still not exactly explained. Previous studies reported

that reported that 36% of patients demonstrated neurologic manifestations, and acute cerebrovascular disease was reported in 6% of severely affected patients (8). Risk factors has been reported as; hypertension, atrial fibrillation, chronic kidney diseases, and diabetes. Especially diabetes is one of the most important factor to increase the severity of cerebrovascular diseases and morbidity nad mortality in COVID-19 patients (19). Cerebrovascular manifestations of COVID-19 may be acute and more severe than chronic cerebrovascular disease symptoms. These manifestations include; small and large ischemic strokes, h**emorrhagic strokes/intracerebral hemorrhage (ICH), cerebral venous thrombosis** and encephalitis/**encephalomyelitis** (19-21). Covıd-19 also reported to increase risk of venous and arterial thromboembolism by the way of proinflammatory cytokines which induce endothelial and mononuclear cell activation with expression of tissue factor leading to coagulation activation and thrombin generation and elevated D-dimer levels (22, 23).

2.4. Seizures

Recent studies reportes that SARS-CoV-2 has already been detected in cerebrospinal fluid of COVID-19 patients and resulted in viral encephalitis (24). As we have mentioned in the previous paragraphs COVID-19 infects the cell by using surface receptors of angiotensin-converting enzyme 2 (ACE2), basigin (BSG; CD147), and neuropilin-1 (NRP-1) (6, 25). Following this infection, virüs leads to inflammatory cascade and cytokine storm and release pro-inflammatory cytokines (TNF-α, IL-6, IL-1B), nitric oxide, prostaglandin E2, and free radicals, and causes chronic inflammation neural hyper-excitability, seizure, and death (6, 24).

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CHAPTER 11

COVID-19 AND CONCOMITANT BACTERIAL SUPER INFECTIONS

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1. Introduction

Until today, these first cases were classified as "pneumonia of unknown etiology" (n = 29), whose etiology was unexplained, detected in Wuhan, the largest metropolitan region of China's Hubei province, and the agent could not be determined(1). At the beginning of the pandemic, the new virus was named 2019-nCoV and afterwards, the international virus taxonomy committee (ICTV), due to the similarities to the virus that caused the SARS epidemic (SARS-CoVs) He named it the SARS-CoV-2 virus(1).The coronavirus disease (COVID-19), which occurred in 2019, has become the most serious problem affecting public health globally in terms of its rapid spread and mortality worldwide(2).On the other hand, bacterial infections are relationship with worse results in patients with viral pneumonia, and data on the role of COVID-19 patients in mortality are only emerging(3).

2. Concomitant Bacterial Super Infections

Bacterial pathogens are often identified in viral respiratory tract infections accompanied by bacteria, and they are also serious risk factors in terms of morbidity and mortality. The frequency of bacterial infections in SARS-CoV-2 infective patients has not been clearly elucidated (4). But on the other hand ; Associations of bacterial co-pathogens, especially in viral respiratory tract infections. The awareness that it is among the important morbidity and mortality causes has been noticed for the first time in social terms with Covid-19. This has increased the tendency and acceptance of bacterial pneumonia and preventive vaccines such as influenza vaccine, although it is viral. SARS-CoV-2 can infect

people of all age groups. However, especially in cases over 60 years old; When associated with comorbidities such as diabetes mellitus, chronic respiratory diseases and cardiovascular diseases, the risk of infection is higher [5]. On the other hand, while the underlying mechanism of SARS-CoV-2 remains unclear, it has been demonstrated that the virus takes advantage of the ACE-2 receptors on the surfaces of cells known as hosts to enter the cell [6]. Cytokine storm caused by high-level plasma proinflammatory cytokines, reduction in lymphocyte count and atypical respiratory findings are the main characteristics of covid-19 patients with high-grade fever and respiratory problems. Affecting the severity of COVID-19 and the occurrence of complex symptoms in various metabolic or infectious diseases make a professional health team essential when applying treatment protocols(7). In Bradley J. Langford et al. shared in the first live broadcast detailed meta-analysis and systematic review on bacterial infections associated with Covid-19 patients, followed in the clinic with screening 1884 studies identified via database search in the literature, and a total of 24 studies that appear to be retrospective were including in this analysis. Co-infection was reported in 3.5% (95% CI: 0.4-6.7%) of patients with COVID-19, and secondary infection was reported in 14.3% (95% CI: 9.6-18.9%). In general, although the reported bacterial infection was found at 6.9% (95% CI 4.3-9.5), these results indicated that the patient subgroups differ slightly. This ratio increased to 8.1% in critically ill patients hospitalized. Also, despite a low bacterial infection rate, over 70% patients have used antibiotics, most of which consist of broad-spectrum agents such as fluoroquinolones and third generation cephalosporinsU(4). Of course, it should not be overlooked that other bacterial infections accompanying Covid 19 are actually in patients with Covid 19 and with co morbidity. In the review analysis made in 2020; In the United States, they stand out with rates of diabetes (58%) and obesity (55%). On the other hand, in Italy, there are hypertension (73.8%), CVD (42.5%), diabetes (35.5%), renal diseases (20.2%). The remarkable feature here is that although co-morbid diseases are found in patients who died due to Covid-19 in China, their percentages are less pertengage. If we look at this situation in more detail; Among the Covid -19 cases with a mortal course in China, the group with the highest co morbidity was obesity with 13% and high blood pressure with 9.5%(8-15). The point to be considered here is how China manages the Covid-19 pandemic process and why the mortality percentages in patients with similar co-mobidity are lower than in other countries, or how this is achieved.

A medical cornerstone that we see as the most important when we examine the literature and studies above; Since antibiotics probably provide minimal

benefit as empirical therapy in COVID-19 and adverse events may occur; Because toxicity is associated with resistance and adverse outcomes such as Clostridioides difficile infections, it is prudent for clinicians to prescribe them rationally.

In the past years, epidemics and pandemic outbreaks in the care of viral respiratory infections and bacterial infections added to these first viral diseases have been reported. On the other hand; During the A (H1N1) influenza pandemic in 2009, bacterial infection was found in 12% of critically ill patients (16,18) and in clinically inpatients not requiring intensive care support (19). The most common bacterial agents among these bacteria were Staphylococcus aureus (s.Aureus) and Streptococcus pneumoniae (S. Pneumoniae)(16,17,19). Surprisingly, it has been observed that these pathogens mentioned above are rarely reported among COVID-19 patients. In addition; There are still insufficient data on bacterial co-infections on cases infected with SARS-CoV-1 and MERS-Co-V(20-22). If we take into account that the current literature on the pathophysiology of SARS CoV-2 is improving the level of knowledge day by day; In terms of bacterial co-infection, it is clear that there are parts we cannot find in pathogenesis. For example, when influenza bacteria and mucociliary dysfunction coexist, it is thought that viral damage to epithelial cells in the lower respiratory tract facilitates attachment to cell surfaces for pathogenic bacteria aspirated from the nasopharynx(23). Ultimately, further damage by preventing repair and renewal in the epithelial cell layer paves the way for bacterial infection(23).

It will be determined whether this mechanism is functional for SARS-CoV-2(23). Unfortunately, our data on the pathophysiology of SARS CoV-2 are still developing and our knowledge about the pathogenesis of bacterial factors added to the virus has not been clarified yet, since it is not complete. Viral damage of epithelial cells in the lower airway, facilitating attachment to cell surfaces by mucociliary dysfunction, pathogenic bacteria aspirated from the nasopharynx have been hypothesized for influenza (23) .

3. Conclusion

As a result, bacterial infection occurs and over time it will become clear whether this mechanism applies to SARS-CoV-2, as is the damage caused by the recovery of the epithelial cell and preventing its regenerative response.

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CHAPTER 12

EVALUATION OF THE CORONA VIRUS PANDEMIC DURATION IN TERMS OF PREVENTIVE MENTAL HEALTH

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1. INTRODUCTION

The COVID-19, which affected the whole world, caused the illness and death of millions of people due to the pandemic it created. The COVID-19 outbreak, which was first identified in Wuhan city of Hubei province of China on December 31, 2019, and then defined on January 13, 2020, was announced as a pandemic by the World Health Organization (1) with its rapid spread throughout the world (2). The COVID-19 is in the family of coronoviruses and is among the causative agents of cold-flu (3) and has affected approximately 185 countries with a mortality rate of 6.8% (4).

Preventive mental health practices are of great importance in the prevention of mental problems, which are among the problems arising from the COVID-19 pandemic. Because mental health disorders create heavy psychological, sociological and economic burdens and increase the risk in terms of physical disorders (1).

Preventive mental health is based on the methods of identifying risk factors that threaten mental health and preventing them. Accordingly, preventive mental health includes measures to prevent mental health disorders before they occur, early diagnosis and treatments, follow-up and support of patients, and creating and developing social mental health awareness. Preventive mental health services can be classified as primary prevention, secondary prevention and tertiary prevention (5).

Primary Prevention includes studies aimed at preventing individuals at risk for diseases and is divided into three categories:

- Universal prevention; studies to protect the whole of society,
- Selective prevention; studies aimed at protecting individuals or groups at higher risk than other people in society,
- Indicated prevention; studies to protect high-risk individuals

Secondary Prevention includes studies to prevent diseases from becoming chronic by early diagnosis in cases where disease symptoms have just started, or risky behaviors are observed

Thirdly Prevention includes studies on the reduction and rehabilitation of disability caused by diseases.

Considering the classification explained above, the evaluation of the COVID-19 pandemic according to primary prevention in terms of mental health and preventive mental health measures that can be taken are given below.

2. PRIMARY PROTECTION IN PREVENTIVE MENTAL HEALTH IN THE COVID-19 PANDEMIC

2.1. Universal Prevention

The problems identified in this framework and the suggested solutions can be listed as follows:

- The speed of spread in pandemics, the ease of human-to-human transmission and the fact that it is deadly bring anxiety (6) and anxiety is higher in the early stages of the epidemic (7). In the COVID-19 pandemic, anxiety and panic were identified as the most basic indicators in the society (8). Psychological resilience of individuals is important in coping with anxiety. Psychological resilience is the ability of an individual to survive by adapting to events without losing control and maintaining vital balance (9). Psychological resilience occurs through the interaction of risk factors and protective factors (10) and individuals with a high level of psychological resilience can protect themselves from anxiety (11). In the COVID-19 pandemic, the anxiety levels of individuals with high psychological resilience were found to be low. This can be attributed to the contribution of psychological resilience to adaptation in difficult conditions and the functioning of mental health protective mechanisms (2). Therefore, psycho-educational group studies based on psychological resilience, information-based bulletins and activities, and awareness group studies will be beneficial. Moreover, psychological support groups, trainings, accurate and applicable information, and studies in which functional decision-making mechanisms are activated to alleviate health concerns should be performed (12).

- Epidemics directly affect people's physiology as well as their mood and create uncertainty with their unknown aspects (13, 14). Uncertainty is

the inability to clarify or categorize a vital situation (15). This leads to intolerance in individuals. In intolerance against uncertainty, the individual behaves negatively against it and four situations occur (16);

- It gives stress and distress,
- It prevents taking action,
- It is inevitable,
- It is unfair because it is unclear

The process in which extraordinary events occurred suddenly in the COVID-19 pandemic has led to uncertainty (17). However, it is inevitable that feelings such as anxiety, fear and helplessness will become epidemic (18, 19) Moreover, information pollution through social media, problems that arise with attention, deterioration of decision-making mechanisms and forgetfulness bring about mental stress and cause anxiety (20). This situation was also seen in the COVID-19 pandemic and affected sleep quality along with anxiety, fear, helplessness and hopelessness (21). In addition, intolerance to uncertainty has been triggered by the addition of uncertainty about the illness and isolation of relatives (parents, grandparents, neighbors) to individual concerns (22). In this respect, it is important that official channels get involved and inform transparently during epidemics (23). Today, the prevalence and frequency of media communication has also shown its effectiveness in the COVID-19 outbreak. The media, which strengthened and enlarged the uncertainty by expanding its sphere of influence from the first days of the outbreak, forced life with its harms as well as benefits. Because social media easily turns into a disinformation environment with the information bombardments that occur in every field (24). In the COVID-19 pandemic, misinformation and fear created by social media have become a major obstacle in the fight against the epidemic, and chaos and panic have occurred in societies thorough post-truth perception managements (25). For this reason, the need for governments to provide accurate information in a transparent and timely manner has also been recommended by the World Health Organization (26). On the other hand, it is considered important in the fight against epidemics to provide the right information on time and to take measures for post-truth applications at the universal level. Moreover, media communication tools can play an active role in the fight against the epidemic. In the first days of the epidemic, the media can be used in prevention, intervention and treatment services in addition to other practices (27), and support can be provided in all kinds of psychological help (first aid, therapy, guidance, treatment) via telephone and online applications (28).

- The incidence of post-traumatic stress disorder will increase. It has been determined that traumas increase with anxiety and stress in epidemics (29, 30) The reason for this can be that the reason for the emergence of the COVID-19 pandemic is not known, the virus cannot be seen, everyone is at risk socially and this situation happens globally (31). For example, the incidence of post-traumatic stress disorder increased in the previous SARS virus epidemic (32), and the incidence of depressive disorders was found to be the most common psychological problem in the long-term (33). Psychological trauma reactions in individuals begin with denial, shock and bewilderment (31). Then, together with the sudden onset, vital threats and extraordinary processes continue with losses (34). The rapid and large number of deaths in the COVID-19 outbreak from the very beginning, and the witnessing of the burning and abandonment of corpses on the streets outside the traditions in some countries by millions of people through social media laid the groundwork for trauma. Because sudden development, inability to control this situation, and experiencing or the possibility of suffering are the basic criteria in psychological trauma (35). Accordingly, gaining skills to cope with trauma within the framework of preventive mental health gains importance in terms of protecting individuals' mental health. Suggestions were made to continue with the normal routine of living, to pray and to share the problems experienced with other people in coping with trauma, and it was stated that not going out the house, being isolated from normal life and using drugs were not appropriate (36). It is not possible to adapt these suggestions to the normal life pattern in the COVID-19 outbreak. Because the measures related to isolation were seen as the most important factors in not catching and spreading the disease, and generally, preventions were made for this. Furthermore, the situations of not leaving the house and not being isolated from normal life, which are shown as inappropriate situations, are also among the things that cannot be done in the outbreak. Thereafter, working at home (home office), helping others, performing sports activities and religious rituals at home as much as possible can be offered in terms of preventive mental health. Conversely, the positive side of the COVID-19 pandemic is that individuals can develop after trauma. Development after trauma includes being able to approach the negativities experienced more wisely, learn lessons, spend quality time with loved ones, accept against uncontrollable life uncertainties, be open to

new experiences and withstand difficulties (37). Accordingly, suggestions for awareness trainings, information studies and psycho-educational groups can be presented.

- Beliefs, eating habits, lifestyles, communication styles and relationships are important factors in the pandemic duration. The chaotic environment specified has caused secondary social complexities after a while (38, 39). Because problems in basic vital needs such as security, shelter and nutrition, dissemination of incomplete and incorrect information, increase in quarantine periods, inadequacies of social support systems, financial problems, anxiety about catching or contaminating the disease and tiredness of the measures taken in this period are psychologically important risk factors (40). From another point of view, compulsory isolation has reduced social relations and negatively affected psychological well-being along with the feeling of loneliness (41). This situation has caused socialization problems and increased depression, especially in elderly individuals living alone within the scope of social isolation, and inadequacies in social communication related to family ties have emerged as another risk factor (22). Moreover, social isolation has increased domestic violence and alcohol use along with many psychological and social problems (42, 43). Differently, restrictions on personal freedom and moving away from their comfort zones during the pandemic of individuals who prefer a solitary life, which is increasing rapidly today (44, 45), are also problems. Because some of the individuals living alone due to social-economic reasons had to live with their families (46). Effective and widespread use of social support systems is essential in combating the problems encountered in social isolation (47). In addition, it is a fact that home life is an important living space where quality time can be spent as an area of freedom and security (38). In this context, family communication, family games, suggestions for occupational therapy practices, acquiring new hobbies, online trainings aimed at gaining vital skills such as the appropriate use of media, psychoeducation group studies, newsletters and support group activities can be created. Furthermore, having a pet will be a good option for loneliness and leisure time during the mandatory quarantine period (15).
- Due to the COVID-19 outbreak, anxiety levels in societies have increased (48, 49) and xenophobia has increased in almost all societies, especially against Asians (50, 51). On the other hand, the rapidly increasing anti-

immigrant discourses led to an increase in the xenophobic trend (52), and the President of the United Nations, Guterres, declared after a while that the COVID-19 pandemic created a tsunami of hatred and xenophobia (53). Accordingly, it is essential for non-governmental organizations and religious actors to work on the basis of respect within the framework of preventive mental health (54). Moreover, people with social prestige, such as artists, thinkers and politicians, should take all kinds of actions against racism through social media. Furthermore, studies within the framework of tolerance and respect for all stakeholders (students, parents, teachers and school administrators) within the scope of values education in schools will be effective.

- The incidence of many psychological problems has increased during the pandemic duration. In this context, quarantine practices within the framework of the measures taken against the pandemic increased stress levels and caused emotional problems (54). On the other hand, quarantine practices as well as restrictions on work life increased the levels of depression and anxiety (55, 56) and increased the risk of permanent psychological problems along with the triggering factors of psychological crises (57). Similarly, in addition to increasing psychological traumas, increased anxiety and stress levels in pandemics (29, 30, 58), psychosis, mania, depression, fatigue, physical and mental withdrawal, Guillain-Barre syndrome, persistent chronic fatigue and depression attacks, and behavioral disorders were detected. Mood disorder (1/3), and rarely psychosis and dementia were detected in individuals who were not patient (38). Moreover, the uncertainty and continuity of the pandemic threat has led to the chronicity and worsening of the fear experienced (59). Therefore, it is crucial to conduct awareness trainings through social media and other training areas (face-to-face, newsletters, written communication tools, etc.) within the framework of preventive mental health, and to increase the early diagnosis processes in line with a plan. Furthermore, it is necessary to carry out mental health preventive studies in accordance with the socio-cultural structures of societies related to quarantine practices, restrictions on work life, uncertainty and intolerance, which are determined as triggering factors for psychological problems in the pandemic.

- Domestic violence and divorces, which have increased globally, intolerance, hatred and selfishness have also emerged in the duration of the pandemic (38).

This situation can be attributed to the increase in domestic violence along with many problems caused by social isolation (42, 43). Moreover, positive effects of family life with a regular income in the urban environment were found during the COVID-19 pandemic (60). In addition, one of the external factors increasing the psychological resilience of the individual, which is an important factor in terms of preventive mental health in the pandemic, is the family institution (61, 62). The family has an effective intermediary role in increasing the psychological resilience of the individual in stressful situations together with other social factors (63). Accordingly, preventive policies should be established in terms of preventive mental health in pandemics, assuming that domestic violence will increase with socio-economic reasons and social isolation. In these studies, studies in line with the positive effects of the family on mental health in pandemics should be included.

Due to the mandatory isolation practices in the fight against the pandemic, depression and health anxiety have increased with the decrease in social relations and the feeling of loneliness (64, 65). The tangible feeling of loneliness caused by the COVID-19 pandemic is an unpleasant experience and is characterized by a state of chronic emotional strain (66). This situation increased suicide along with the risk of fear and stigma (67). Because there is a close relationship between social connections and suicide (68) and social isolation created will trigger loneliness and suicide (69). On the other hand, the problems that this situation will cause in the short and long term are uncertain (70). Correspondingly, it is essential to prevent information pollution, increase social support, develop policies against stigma and discrimination, ensure the continuity of all kinds of daily work, and easily access psychological support resources, within the framework of preventive mental health (69).

2.2. Selective Prevention

Visual Capitalist conducted research through the Occupational Information Network in the USA in order to identify the riskiest occupations during the COVID-19 pandemic duration. Accordingly, the riskiest occupations were listed as health personnel, flight personnel, coaches, barbers, special education teachers, bus drivers, kindergarten teachers and firefighters (71). On the other hand, in the study of the British Office of National Statistics, in which the occupations of 4700 people who aged 20-64 and died in England and Wales between 9 March and 25 May due to the COVID-19 pandemic were evaluated,

the ranking of the occupations with the highest number of deaths by gender is as follows (72):

Occupations where COVID-19 has caused the most death in men:

1. Security guards - 74 per 100,000
2. Factory workers - 73.3 per 100,000
3. Waiters - 69.6 per 100,000
4. Taxi drivers - 65.3 per 100,000
5. Chiefs - 56.8 per 100,000
6. Caretakers - 50.1 per 100,000
7. Bus and shuttle drivers - 44.2 per 100,000
8. Cleaners - 38.3 per 100,000
9. Sales assistants - 34.2 per 100,000
10. Healthcare workers - 30.4 per 100,000

Occupations where COVID-19 has caused the most death in women:

1. Hairdressers and barbers - 31.0 per per 100,000
2. Government executives - 23.4 per per 100,000
3. Caretakers - 19.1 per per 100,000
4. Sales assistants - 15.3 per per 100,000
5. Nurses - 15.3 per per 100,000
6. Hotel and accommodation service workers - 14.8 per per 100,000
7. Rehabilitation workers - 11.8 per per 100,000
8. Childcare related services - 6.8 per per 100,000
9. Secretaries - 6.2 per per 100,000
10. Teachers - 6 per per 100,000

As a result, it is fact that some occupations are riskier according to social differences. Accordingly, preventive mental health services should be planned. Within this framework, the identified problems and suggested solutions can be listed as follows:

- Health professionals, including administrative personnel, should be evaluated first. Because healthcare professionals are at great risk in the fight against the COVID-19 pandemic in terms of both high rates of illness due to the high risk of transmission (73, 74) and showing symptoms of

depression, anxiety and post-traumatic stress disorder (75, 76). On the other hand, health professionals and their families also experience problems in terms of stigma (77). Studies have found that healthcare professionals are not only concerned about stigma (78) but also have problems due to stigma (79). A similar situation has been observed in the fight against diseases such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and Ebola (80). This situation may cause health professionals to hide the disease, as well as create problems with respect to spreading the disease and disrupting preventive health studies (81, 82). In a study conducted to determine the demands of healthcare professionals during the pandemic period, it was observed that health workers didn't demand psychological support, they wanted long rest leaves and adequate protective equipment, and their ability to cope with stress was low (83). In this context, as preventive health services, action plans should be prepared in order to provide services for the protection of psychological health and effective treatment after diagnosis, as well as social awareness studies for the stigmatization of health workers. Moreover, it should be ensured that long rest leaves and protective equipment in sufficient amounts and with high quality are provided.

- Aviation sector can be considered as another priority profession within the scope of selective measures in terms of preventive mental health. Because the plane, which is indispensable as the fastest and easiest means of transportation, has also been considered as the most important factor in the spread of the COVID-19 pandemic to the whole world. Accordingly, aviation industry employees will be very likely to catch the COVID-19 outbreak. For this reason, precautions for flights and protective measures related to the outbreak have been introduced all over the world (84, 85). The measures taken in air transport have covered all segments, from passengers and all personnel working in ground services to flight personnel. However, the measures taken are aimed at preventing the outbreak and preventing its spread, and do not include any measures in terms of protective mental health. In this direction, it is essential to take measures to protect the mental health of all stakeholders from the first days of the outbreak. The benefits of action plans for this will make very important contributions to the fight against the pandemic in an integrative way. As suggestions, starting from the

first days of the pandemic, the introduction of social support services for all aviation sector employees, the establishment of psychoeducational groups and group psychological counseling services, as well as accessibility to individual psychological counseling services and family support programs will be beneficial.

- Other occupations will vary according to the type of occupation and the sociological structure of the regions in which they live. In the period of applying the occupation, determining factors such as the status of measures to protect social distance, suitability for remote working and income levels of professional staff and general socioeconomic conditions will increase the effectiveness of the measures to be taken. For example, it has been determined that occupations suitable for working from home are generally included in groups with a high level of welfare (86). In line with all these factors, local measures should be taken within the framework of preventive mental health.

2.3. Indicated Prevention

In this context, the protective mental health status of the elderly, children, those with chronic diseases and immigrants will be evaluated.

- Within the framework of the specified measures, the elderly are shown as the most risky group (27, 56). Because, the high rates of morbidity and mortality (87) and the death anxiety caused by the risk of being infected in the elderly in the outbreak develop serious psychological symptoms (83). On the other hand, loneliness, uncertainty, depression and exclusion caused by social isolation lead to aggravation of the problem (22). In particular, depression has greatly increased with the curfews, within the framework of social isolation assuming that there is a great risk (87, 88). Moreover, the increased risk of stigma and suicide are important factors (65, 89, 90). Another risk factor is the elderly living alone. It is more difficult for elderly living alone to cope with stress than the elderly living together, and on the contrary, family, kinship and friendship relations increase life satisfaction and adaptation (91, 92). Accordingly, it would be beneficial to establish social support units for the elderly in terms of preventive mental health (22). In addition, projects related to pet adoption and care can be carried out in

line with the fact that keeping pets is effective in preventing depression and anxiety in the elderly (93). Moreover, it was found that spirituality increased life satisfaction in the elderly, reduced stress levels and played an important role in coping with life problems (94). In particular, spirituality is effective in evaluating stress, reducing its effect and managing the source of stress while coping with stress (95). In this context, the elderly can get rid of the problems caused by social isolation with the emotional support of their spiritual tendencies (96). Therefore, it is necessary to include practices with spirituality in services for the elderly in line with a holistic approach (94).

- Children are at great risk in pandemics. Because, when compared to adults, it is very difficult for children to meet their developmental, social and spiritual needs without help, especially in pandemics, traumatic events and natural disasters (97). Particularly, the fear of catching the disease, possible disappointments, boredom, insufficient information, lack of face-to-face contact due to social isolation, lack of personal space at home and financial losses of the family in pandemics will make many psychosocial problems permanent (98). Thereof, children are more likely to be harmed by the reflections of crisis experiences (99). Accordingly, it is clear that if the acute psychosocial needs of children, who make up approximately 42% of the world's population, are not met, it will cause many problems (100). It was observed that in the studies conducted, children more often experienced problems like stigma (82), stress, distraction, irritability, fear (101), depressive disorders, post-traumatic stress disorders, panic, anxiety (102), domestic abuse (103), acute stress and adjustment disorders (104) in pandemics. In addition, isolation, which is widely applied in the fight against pandemics, poses a direct risk factor for children's physical, social and mental well-being (105). On the other hand, children who do not receive adequate mental health support in crisis situations are more likely to experience mental problems in their adulthood (106), their academic success falls behind their peers (107), communication problems increase significantly (108), and secondary trauma can be triggered (109). Correspondingly, in line with the developmental characteristics of children within the framework of preventive mental health;

  - Plans including appropriate disclosures and exercises for gaining active coping and problem-solving skills should be made (109),

- Since maintaining the routines of children's lives will make them feel comfortable and safe, approaches towards this can be performed (110).
- It has been determined that parents generally underestimate their children's problems related to the pandemic process, and they easily make their experiences and discussions related to the pandemic (111). It may be beneficial for parents to pay attention and create a good model to avoid problems arising from this,
- Intervention programs for negative psychosocial effects can be established, and parents can be asked to take their children to mental health professionals for symptoms such as sadness, anxiety, loss of appetite and sleep problems (112).
- Preventive and risk factors of children can be determined and studies can be carried out accordingly (108).
- Family, school and mental health professionals can cooperate in order to make studies for children more beneficial within the framework of preventive mental health (113).

- Another group at risk in pandemics is those with chronic diseases. Because it was determined in the studies performed that 23.7% of the patients identified had at least one chronic disease (hypertension, diabetes, chronic obstructive pulmonary disease, etc.) in the first data of COVID-19 (114). Moreover, the course of COVID-19 disease is difficult and fatal in individuals with chronic diseases (22). In this context, individuals with chronic diseases were especially evaluated, and it was observed that isolation, which is one of the methods of fighting with the pandemic, reduces the risk of catching the disease, while it brings loneliness and many mental problems with it at the same time (115). It was determined in a study conducted that those with chronic diseases in terms of anxiety, stress and depression levels showed more symptoms than the rest of the population (116). In a study designed in a similar way, health anxiety was reported as a risk factor in individuals with chronic health problems (117). Accordingly, it would be beneficial to consider individuals with chronic diseases as primary risk factors and to implement social support programs for their loneliness within the framework of preventive mental health. Moreover, solutions to the problems of inactive life brought by isolation are also important. Because regular exercise reduces the risk of catching other diseases, reduces or eliminates the use

of drugs, strengthens the immune system, helps to lose weight, strengthens muscle and bone structure in chronic diseases. In addition, it reduces stress, increases self-confidence, and increases life expectancy and quality (118). On the other hand, how to do physical activities at home is also important. Therefore, it is necessary to make personalized home-based exercise programs according to the course of the chronic disease. For instance, two-minute walks every 30 minutes with the strategy of "sit less and move more during the day" can contribute to reducing cardio-metabolic risk factors (119).

- Refugees/asylum seekers have been identified as another at-risk group in pandemics in the studies carried out (26, 55). Today, two-thirds of countries (134 countries) host refugees (120) and approximately 1% of the world's population consists of displaced people (121). In this extraordinary process, the risk of immigrants catching COVID-19 increases, access to primary care services becomes more difficult, new psycho-social problems arise/existing ones getting deeper, and income problems are experienced (122). Furthermore, xenophobic tendencies have increased with increasing anti-immigrant discourses (52). It is inevitable that xenophobia and discrimination will reveal stigma (123). Because it has been reported that immigrants and refugees, along with other disadvantaged groups, were exposed to discrimination and stigmatized in previous epidemics in the world (124). It was stated in the report of the Association of Public Health Physicians titled "The Situation Regarding Refugees and Asylum Seekers During the Pandemic Process" that the stigma caused that even the cases of being positive for the COVID-19 test were not explained by the immigrants (125). It was also reported that prejudice and discrimination regarding refugees led to feelings of guilt and confidentiality also increased the risk of outbreak (125).
- On the other hand, it should not be ignored in the context of refugees that women are more likely to experience domestic violence during the isolation process in camps, slums and unsanitary conditions (126). Moreover, the closure of schools due to the pandemic may create serious problems for girls living in refugee camps or internally displaced (127). Another problem is the follow-up and control of comorbidities (cardiovascular diseases, diabetes, chronic respiratory disease, hypertension, cancer, etc.) of COVID-19 (128).

Accordingly, the following recommendations can be presented within the framework of preventive mental health;

- In order to prevent refugees from being exposed to verbal or physical discrimination and stigmatization, fair behavior should be performed in common responsibility, and counseling and support services should be provided and relevant measures should be taken to cope with psychological problems such as loneliness, anxiety and fear (129).
- It should be clearly and comprehensibly explained that they will not be discriminated against due to the pandemic, and the isolation is for protection against the pandemic (125).
- Studies should be carried out on exposure to domestic violence of refugee women, and access to services and information should be shared with interpreter support (126).
- It should be ensured that refugee girls continue to school during the pandemic and receive additional support when they cannot go to school.

3. CONCLUSION

According to the results obtained in the study, preventive mental health services should be engaged in addition to the first preventive health services to prevent the spread of the outbreak in pandemics. This will be more effective in fighting with the pandemic as a whole. Because studies based on preventive and curative health services reveal deeper and permanent problems in terms of mental health problems after a while. Therefore, the struggle is negatively affected during the pandemic duration and the problems continue after the pandemic, as seen in the past pandemics.

While the experience in past similar outbreaks is important in pandemics, the specificity of each pandemic is clear. Accordingly, regional reconstitution in the fight should be created with a holistic policy that are preventive, curative and including preventive mental health, both in line with the characteristics of the virus causing the pandemic and considering the social dynamics. On the other hand, these studies should be coordinated on a universal scale and cooperative studies should be carried out according to the determined criteria.

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CHAPTER 13

NURSING CARE CASE STUDY OF PATIENT OF COVID-19

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Introduction

Coronaviruses (COV) are a large family of viruses that are common in the society, such as colds, and can cause self-limiting mild infections up to more serious infection pictures like Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) (1). In December 2019, a pneumonia outbreak associated with a novel coronavirus called SARS-CoV-2 was reported in Wuhan in the China's Hubei province. The World Health Organization named the disease caused by the new coronavirus as Coronavirus Disease 2019 (COVID-19) on February 12, 2020. The disease has become a complicated and rapidly evolving global problem with the gradually increasing COVID-19 cases reported in countries around the world as of March 9, 2020 [2]. The first COVID-19 case in our country was confirmed on March 11, 2020. In the following period, the number of cases continued to increase both in the world and in our country (1).

The disease mainly indicates that COVID-19 is transmitted from symptomatic people to individuals through droplets, direct contact with

infected people, or contact with objects and surfaces [3]. COVID-19 infection is transmitted by contact with other people's hands to droplets emitted by sick individuals through coughing, sneezing and rubbing their hands on the mucous membranes of the mouth, nose or eyes. Incubation time usually ranges from 2 to 14 days (1). According to available data, the risk of contagion when symptoms occur is higher than the risk of contagion in the later stages in patients (3).

Respiratory symptoms, fever, cough, and dyspnea are the common symptoms of infection. Symptoms such as headache, sore throat, nasal discharge, muscle and joint pain, excessive fatigue, newly emerged loss of sense of smell and taste and diarrhea can also be observed. Although the disease can be asymptomatic, severe cases of pneumonia, severe acute respiratory infection, renal failure and even death may occur (1).

The measures required to reduce the transmission of COVID-19 are specified in the 72nd coronavirus report of World Health Organization (WHO). According to this report, social and physical distancing measures are among the necessary measures, including individual and environmental measures, detection and isolation of cases, quarantine, prevention of crowded gatherings, international travel measures, vaccines and treatments. Social and physical distancing measures aim to slow the spread of the disease by stopping the transmission chains of COVID-19 and preventing the appearance of new ones. These measures promote virtual and social connections for families and communities, while reducing physical distance (at least one meter) between people and contact with contaminated surfaces. General public measures include flexible working, remote working, distance learning, reduction and prevention of crowding, closure of unnecessary facilities and services, and home stay measures. All of these measures should be followed together with individual precautions, such as frequent hand washing rules and compliance with the rules to be considered when coughing against COVID-19 (4).

Not only physical but also psychological care and support are provided in the fight against the new coronavirus through nursing care, as in the past infectious diseases. Throughout the pandemic, nurses did not leave patients alone and often continue to be with them even in the last moments of their lives. Even in the post-mortem period, nursing care continues by making preparations until the patient's transport, providing transport procedures appropriately and supporting the mourning process of their relatives (5).

In this case, an individual diagnosed with COVID-19 was evaluated according to Marjory Gordon's Functional Health Patterns (FHP) Nursing Care Model (6,7). The patient was diagnosed with NANDA nursing (8,9), and nursing

process care was administered. This model, which considers the individual as a holistic bio-psycho-social aspect, examines the needs of individuals in 11 functional areas. These areas allow systematic and standardized data collection and analysis of data in line with nursing philosophy. Gordon's functional health patterns are a process described to be used by nurses to make a more comprehensive assessment in patient care practices and to administer the nursing process (7,10).

CASE REPORT

N.B. is a 32-year-old female patient, a teacher, and married having a child. N.B. has no history of a chronic disease and surgery related to the respiratory system before her current disease. She has no history of known food and drug allergy, a past operation and any medication she takes.

N.B. has no known illness and a polymerase chain reaction (PCR) test was conducted on August 5, 2020 as a result of COVID-19 filiation studies due to contact with an individual with COVID-19 infection. She admitted in emergency outpatient department on August 7, 2020 upon positive polymerase chain reaction test, having throat ache, fatigue, tiredness, dry cough and high fever (38.8°C) persisting for four days. The patient, who has no history of comorbid or chronic diseases, does not smoke and does not use alcohol or any substance. The patient who contacted an individual with COVID-19, has never been hospitalized and has no familial risk factors. The computed tomography (CT) report of the patient was evaluated, found to be compatible with COVID-19 pneumonia, and hospitalized in the COVID-19 inpatient department. The patient's overall condition is good, conscious and cooperating. Vital signs of N.B. are stable and she is monitored under spontaneous breathing.

Current medications of N.B.: She was started on Favimol 200 mg 2x8 tablet (oral) treatment on the first day. She was started on Favimol 200 mg 3x2 tablet, Vogast 30 mg 1x1 (oral), Enox 4000 Anti-xa IU/0.4 ml 1x1 (subcutaneous), Lansopral 30 mg 1x1, Isotonic Sodium Chloride Solution 1000 ml 1x1 (IV) as of the second day of treatment.

Medical diagnosis of N.B: COVID-19 disease.

EVALUATION OF THE CASE ACCORDING TO THE FUNCTIONAL HEALTH PATTERN MODEL

1. Perception of health – Management of health

N.B. stated that her condition was moderate, did not have regular health checks, dose exercise occasionally, and has no history of smoking and alcohol. Body mass index (BMI) was calculated 26.4 kg/m^2. N.B. has severe back pain, joint pain, headache as well as sore throat and chest pain secondary to cough. She shows incompatibility with the diet and fluid plan. She cannot do her works that takes effort, shows extreme tiredness, weakness and an increased respiratory rate when going to the toilet.

Nursing diagnosis 1: Acute Pain *(NANDA Field 12: Comfort, Class 2: Physical Comfort)*

Purpose of nursing care: It is the patient's experience of less than 3 pain according to the 0 to 10 pain scale and verbal and non-verbal expression of his/her pain.

Interventions:

- Assessment of the location, severity and nature of pain; determining its level according to the pain scale and monitoring it at intervals,
- Investigating the factors that reduce and increase pain and eliminating the factors that increase pain (light, stress, noise, position disorder),
- Administering the appropriate analgesic treatment ordered by the physician and evaluating the results,
- If not contraindicated, applying non-pharmacological methods for pain control (back massage, darkness, muscle relaxation exercises, position change, etc.) (11),
- Keeping the patient away from situations causing stress and discomfort,
- Ensuring the patient's bed rest,
- Informing the patient about the causes of the pain, its occurrence due to the disease and when it will disappear,
- Ensuring the patient's participation in care with a calm and supportive approach,
- Explaining the importance of breathing exercises in the treatment of COVID-19, and planning exercise in 3 periods per day (puckered lip breathing, diaphragmatic breathing, deep breathing exercises) (12).

Nursing diagnosis 2: Ineffective health management *(NANDA Field 1: Improving Health, Class 2: Management of Health)*

Purpose of nursing care: It is ensuring that the patient maintains his/her health effectively, recognizes complications early, prevents from COVID-19 infection and maintains his/her own care effectively by knowing the risks of transmission.

Interventions:

- Providing information on the COVID-19 infection and how to reduce the risk factors that worsen its effects,
- Supporting and encouraging every correct behavior for the health of the individual,
- Informing the patient and his/her family about isolation methods to prevent COVID-19 transmission.
- Explaining the importance that the patient and those contact with the patient should wear all protective equipment completely and completely (13).
- Providing information on the importance of ensuring full social isolation and informing the patient and his/her family as necessary to minimize the risk of COVID-19 infection transmission (14).

2. Nutrition-Metabolic Status

N.B. stated that she had fatigue, loss of appetite and nausea during the disease. N.B. further stated that her cough induced sore throat and sensitivity in the throat reduced the desire to eat, experienced dry mouth because she was breathing through the mouth due to nasal congestion, and that these are the factors for decreased nutrition. She had complaints of excessive sweating and fatigue due to high fever ranging 38.5°C to 39.1°C.

Nursing diagnosis 3: Malnutrition: Nutrition less than body requirement (*NANDA Field 2: Nutrition, Class 1:* Swallowing)

Purpose of nursing care: It is the patient's understanding of the importance of nutrition during the COVID-19 infection, complying with the planned diet, maintaining a normal weight and not losing weight.

Interventions:

- Monitoring the weight of the patient and evaluating the food taken,
- Explaining that a weak immune system increases susceptibility to infections (1),
- Explaining the relationship of strong immune system with food in COVID-19 infection (15, 16),
- Providing information about the importance of good nutrition in creating a strong immune system in COVID-19 infection (17),
- Supporting and encouraging the adoption of appropriate nutrition in the fight against COVID-19 infection,

- Planning a daily diet rich for antioxidants, vitamins, vitamin D, omega 3, zinc, pre- and probiotics known to have positive effects on the immune system (17,18),
- Explaining the importance of patient's attention to fluid intake and encouraging them to drink 8 to 10 glasses of water daily,
- Foods consumed should not be too cold, too hot, too bitter or too spicy in order to prevent throat sensitivity,
- Not doing exercises that require excessive effort before meals and, if possible, resting before meals to prevent anorexia secondary to fatigue,
- Ensuring oral hygiene before and after meals and to encourage oral care,
- Ensuring the consumption of soft and liquid foods to prevent sore throat caused by cough,
- Informing patients about the importance of disposable plates, spoons and forks due to the risk of COVID-19 transmission (19).

Nursing diagnosis 4: Fluid volume deficiency risk *(NANDA Field 2: Nutrition, Class 5: Hydration)*

Purpose of nursing care: It is moist mucous membranes to show fluid balance, good skin turgor, stable vital signs and normal capillary filling.

Interventions:

- Following up the intake and output balance and determining the fluid amount that the patient should take,
- Informing the patient about the importance of adequate fluid consumption,
- Evaluating dehydration findings (headache, cracked lips, dry skin, dark urine color, dry mouth, dry and sticky mouth, decreased need for urination, muscle cramps, thirst, dizziness),
- Informing about consuming liquids with diuretic effects such as coffee, tea, grapefruit juice carefully [20,21],
- Determining fluids lost by vomiting, diarrhea, hyperthermia,
- Assessing the patient's skin turgor,
- Monitoring vital signs due to the risk of developing symptoms such as hypotension and tachycardia,
- Administering an antiemetic therapy suitable to the patient in case of nausea and vomiting,
- And monitoring the patient's body temperature.

Nursing diagnosis 5: Hyperthermia *(NANDA Field 11: Safety/Protection Class 6: Thermoregulation)*

Purpose of nursing care: It is to keep the body temperature within normal limits.

Interventions:

- Monitoring the patient's body temperature at frequent intervals,
- Monitoring the fluid intake and urine output,
- Regulating the room temperature and environmental factors,
- Ensuring that the clothes are comfortable, thin and cotton,
- Administering drug therapy under the control of the physician when the metabolic rate and oxygen consumption will increase if the patient has tremor,
- Supporting the patient's fluid intake (18),
- Monitoring vital signs at regular intervals,
- Cold application to lower body temperature,
- Explaining to patients that they should change her clothes and bed linen after sweating and put dirty items in a special bag and close it,
- Administering antipyretic drugs according to the physician's order and monitoring the sweating level following antipyretic treatment.

Nursing diagnosis 6: Deterioration of the Oral Mucous Membrane *(NANDA Field 11: Safety/Protection, Class 2: Physical Injury)*

Purpose of nursing care: It is ensuring oral membrane integrity and moisture, maintaining adequate nutrition and fluid intake and ensuring optimal oral hygiene.

Interventions:

- Evaluating the oral care habits of the patient and explaining the importance of oral care at regular intervals and following it up,
- Evaluating the oral cavity in terms of bad breath, lesions, pain or bleeding,
- Applying moisturizing cream to lips every 2 hours and/or as needed (10).
- It is informing the patient about feeding with small and frequent meals and not eating very hot and very cold foods and avoiding hard-shelled foods in order not to increase oral irritation.

Nursing diagnosis 7: Nausea-Vomiting *(NANDA Field 12: Comfort, Class 1: Physical Comfort)*

Purpose of nursing care: It is minimizing nausea and vomiting and to ensure that the patient eats normally.

Interventions:

- Evaluation of factors and potential risks that may play a role in nausea and vomiting,
- Monitoring the intake and output balance and evaluating the vital signs and dehydration of the patient,
- Administering antiemetic suitable for the patient when needed,
- Planning a less and frequent diet,
- Explaining the importance of slow consumption of fluids to prevent nausea and to recommend a liquid-weighted and soft diet to reduce nausea,
- Stating that very hot foods should not be preferred as they may increase the feeling of nausea,
- Informing the patient about that he/she has nausea due to the infection and when it will end,
- Teaching the patient to use deep and slow breathing, visualization, meditation and relaxation techniques such as yoga when the nausea reflex occurs,
- Menthol sugar can be eaten to reduce nausea,
- Choosing loose and non-tight clothing,
- Explaining that nausea and vomiting are caused by COVID-19 infection (22,23).

3. Defecation

The patient stated that her normal defecation was once a day, but now she has defecated 7-8 times a day. The patient's bowel sounds were determined as 15/min. N.B. stated that her stool is soft and fluid.

Nursing diagnosis 8: Diarrhea *(NANDA Field 3: Defecation/Gas Exchange, Class 2: Gastrointestinal Function)*

Purpose of nursing care: It is to ensure that the feces are in the amount and consistency of normal defecation.

Interventions:

- The onset of diarrhea and the number, content, amount and color of defecation during the day,
- Monitoring the intake-output balance and weight,
- Observing the vital signs,
- Monitoring the patient for signs of dehydration due to fluid loss (24).
- Increasing liquid food intake (soup, fruit juice, etc.),
- Avoiding foods prepared without cooking and planning a diet with a restricted fiber ratio for the patient,
- Ensuring that liquid foods are not consumed too hot and too cold,
- Ensuring that light and easy-to-digest foods are consumed at short intervals,
- Evaluation of the presence of abdominal pain,
- Informing the patient about the importance of the personalized toilet and toilet hygiene in order to prevent contamination with stool (25,26),
- Informing the patient about the importance of hand washing (17,27,28).

4. Activity-Exercise

N.B stated that her energy was insufficient and she was inadequate to perform daily life activities due to weakness, fatigue and intense back and joint pain. She also stated that she was out of breath during the activity and had increased pain in her legs and heels.

Nursing diagnosis 9: Activity Intolerance *(NANDA Field 4: Activity/Rest, Class 4: Cardiovascular/Pulmonary Responses)*

Purpose of nursing care: Enabling the patient to continue daily life activities without pain, dyspnea and fatigue.

Interventions:

- Determining the patient's tolerance to exercise and to what extent she is able to do daily living activities,
- Monitoring the cardiorespiratory response after activities (tachypnea, tachycardia, sweating, dyspnea, pale/pallor),
- Explaining the importance of regular physical activity and exercise for preventing chronic and metabolic diseases and ensuring psychological well-being,

- Encouraging the patient to use controlled breathing techniques (puckered lip and diaphragmatic breathing) during emotional and physical stress and during excessive activity (27,29),
- Determining appropriate exercise plans such as knee-elbow exercises, yoga, stretching that can be done at home without using any equipment (30,31),
- Teaching simple practices to support activities such as standing while talking on the phone, taking steps in the room of isolation, doing arm and leg exercises where she sits in order to prevent immobility and regain muscle strength,
- Informing the patient that activity and exercise are important to increase physical activity, stay healthy and increase body immunity,
- Adopting regular sleep and eating habits in order to protect and maintain sufficient energy resources and following them up,
- Explaining to the patient that the activity should be stopped when she feels chest pain, dyspnea, dizziness or fatigue,
- Determining sufficient time between exercises for the patient to rest and encouraging the patient for activity,
- Eliminating the factors that prevent the patient's energy from being released,
- Teaching energy conservation techniques (such as putting things in easily accessible places, pushing instead of pulling, sliding instead of lifting),
- Supporting the patient in carrying out activities when needed,
- Avoiding clothes that may affect blood flow, breathing rhythm and physical comfort, and choosing appropriate clothes that provide physical comfort,
- Encouraging to increase the activity level, providing emotional support.
- To regain muscle strength by doing exercises such as airing the isolation areas frequently, walking in the room, doing arm and leg exercises while sitting, and squatting while standing (12,32,33).

5. Sleep-Rest

N.B. stated that she could not wake up in the morning rested and woke up frequently at night with sweating secondary to severe cough, headache and high fever. The need for frequent urination at night secondary to diarrhea disrupts the sleep pattern of a patient.

Nursing diagnosis 10: Disruption to sleep pattern (*NANDA Field 4: Activity/ Rest, Class 1: Sleep/Rest)*

Purpose of nursing care: It is providing adequate and quality sleep and feeling rested in the morning.

Interventions:

- Determining the sleep habits of the patient,
- Explaining that maintaining sleep pattern will accelerate recovery of the COVID-19 disease and its importance to increase immunity (34,35),
- Providing a quiet and calm environment while the patient is sleeping,
- Teaching the application of relaxation therapy (trying to focus on good thoughts in a calm environment), cognitive therapy (avoiding guiding the brain with false thoughts such as thinking that they will not be able to fall asleep in bed) to make it easier to fall asleep,
- Evaluating the patient in terms of individual, environmental and treatment factors during sleep hours (32,36),
- Determining the resting hours by considering the patient's nutrition and medication hours,
- Supporting the patient to express her fears and concerns about adaptation to the environment,
- Eliminating factors that prevent falling asleep such as hyperthermia and pain,
- Avoiding stimulating mental activity right before bedtime (for example, watching action movies, encouraging speech), applying relaxing events such as warm shower, massage and touch, relaxation exercises, listening to music to ensure comfort,
- Ensuring that the patient wears comfortable and cotton clothes,
- Informing patients that they should not drink stimulants such as caffeine (28,37,38).

6. Cognitive-Perceptual State

N.B. has a time, place and person orientation. Her Glasgow Coma Scale is 15. She stated that she did not experience any problem in her hearing, feeling and touch senses, but there was a change in the taste and smell senses. N.B. stated that she does not know much about the new disease COVID-19 and she is very scared. She said that she did not know exactly how to cope with the disease and the isolation rules.

Nursing diagnosis 11: Lack of information (*NANDA Field 5: Perception/ Comprehension Class 4: Comprehension)*

Purpose of nursing care: It is the elimination of information deficiencies about the disease.

Interventions:

- Evaluation of the patient's level of knowledge about COVID-19,
- Providing information about known false and incomplete information about COVID-19 disease,
- Informing about isolation rules (using private toilet and bathroom at home, wearing masks, airing the room properly, using personal items, hand hygiene, separating masks and other garbage, etc.),
- Encouraging the patient to ask questions,
- Reevaluating the patient's level of knowledge after providing necessary information (39,40).

7. Self-Perception-Self-Concept

N.B. stated that she generally had death anxiety. She expressed that she had a young child of sixteen months and was worried that she was away from his/her. She said that she was feeling tired and bored with isolation. She said that she lost hope because the disease had no cure and vaccine.

Nursing diagnosis 12: Death Anxiety *(NANDA Field 9: Coping/Stress Tolerance, Class 2: Coping)*

Purpose of nursing care: It is taking the responsibility of active participation in treatment and achieving effective coping methods by reducing anxiety and relaxing the patient.

Interventions:

- Evaluating the isolated patient in terms of behavior and situation related to the presence of fear of death anxiety and questioning whether the coping methods used in the past were effective, and, if ineffective, teaching effective coping methods,
- Informing the patient about the procedures related to the isolation and treatment process,

- Identifying situations that increase the patient's anxiety and minimizing these stressors (41).
- In order to teach appropriate coping methods, an empathetic approach should be adopted and the patient should be encouraged to ask questions and express their feelings to develop a relationship based on trust,
- Ensuring a simple and honest communication with the patient based on the information that is consistent and heard and understood by the patient
- Explaining the reasons for isolation to the patient to ensure his/her own control,
- Application of relaxation methods such as muscle stretching, deep breathing exercises, massage and creating a calm and quiet and relaxing environment (42).

Nursing diagnosis 13: Fatigue *(NANDA Field 4: Activity/Rest Class 3: Energy Balance)*

Purpose of nursing care: It is minimizing the fatigue level of the patient.

Interventions:

- Determining the factors that cause fatigue,
- Evaluation of the patient's fatigue level and perception,
- Determining the factors that increase and decrease fatigue,
- Supporting the patient while performing daily life activities,
- Preventing unnecessary energy consumption and teaching energy conservation techniques (such as putting things in easily accessible places, pushing instead of pulling, sliding instead of lifting),
- Regular rest planning during the day to reduce the patient's fatigue.

Nursing diagnosis 14: Hopelessness *(NANDA Field 6: Self-Perception, Class 1: Self-Concept)*

Purpose of nursing care: It is eliminating the patient's hopeless situation and enabling the patient to see life positively and to express his/her positive thoughts about the future.

Interventions:

- Determining the reasons that make the patient feel hopeless,
- Encouraging the patient to express his/her feelings and thoughts that make his/her feel negative,

- Encouraging the patient for effective participation in terms of complying with the treatment,
- Positive feedback for participation in care,
- Strengthening the patient's self-confidence and competencies,
- Strengthening the role of the patient according to his/her values and life satisfaction for the purpose of life,
- Informing the patient in general about the COVID-19 treatment process,
- Stating that the COVID-19 disease is a global problem despite the patient's reaction against the disease and explaining the issues that the patient is curious about,
- Disclosure of the correct information about the disease,
- Providing a realistic perspective to the patient about the treatment process and condition while informing him/her.

8. Role-Relationship

N.B. stated that he lives with her husband and child and that they have good familial relations. She said that she was uncomfortable because she could not fulfill her motherhood duty due to droplet and respiratory isolation because of the COVID-19 disease. She expressed regret that she could not meet with her family and relatives.

Nursing diagnosis 15: Social Isolation *(NANDA Field 12: Comfort, Class 3: Social Comfort)*

Purpose of nursing care: It is explaining the importance of isolation and minimizing the feeling of loneliness during the disease.

Interventions:

- Explaining the importance of social isolation in reducing infection in COVID-19 disease with a high rate of infection spread,
- Determining the methods to communicate with the family during the day in order to prevent the patient from feeling lonely (such as video conversation by means of technological devices),
- Providing the necessary information to the patient about the infection process,
- Supporting the patient for verbal communication,

- Observing the patient in situations such as anger, nervousness, anxiety
- Ensuring that anxiety and stress are minimized (26,43).

Nursing diagnosis 16: Ineffective Role Performance *(NANDA Field 7: Role Relationships, Class 3: Role Performance)*

Purpose of nursing care: It is preventing the individual from feeling inadequate by supporting his/her role performance.

Interventions:

- Determining the role of the patient in the family,
- Determining the factors that cause deficiencies in the individual's role performance,
- The patient should be encouraged to express his/her feelings and thoughts and to develop alternative adaptive coping strategies (breathing, relaxation exercises, positive thinking, stopping thinking),
- Explaining that the situation is curable and temporary,
- Providing a suitable environment for familial communication,
- Providing information to family members about the process (44).

Nursing diagnosis 17: Interruption of family processes *(NANDA Field 7: Role Relationships, Class 2: Family Relations)*

Purpose of nursing care: It is the positive adaptation of family members to this change experienced due to disease.

Interventions:

- Determining the characteristics of the family (family values, the role of the patient in the family, support strengths of the family, health habits, etc.),
- Determining the developmental stages of the family (marriage process, time of having a baby, illness, death, etc.)
- Identifying the coping methods used against short-term or long-term stress, defining the coping strategies developed by family members in response to the pandemic (adaptive, maladaptive), and supporting the family to develop alternative adaptive coping strategies for the future (breathing, relaxation exercises, thinking positive, stopping thinking, etc.) (45,46,43),
- Teaching the patient effective coping methods,

- Informing the patient about the COVID-19 disease process,
- Using communication resources (telephone, PC, etc.) to communicate with the patient's family, psychosocially supporting family members who are in quarantine due to the risk of being infected with COVID-19 disease, enabling them to communicate with other family members via e-mail, social media, video and telephone and encouraging them to express their feelings in different ways (writing, reading, painting, etc.),
- Providing frequent and regular remote communication in order to prevent the patient from feeling himself/herself alone,
- Expressing the feelings of anger, stress and fear occurred in the family after the disease and providing support.

9. Sexuality-Reproductive Form

The patient expressed that there was no problem in her sexual life before COVID-19, and that she took a break from her sexual life due to isolation.

10. Coping-Stress Tolerance

N.B. expressed that she normally has a calm nature, but is experiencing fear and stress because she is currently fighting a disease that has no definitive treatment. The patient also explained that her fear was exhausting her and she had difficulty coping with it.

Nursing diagnosis 18: Ineffective individual coping (*NANDA Field 9: Coping/ Stress Tolerance, Class 2:* Coping reactions)

Purpose of nursing care: Showing positive coping skills.

Interventions:

- Evaluation of positive and negative coping methods,
- Discussing effective coping methods and helping to use them,
- Ensuring active participation in treatment and care.

11. Belief-Values Form

The patient stated that communication with his family and visits of relatives were very important for her, but she was sad that no visits are allowed due to the isolation because of illness, and she was especially worried about her

16-month-old baby who was in the developmental period. The patient stated that she always prayed and continued to pray during this process, and that this situation was not contrary to her religious beliefs.

CASE ANALYSIS

For this case, a care plan was prepared and implemented using Marjory Gordon's Functional Health Patterns Nursing Care Model (5,6) and NANDA nursing diagnoses (7,8) to solve the problems of the patient diagnosed with COVID-19. Respiratory symptoms, fever, cough, and dyspnea are common signs of infection in patients with the diagnosis of COVID-19. Symptoms such as headache, sore throat, nasal discharge, muscle and joint pain, excessive fatigue, newly emerged loss of sense of smell and taste and diarrhea can also be observed. Although the disease can be asymptomatic, severe cases of pneumonia, severe acute respiratory infection, renal failure and even death may occur (1,47,48).

Throughout the COVID-19 disease process, N.B. was followed up for 48 hours at the clinic and then at home. During this period, the patient was taken into isolation in a separate room and started on COVID-19 treatment. Throughout the disease process, N.B. was followed up for the diagnoses of "acute pain, ineffective health management, malnutrition: nutrition less than body needs, risk of fluid volume deficiency, hyperthermia, disorder in the oral mucous membrane, diarrhea, activity intolerance, disturbed sleep pattern, knowledge deficit, nausea-vomiting, death anxiety, tiredness, despair, social isolation, ineffective role performance, interruption of family processes and ineffective individual coping" according to her symptoms and findings.

N.B. verbally stated that her persistent pains decreased after the nursing care administered for the diagnosis of "acute pain". A quiet, calm and dark environment was prepared for the patient's headache. Analgesic treatment was administered when N.B.'s recurrent and persistent pains recurred, and the patient was taken to bed rest. The nursing care of the patient was supported by massage and practical breathing exercises. As a result of all the nursing interventions, the patient reported the pain as Visual Analogue Scale (VAS) 2/3 during this period, which was previously VAS 7/9, and the pain decreased.

Measures were taken for droplet isolation for the diagnosis of "ineffective health management". A hygienic and safe environment was prepared in a special room for the patient. In order to minimize the risk of social isolation and infection transmission, both the patient and her family were given the necessary training. As a result of nursing interventions, N.B. and her family have adapted to the

measures taken for COVID-19 and said they have learned through training on what to watch out for against COVID-19.

After the nursing diagnosis of "malnutrition, less than body requirement", N.B. was trained about the importance of the strong immune system's relationship with food in COVID-19 infection and was encouraged to apply the diet. A daily diet plan rich for antioxidants, vitamins (B, C, D vitamins), omega 3, zinc, pre- and probiotics was implemented for N.B. Because of the loss of appetite of N.B, vitamins C, D and zinc supplements were given for immunity. N.B. adapted to the trainings given on the diet in terms of fluid intake (8 to 10 glasses of water a day). N.B. used disposable plates, spoons and forks due to the risk of contamination. N.B. kept her normal weight.

The patient's intake and output balance were monitored for the fluid volume deficiency risk" nursing intervention. N.B. Was evaluated for dehydration and symptoms such as headache, thirst, dark urine, and dry mouth were observed and the patient was supported for fluid intake. She was informed about consuming liquids with diuretic effects such as coffee, tea, grapefruit juice carefully. The patient's urine color (light yellow), thirst, and dry mouth symptoms returned to normal and fluid balance was restored.

For the nursing diagnosis of "hyperthermia", the patient's body temperature was monitored frequently. Fluid intake was supported by monitoring urine output and sweating. The temperature of the room was measured and ventilated frequently. Fatigue symptoms were observed due to hyperthermia and the patient was rested at these times. An increase in body temperature up to 39.1°C was noted and antipyretic drugs were administered by the physician order. Cold application was made during frequent high fever at nights. N.B., based on the training she received, changed her clothes and bed linen after sweating and put the dirty items in special bags and washed them in the washing machine at 60 degrees when necessary. As a result of all the nursing interventions, N.B.'s body temperature was reduced to 36.4°C. Oral care practice habits of N.B. were evaluated for the nursing diagnosis of "Oral Mucous Membrane Deterioration". N.B. stated that she understood the importance of oral care during COVID-19 and did regular oral care. Oral membrane integrity and moistness was provided.

As a result of nursing interventions for the nursing diagnosis of "Nausea-Vomiting", N.B. stated the severity of her nausea and vomiting in terms of dehydration and her findings were followed up. In order to reduce the fatigue of the patient, the patient was recommended to eat less and often after each rest. The patient's daily fluid intake-output balance was supported, and her intake and weight were monitored. N.B. was weighed 70 kg on the first day of the

disease. However, at the end of the day 4, she was weighed 67 kg. As a result of all the nursing interventions and training, she was weighed 70 kg on the last day of the disease. Relaxation techniques were taught to N.B., she adopted these methods and applied them when she had nausea. As a result of the nursing interventions, N.B. stated that she understood the importance of nutrition, loss of appetite disappeared, and deep and slow breathing exercise was an effective method in reducing nausea.

For the nursing diagnosis of "diarrhea", N.B.'s intake-output and weight were followed up and her fluid intake was supported. N.B. arranged her own diet according to the education on nutrition. Training was given on the importance of toilet hygiene and hand washing in COVID-19. N.B. stated that she understood the importance of toilet hygiene in order to prevent contamination risk. N.B. stated that her complaint of diarrhea was intense on the second day of her illness. After the nursing interventions, the complaint of diarrhea disappeared and the patient adapted to hygiene training.

According to the diagnosis of "activity intolerance", N.B.'s activity tolerance was evaluated. It was found that her skin was in normal color and temperature during the activity, but was dry. When not resting between activities, the patient was found to be out of breath and experienced also excessive sweating. The patient was trained on the harms of uncontrolled exercise, and instructed to terminate the exercise when she realizes that negative symptoms emerged during the exercise. It was found that the patient complied with these explanations and her tolerance to activity improved. N.B. practiced activities such as walking in the room, doing arm and leg exercises where she sat, not sitting and walking in the room while talking on the phone and knee-elbow exercises during the day in order to prevent immobility in the room. After nursing interventions, the patient experienced minimal pain (VAS 3/10) while performing daily life activities and her activity tolerance increased, but tachypnea and weakness continued when she exerted excessive effort.

For the nursing diagnosis of "Sleep Disruption", the patient was evaluated in terms of sleep habits and individual, environmental and treatment-related factors during sleep hours. N.B. understood the immunological importance of regular sleep during COVID-19 disease. A quiet and calm environment was provided to the patient during bedtime; N.B. stated that she understood training on avoidance of stimulating mental activity just before going to bed, warm milk, relaxation exercises, relaxation therapy to make it easier to fall asleep and practiced all of them. Medication times were adjusted, she was allowed to take a warm shower before going to bed at night, she was ensured not to sleep much

during the day, night sleep was arranged, and N.B. was ensured to be rested in the mornings and get enough sleep after nursing interventions.

The knowledge level of the patient before and after the training was evaluated for the "Knowledge Deficit" nursing diagnosis. The patient realized that pre-training COVID-19 information was inadequate and inaccurate. N.B. was provided correct information and a general information (for example what is COVID-19, how to protect from COVID-19, what is the importance of isolation, the importance of adherence to treatment) was also provided considering the facts about COVID-19 disease. After nursing interventions, N.B. reached the required level of knowledge and stated that she left her fear behind.

At the onset of the disease N.B. stated that she had a high fear of death and the interventions for the "Death Anxiety" nursing diagnosis were applied. The patient's fear was identified and she was informed that she had the disease, but that did not mean that she would die. The patient was informed about the isolation process and was encouraged to ask questions. N.B. practiced coping methods including deep breathing exercises, massage, creating a calm and quiet and relaxing environment to leave her anxiety behind. After trainings, changes in the patient's general behavior and attitudes were observed, and her active participation in treatment was ensured. N.B. said that she left death anxiety behind as a result of the nursing interventions.

For the "fatigue" nursing diagnosis, the patient prevented unnecessary energy consumption through controlled energy consumption, and a rest plan was created during the day. After the nursing interventions, the patient's fatigue complaint decreased, but she stated that even if a little, the feeling of fatigue reappeared as a result of fast and heavy exercises. The reasons for the patient's hopelessness were evaluated for the "hopelessness" nursing diagnosis. Those who died from the COVID-19 disease around her, inadequate and incorrect information about the disease, and the fear of losing her family and especially her young son by thinking that she would infect him were determined as reasons that drove N.B. to hopelessness. A realistic perspective was presented to N.B. about the COVID-19 treatment process, general information was provided, and the level of hopelessness was minimized by correcting the wrong information she had. N.B. stated that she can think positively for the future as a result of the nursing interventions.

For the "social isolation" nursing diagnosis, the patient was informed about the importance and necessity of isolation. The patient's questions about the importance of isolation in reducing the risk of transmission in COVID-19 disease were answered. In order to prevent loneliness, a video call was established

with the patient's family over the phone. N.B. stated that she understood the importance of social isolation and that the feeling of loneliness decreased with the communication provided.

For the "ineffective role performance" nursing diagnosis, the factors that cause ineffectiveness in N.B.'s role in the family and role performance were determined. The patient encouraged herself to express her feelings and thoughts, and she practiced positive thinking and stopping thinking, which are included in alternative adaptive coping strategies. N.B. stated that the situation is curable and temporary and that she understood the importance of the isolation process for herself and her family. Her reaction to the lack of role performance ended at the end of the nursing interventions.

The familial characteristics of the patient for the "interruption of family processes" nursing diagnosis were determined. Video conversation was made using technological devices to prevent interruption of family communication and to prevent the feeling of loneliness of the patient. As a result of nursing interventions, N.B. and her family members were ensured to adapt positively to this change experienced due to the disease.

Positive and negative coping methods of the patient were determined regarding the "ineffective individual coping" nursing diagnosis. The patient's active participation in the treatment was ensured by supporting coping methods to cope with the stress and anger that occur when she was inadequate.

DISCUSSION

In COVID-19 cases, nurses should have sufficient knowledge and skills for patient follow-up, management of symptoms and evaluation of conclusions. Therefore, for the nursing care to be given to COVID-19 patients, detailed evaluation of the patient is important. N.B. was followed up in the clinic for 48 hours with the diagnosis of COVID-19 and at home after discharge, evaluated according to Gordon's FHP Model, and nursing care was given, interventions for the problems she experienced were planned and put into practice.

Respiratory symptoms, fever, cough, and dyspnea are the common symptoms of the COVID-19 disease. Symptoms such as headache, sore throat, nasal discharge, muscle and joint pain, excessive fatigue, newly emerged loss of sense of smell and taste and diarrhea can also be observed. Although the disease can be asymptomatic, severe cases of pneumonia, severe acute respiratory infection, renal failure and even death may occur (1). Fever, cough, sore throat, muscle and joint pain, weakness, loss of sense of smell and taste, diarrhea and insomnia symptoms were also observed in N.B.

Caution should be exercised about the combined use of possible treatment options, the interactions and adverse effects of the drugs used for COVID-19 patients (49). N.B. was started on favipiravir 2x8 on the first day and 2x3 200 mg tablet on other 4 days for COVID-19. It was observed that the drug taken did not interact with other drugs and had toxic effects.

Pain may be the first symptom before the known symptoms of COVID-19 infection appear. The management of pain caused by COVID-19 infection, secondary pain due to complications of the disease, and chronic painful conditions should be reviewed during the pandemic. Additional factors such as anxiety, depression, social isolation and economic stress can make pain management difficult (50). Pain is one of the first symptoms to occur in N.B. In addition to anxiety, social isolation and fear of death, N.B.'s pain increased. Nursing interventions for anxiety and death anxiety were planned and put into practice. A decrease was observed in the pain level of the patient supported by coping methods.

Studies have shown that physical activity can improve the immune system as immune cells increase. In this context, it is recommended to increase the immune function that will protect the body against the virus through appropriate physical activity (51). Due to COVID-19 infection, N.B.'s physical activity decreased. For the activity intolerance nursing diagnosis interventions, the patient was informed about the importance of physical activity on immunity and an exercise plan was created. N.B. increased her physical activity tolerance by practicing activities such as walking in the room, doing arm and leg exercises where she sat, not sitting and walking in the room while talking on the phone and knee-elbow exercises during the day in order to prevent immobility in the room.

Loss of appetite, malnutrition, dehydration caused by high fever and hypovolemic shock often concomitant to the main symptoms of COVID-19. Consuming adequate amounts of food and water is crucial to the treatment of COVID-19. Dynamically evaluating the patient, creating an individual treatment plan, monitoring the patient and making necessary changes are the main approaches in the treatment process of the disease [50]. N.B.'s daily fluid intake was evaluated and it was determined that she drank 3 to 4 glasses of water. She was informed about the importance of fluid intake in COVID-19, and N.B. increased her fluid intake by drinking 8 to 10 glasses of water a day. Dehydration and hypovolemic shock picture were not observed in N.B.

Diet is important for increasing body immunity in COVID-19 infection. A daily diet rich for antioxidants, vitamins, vitamin D, omega 3, zinc, pre- and

probiotics known to have positive effects on the immune system is of great importance in the fight against COVID-19 (21,52). N.B.'s diet was evaluated and a daily diet plan rich for antioxidants, vitamins (B, C, D vitamins), omega 3, zinc, pre- and probiotics was applied. Because of the loss of appetite of N.B, vitamins C, D and zinc supplements were given for immunity.

Patients in our country go through this process at home when hospitalization is not required, and isolated as one person in hospital rooms when hospitalization is required. Bed rest for just one week can cause serious muscle loss of up to 20% of the individual. Joint range of motion, stretching, and strengthening exercises can be included in the treatment plan during this period to increase muscle strength and endurance depending on the patient's condition (53). N.B. exercised in the room in order to prevent muscle weakness during the infection process, reduced the rate of inactivity and increased the exercise duration every day. N.B. had no muscle loss.

Strengthening the social support networks by improving the coping skills of individuals and evaluating the stressful event can reduce the prolonged immune response induced by stress. Thus, both psychological and physiological well-being of the individual can be protected (54). N.B. has put into practice adaptive coping strategies (breathing, relaxation exercises, positive thinking, stopping thinking) that are taught to eliminate the stress she experienced about the fear of COVID-19 infection and how to cope with the infection. N.B. struggled with the infection more effectively when her stress and fear were gone.

Routine changes in body posture such as half-sitting position, lateral position, and prone position should be made to reduce the work of respiratory muscles and conserve energy. In addition, abdominal breathing and puckered lip exercises, which are respiratory control techniques, should be used to expand the lower part of the chest and relieve breathing difficulties (21). Correct breathing exercises were taught to N.B. to strengthen the respiratory muscles and prevent energy loss. During the day, N.B. Practiced the prone position and lip exercises, and it was observed that she was breathing effectively using her respiratory muscles.

CONCLUSION

In the COVID-19 epidemic, which the World Health Organization regards as a "pandemic", nurses are fighting at the forefront and will continue to fight at the forefront in the future. The World Health Organization stated that "nursing should be seen as a health investment in a country, not a cost" and "nurses are the backbone of the health system and are at the forefront of fighting COVID-19"

and emphasized the importance of nursing care. Failure to follow the symptoms and pay attention to treatment and care in individuals with COVID-19 infection can be fatal. In this case, nurses play an important role in the care and treatment of COVID-19 patients.

As a conclusion, an individual diagnosed with COVID-19 was evaluated according to Gordon's Functional Health Patterns Model in this study and nursing care was administered besides NANDA nursing diagnoses. It was found to the care administered increased the patient's abilities and beliefs to fight COVID-19, provided psychological recovery, prevented fear of loneliness and COVID-19 infection, gained the ability to manage symptoms, increased coping tolerance and the trainings provided increased the patient's level of knowledge. In order for nurses to provide quality and holistic care to patients and their families, it is recommended to evaluate patients and administer nursing care with Gordon's Functional Health Patterns Model, which primarily deals with individuals in a bio-psycho-social dimension.

Abbreviations

BMI: Body Mass Index; CT: Computed Tomography; COV: Coronaviruses; COVID-19: Coronavirus Disease 2019; FHP :Functional Health Patterns; MERS: Middle East Respiratory Syndrome; PCR: Polymerase Chain Reaction; SARS: Severe Acute Respiratory Syndrome; WHO: World Health Organization; VAS: Visual Analogue Scale.

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CHAPTER 14

APPROACH IN HIV-INFECTED MOTHER AND NEWBORN

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APPROACH IN HIV-INFECTED MOTHER AND NEWBORN

Human Immunodeficiency Virus (HIV) is a Retrovirus of the Lentivirinae subfamily. It causes a chronic disease shaped by AIDS (Acquried-immunodeficiency syndrome), which progresses with opportunistic infection with suppression of the immune system. Serological tests used in the diagnosis of HIV infection were developed and put into use in 1985 (1).

The main target of infection is CD4+ T lymphocytes. As a result of the decrease in T lymphocytes, suppression of the immune system develops and causes life-threatening opportunistic infections (2). In addition, malignancy can be seen in organs. Infection, also called acute retroviral syndrome, develops within the first 1-6 weeks after the agent enters the body (3). The clinical findings in this picture are not specific to HIV infection and are highly variable. Fever (96%), lymphadenopathy (74%), pharyngitis (70%), skin rash (70%), muscle or joint pain (54%), diarrhea (32%), headache (32%), nausea and vomiting (27%), liver and spleen enlargement (14%) can be seen (4). Although these symptoms disappear within 2-4 weeks, they are contagious from this period. Despite the presence of virus in the blood of the infected person in the early period of infection, antibodies and antigens cannot be detected. This period is the 'window' period. Antibodies against the virus can develop in 6-12 weeks in most of the infected cases. Although the symptomatic phase develops within 5-8 years after infection, there are cases where the asymptomatic phase lasts for a short time, especially as a result of infection with virulent strains. In the group called long-term survivors (LTS), this period can reach 18 years. Viruses isolated from the infected person in

this patient group do not have a cytopathic effect and the proliferation rate is slow and the viral load is low (5).

According to UNAIDS (The Joint United Nations Program on HIV/AIDS) data; As of 2019, there were 39 million HIV-infected cases worldwide (6).

Contamination rate with blood products has decreased due to routine HIV screening test before transfusion. People with sexually transmitted diseases are at high risk of transmission and transmission of the virus. Although there is a small amount of virus in fluids such as saliva or tears, there is no clear information showing that it plays a role in transmission. Another mode of transmission is transmission to the baby of the infected mother transplacentally or with milk at the time of birth or during breastfeeding (7-10).

Diagnosis And Management In Newborns And Infants Younger Than 18 Months, Whose Mother Is HIV-Positive

Diagnosis of newborns and infants younger than 18 months is special because of the long-term positive detection of transplacental antibodies transmitted from the mother. Due to maternal antibodies passed from mother to baby, ELISA can remain positive up to 18 months. In cases where there is a risk of fetal transmission from the mother, not delaying diagnosis and treatment will reduce morbidity and mortality. Therefore, ELISA is not used in infants younger than 18 months. Instead, molecular tests that allow detection of HIV DNA or RNA should be used for diagnosis (11).

The risk of HIV infection is low if the seropositive mother received the correct anti-retroviral therapy during her pregnancy and viral suppression was achieved. The first diagnosis is between 14-21 days; the second test is between 1-2 months; 3. The test is recommended to be done between 4-6 months (12). Babies born to mothers with a seropositive diagnosis, with detectable viral load near birth, or to mothers whose viral suppression could not be achieved despite treatment are in the high-risk group. In this case, serial HIV tests are performed immediately after birth. It is recommended that the second test be done between 14-21 days, the third test between 1-2 months, and the fourth test between 4-6 months. If HIV-1 DNA or RNA tests are positive, the test is repeated as soon as possible and if it is positive again, it is considered HIV-1 positive. If HIV-1 DNA or RNA tests are negative, the baby is considered HIV-1 negative. If infant becomes symptomatic, tests are repeated (13).

Breastfeeding is not recommended for the baby. It should not be forgotten that the baby is at risk during the period of breastfeeding**.**

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CHAPTER 15

BREAST MILK AND MICROBIOTA

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1. INTRODUCTION

Microbiota is the whole of the microorganisms (including bacteria, viruses, archaea and fungi) that live together in various parts of the human body (1, 2). Microbiota elements such as bacteria have been detected in fluids that were previously thought to be sterile, such as amniotic fluid and breast milk (3). It is emphasized that the development of a healthy microbiota is of great importance for the future health of children. Many diseases such as asthma, diabetes and obesity have a close relationship with the damaged or underdeveloped gut microbiota. Breast milk contains a large number of non-pathogenic bacteria that are transferred to the baby for the development of a healthy intestinal microbiota.

2. DISCUSSION

During pregnancy, the mother's health, the drugs used, the mode of delivery, breastfeeding, factors related to the baby's common living space and other nutrition-related factors of the baby cause changes in the microbiota composition.

In a study, it was reported that the most decisive effect among the factors affecting the intestinal microbiota of the infant in the first 3 years of life is breastfeeding. Up to 80% bifidobacteria were found to be dominant in the intestines of exclusively breastfed infants (4). Breast milk microbiota differs according to the mode of delivery and gestational week (5).

Breast milk contains predominantly Streptococcus, Staphylococcus, Lactobacillus, Bifidobacterium, Enterococcus, and Propionibacterium (6). Obligate anaerobic microorganisms of intestinal origin Blautia, Clostridium, Collinsella, and Veillonella species and short-chain fatty acid producing Coprococcus, Faecalibacterium and Roseburia are present in breast milk (7).

Staphylococcus and Streptococcus species in breast milk have been reported as the dominant microorganisms in all studies, while Pseudomonas and Lactobacillus strains have been reported as common strains in many studies (8).

It has been included in different studies that the content of maternal microbiota varies with geographical regions, ethnicity, mother and baby factors, and the presence of siblings at home, baby's gender, baby's birth weight variables were also evaluated (9). It has been reported that the most effective factors in breast milk microbiota are mother's body mass index, mode of delivery and only breastfeeding (10).

Microbial diversity is higher in the milk of women who have given birth normally. It has been reported that Bifidobacterium and Lactobacillus are predominant in breast milk. Cesarean section also has an effect on breast milk microbiota. There are also differences in the breast milk microbiota of those who have had an emergency or elective cesarean section (11). Antibiotic use in the intrapartum period adversely affects breast milk microbiota, regardless of normal delivery or cesarean delivery (12).

Breast milk microbiota content of mothers with a high body mass index and obese mothers is less diverse (13).

In a study published in 2019, it was reported that expressing breast milk by hand and pump affects the diversity of breast milk microbiota. It has been reported that Bifidobacterium strains are more common in hand-expressed breast milk (14).

The rate of feeding only with breast milk in the first 6 months of life in Turkey is 41% (15). Babies who are not breastfed are more susceptible to pathogenic microorganisms and infections. Breast milk is the main source of bacteria in the gut of infants receiving breast milk. $1X10^5$ to $1X10^7$ bacteria can develop in the intestines of a baby who consumes 800 ml of milk a day (16). It is expected that the relationship between pregnancy, childbirth and breastfeeding periods and the microbiota will be understood and the uptake of microorganisms, which are seen as determinants of health, in infancy will increase. Changes in the microbiota can affect the pregnancy process and the baby positively or negatively. From the beginning of the intrauterine life, the mother's vaginal microbiome, being obese, malnutrition, antibiotic use, allergy status, mode of delivery, newborn birth weight, and breastfeeding status affect the microbiota of the baby. It is important for health professionals to know the impact of microbiota on health. Especially midwives and nurses working in the field of women's health have an important role in the development of a healthy microbiota.

It is important for midwives and nurses to know the conditions that will affect the fetus and newborn microbiota, to be aware of the physiology of normal labor and to create an environment that supports vaginal delivery as of the prenatal period. It is recommended to follow the necessary steps for normal successful breastfeeding, to use evidence-based practices, to pioneer in supporting breastfeeding and to provide counseling.

3. CONCLUSION

Breast milk is an important nutrient that contains non-pathogenic microorganisms and contributes to the development of the baby's microbiota. Microbiota development in the early period is decisive for the future health of the baby. Therefore, it is important to refine breastfeeding rates. In order to increase breastfeeding rates, it may be recommended to take initiatives to encourage breastfeeding. In addition, it may be recommended to conduct new research on maternal nutrition in order to improve breast milk microbiota during breastfeeding.

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CHAPTER 16

RATIONAL DRUG USE IN PREGNANCY

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Rational Drug Use, as defined by WHO in Nairobi in 1985, is "the state of individuals to provide the appropriate drug according to their clinical findings and individual characteristics, in the appropriate time and dose, at the most affordable cost and easily. The failure to meet one or more of these conditions is characterized by irrational drug use (1).

Pregnant women frequently take prescription, over-the-counter (OTC) and herbal products. Many organ systems undergo structural and physiological changes as a result of the pregnancy. The pharmacokinetics and pharmacodynamics of medications may be affected by these changes (2).

Pregnancy has a significant impact on the body's physiology. These are (3,4);

- Plasma volume constantly increases.
- Pregnancy causes a two to threefold increase in iron requirement both for hemoglobin synthesis and for the fetus and the production of certain enzymes.
- The need for folate and vitamin B12 is multiplied by 10–20 times and by two times, respectively.
- It increases the risk of venous thrombosis in women during pregnancy and postpartum.
- Myocardial contractility and cardiac compliance are enhanced.
- The mucous membranes of the upper respiratory tract increase risk of edema.
- It becomes prone to urinary infections.
- It delays gastric emptying and prolongs small intestine transit time by approximately 30-50%.
- The thyroid gland produces more thyroid hormones during pregnancy.

1. Risk Assessment

In 1979, the FDA introduced a five-letter risk category for drugs as A, B, C, D, or X that could lead to the development of birth abnormalities if taken by pregnant women. Pregnancy risk categories are shown in Table 2 (5).

Table 2. FDA Pregnancy Risk Categories

Categories	Definition
A	In controlled studies, it has been stated that it does not show a teratogenic risk for the fetus in the first trimester of pregnancy.
B	There is no evidence of teratogenicity in preclinical investigations or research in pregnant women.
C	Even though teratogenicity has been revealed in preclinical studies and there are no adequate or well-controlled studies in humans, the prospective advantages of the medicine may justify its usage in pregnant women.
D	Even though research and post-marketing experience or trials on people have shown that the medicine poses a risk to fetus, the potential benefits may outweigh any concerns.
X	It has been established in preclinical and clinical trials that the drug has the potential to harm a fetus, and there is proof of this risk based on research or data gathered after a product has been on the market for some time.

FDA has been using this classification for many years, but in 2015, devised a new evaluation model for the use of drugs during pregnancy, considering that this classification was insufficient. As shown in Table 3, the evaluation model has been in use since that year (6).

Table 3. FDA new model of expression of drug use in pregnancy

Title	Contents
Pregnancy registration system	Pregnancy Information.
Risk statement	In all pregnancies, regardless of prior drug usage, there is always a potential of an abnormality, loss, or other unfavorable events. Pregnant women who take this drug may have an increased risk of developmental issues during their pregnancy.
Fetal risk summary	Based on all available research, this section discusses the drug's potential to increase the risk of developmental abnormalities in people as well as other pertinent concerns. It also considers how the medication is administered.
Clinical Assessment	This section delves into the following topics in depth: Accidental Exposure Prescriptions for pregnant women: Some of the things during pregnancy should know are how to modify dosage during pregnancy, pregnancy-specific or enhanced maternal adverse reactions, the effects of dose, timing, and duration of drug exposure during pregnancy, and potential newborn problems and essential interventions.
Data	Human and animal data are presented separately, with human data first. If any problems in embryonic development or other harmful consequences are found during the trial, they are listed below. It includes information on the type of study, the type of exposure (dose, duration, timing), and any fetal developmental defects or other harmful effects that have been detected. Positive and bad experiences, the number of volunteers, and the length of the study are all examples of human data. Animal data comprises the types of animals tested and doses are expressed in human dose equivalents.

Medical and scientific professionals in Australia have created a database and prescription system for pregnancy drugs based on the best-known research about the dangers of taking specific medications while pregnant. Pregnant women's healthcare providers have access to this information, which is not available to the general public. There is no hierarchical structure in the Australian system, unlike the FDA system. A class B drug is not necessarily safer than A class

C drug. According to the Australian Drug Evaluation Committee (ADEC), medicines are categorized into pregnancy risk categories in Table 4 (7).

Table 4. ADEC Pregnancy risk categories

Categories	Definition
A	Many pregnant and childbearing women take these drugs, and there has been no increase in the incidence of abnormalities or injury to the fetus, either directly or indirectly.
B1	Drugs that do not increase the risk of abnormalities or other negative effects on the fetus can be safely used by pregnant women and women of reproductive age. In animal studies, no evidence of an increased risk of prenatal damage has been discovered.
B2	Drugs that do not increase the risk of abnormalities or other negative effects on the fetus can be safely used by pregnant women and women of reproductive age. There is no evidence of an increased risk of fetal damage in animal trials, according to the available data.
B3	Drugs that do not increase the risk of abnormalities or other negative effects on the fetus can be safely used by pregnant women and women of reproductive age. Animal studies have revealed evidence of an increased risk of embryonic damage, but the significance of this discovery is still debated.
C	Fetal and neonatal toxicity is defined as a pharmacological effect on the fetus or neonate that does not result in deformities.
D	Drugs that are known to cause, or are suspected of causing, an increase in human prenatal abnormalities or irreversible damage. These drugs could possibly have negative pharmacological consequences.
X	Drugs that have a high chance of causing harm to the fetus. It should not be used if you are pregnant or think you might be pregnant.

Drugs are able to pass into breast milk in specific amounts. The importance of safe medication use during breastfeeding cannot be overstated. The American Society of Obstetrics and Gynecology's classification system for lactation medication use is widely acknowledged. Classifications of medications range from L1 to L5, according to this approach (8).

2. Antianemic Use in Pregnancy

For all three trimesters of pregnancy, the World Health Organization (WHO) defined anemia as a Hgb value below 11 g/dl (9). It's critical to give oral iron in the appropriate dose and for a sufficient time. Oral iron is a low-cost, effective

and widely used drug. In order to treat anemia and replace iron storage, oral iron should be taken for six months. Severe anemia, inadequate absorption due to small bowel disease, inflammatory bowel disease, chronic kidney disease, cancer patients and the need for rapid correction of anemia are some of the conditions where bleeding persists despite oral iron therapy (blood loss is greater than the amount absorbed from the gastrointestinal tract). It is possible to administer a single parenteral dose of 1000 mg of iron, despite the fact that a maximum of 25 mg of iron can be absorbed per day. Parenteral iron avoids intestinal absorption and serum protein binding. Because of this, iron that isn't bound to protein in the serum or bloodstream is harmful. Due to peroxidation, which destroys cells and tissues by generating hydroxide and oxygen radicals, free iron should be avoided at all costs. In order to prevent iron overload, parenteral iron should only be administered to patients with known iron storage (10,11).

3. Antibiotic Use in Pregnancy

Antibiotics should be investigated for potential teratogenic effects. Pregnant women are increasingly prescribed antibiotics, which account for a large percentage of all recommended medications. Various studies have indicated that antibiotics are prescribed to one in four pregnant women.

The use of antibiotics during pregnancy is attributed to the fact that pregnancy predisposes the body to infection. The body's susceptibility to infection is primarily due to changes in hormones and the body's immune system. The rise in genitourinary infections is mostly to blame for an increase in antibiotic use. According to a recent study, vaginal candidiasis, urinary tract infections, and respiratory tract infections account for 72% of antibiotic use in Germany. Pregnant women should be aware of the risks associated with antibiotic use. Both short- and long-term impacts on a developing fetus are possible with antibiotics. The degree of teratogenicity can be modified by a number of factors. These include the gestational period, the dosage and length of medication, genetic predisposition, environmental influences, and the degree of drug transfer across the placenta. Antibiotic use in pregnant women still lacks a standardized strategy for the rational, safe, and effective administration of these drugs. The availability of clinical evidence in this population is limited due to ethical constraints. Doctors treat pregnant patients using a risk-benefit approach depending on the stage of pregnancy, severity of condition and possible risks to fetus. Emerging antibiotic resistance issue has a substantial impact on the use of antibiotics in pregnant women with excessive and incorrect use of these drugs, which are the primary drivers of antimicrobial resistance. Changes in antibiotic

use, increased mortality and morbidity and increased healthcare costs are the consequences of the antimicrobial resistance epidemic (12–16).

4. Enoxaparin Use in Pregnancy

There is a fourfold increase in the risk of thrombosis during pregnancy, which is a prothrombotic state. American Society for Clinical Pathology (ASCP) states that deep vein thrombosis and pulmonary embolism are two of the major causes of maternal death in developed countries. Only a small number of medications are regarded safe and appropriate for usage during pregnancy since anticoagulation poses a risk to both the mother and the fetus (17).

Pregnant women should use low molecular weight heparin as an anticoagulant. Pregnant women at risk of thrombosis and pregnancy difficulties have increasingly been prescribed Enoxaparin over the past two decades. Preventing venous thromboembolism and pregnancy loss in thrombophilic women are the primary uses of anticoagulation therapy. As well as treating thromboembolisms of the veins, it is also used to prevent arterial thromboses in pregnant women with artificial heart valves and to avoid late pregnancy problems such preeclampsia and intrauterine growth restriction (IUGR). Enoxaparin is safe for the fetus because it does not cross the placenta. Mild localized allergic reactions occur in 2% of pregnant women, and increased bleeding occurs in 2% of pregnant women, depending on the dose. This condition is extremely rare, and bone resorption does not pose a threat to the patient's health (18).

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CHAPTER 17

GRAVIN GENE AND CANCER

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1. Introduction

Cancer is a disease caused by the uncontrolled proliferation, growth and spread of abnormal cells. Many hereditary and environmental factors increase the risk of developing cancer. In cancer research, various molecules that can be synthesized incorrectly or abnormally on the basis of various mutations and aberrant methylations in point intracellular signaling pathways have recently attracted attention. A group of molecules that attract attention on this basis are A kinase-binding proteins, which are indirectly required for the effect of tumor suppressor genes, especially in cell pathways. Many studies have demonstrated that the family of A-kinase binding protein is important for signal transduction in cancer (1-4).

2. A-Kinase Binding Proteins

Protein kinase enzymes play an important role in the phosphorylation of proteins. Most of the proteins in the cell are regulated by phosphorylation. Protein kinases phosphorylate their targets by transferring the phosphate group of ATP (or GTP) to its substrate. Protein kinases are important in signal transmission in the cell. When the appropriate signal receive protein kinases adds phosphate to the amino acid serine, threonine, tyrosine, and histidine in other proteins. Addition of phosphate to the target protein (phosphorylation) alters the enzyme activity of the protein, its cellular localization or association with other proteins. There are many types of protein kinases. Protein kinase A (PKA) is cyclic AMP (cAMP) dependent and becomes active with an increase in cAMP level. Activated PKA changes the activities of proteins by providing phosphorus transfer to serine/threonine residues of proteins. PKA is a holoenzyme with serine-threonine kinase

activity. It has four subunits. Its two subunits are regulators. It is denoted by the symbol R. The other two subunits are catalytic. It is denoted by the symbol C. Catalytic subunits are Ca, Cb, Cg. They are expressed by three different genes. Regulatory subunits are expressed by four different genes, namely R1 alpha, R1beta, R2 alpha, R2 beta.

Various signaling molecules, such as hormones, stimulate the signal transduction cascade. Signalling molecules activate the excitatory G protein GS by stimulating G protein-coupled receptors (GPCRs) and activated GS alerts adenylyl cyclases. Cyclic AMP pathway resulting in the formation of cAMP from ATP by the adenylate cyclase enzyme. It is mediated by cAMP-dependent protein kinase (protein kinase A). Inactive protein kinase A includes two catalytic and two regulatory subunits. Binding of cAMP to the regulatory subunit causes a change in its structure, as a result of which the regulatory and catalytic subunits are separated from each other. Activated catalytic subunits phosphorylate target protein molecules (Fig. 1) (5-11). Phosphorylation causes activation of some proteins and inactivation of some proteins (9). cAMP signaling is terminated by degradation of cAMP. Phosphodiesterase enzymes hydrolyze cAMP to AMP.

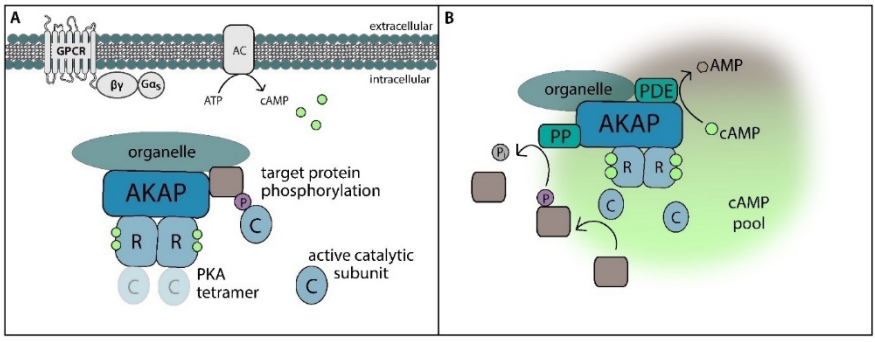

Figure 1. Compartmental pattern of cAMP signaling (11)

Protein kinases are found in the cell bound to some proteins. Proteins that bind PKA are designated A kinase anchor proteins (AKAP). The binding of protein kinase A to some compartments of cell by AKAP increases the protein kinase A signaling specificity and accelerates cellular responses to signals. In addition, AKAP regulate the functions of protein kinases (11).

A-kinase binding proteins are a group of structurally different proteins with the general function of binding to the R subunit of PKA and maintaining it at specific locations in the cell (12). At least 20 AKAPs have been cloned (13).

A-kinase binding proteins are the member of approximately 50 scaffold proteins. Its function is the intracellular positioning of protein kinase A. AKAP interacts directly with other signaling proteins to cross-react between signaling systems. AKAPs localize intracellular signals. Different AKAPs can be connected to the same intracellular component. Some AKAPs also bind to different kinases, such as protein kinase C. AKAP and its interactions play a key role in various physiological functions such as cardiac myocyte contractility and vasopressin-mediated water reabsorption (11–13). AKAPs are attach to various structures inside the cells such as cell membrane, sarcoplasmic reticulum, mitochondria, nucleus, and actin cytoskeleton.

AKAP is usually named according to the molecular masses of each anchor protein and consists of two functional regions. Amphipathic helical portion complexing with the first region regulator; the second is the region that provides attachment to intracellular structures.

Disturbances in intracellular signaling pathways can cause cells to proliferate uncontrollably and become resistant to apoptosis. Treatments targeting disturbances in signaling pathways are intensively researched and come into clinical use. cAMP is the important signal transmission pathway. The cAMP pathway exerts its intracellular effects through protein kinases. A kinase-stabilizing protein family regulates the intracellular localization and functions of protein kinases. Some studies have shown that expression of the AKAP family is associated with cancer development (11).

2.1. Gravin (AKAP 12/AKAP 250)

Gravin (AKAP 12) encodes a fixative protein that is a member of the AKAP family. Gravin is associated with PKA and PKC, and it plays a role in the tumor supression (11–14).

AKAP 12 was originally named gravin because it was first detected in the serum of patients with myasthenia gravis as minor autoantigen. It was later shown to be orthologous to src supressed C kinase and identified as a tumor suppressor gene in rodents. It is demonstrated that gravin also binds RII isoforms of PKA led to its renaming as A kinase-binding protein-12 (11–17).

Gravin (AKAP 12), a molecule from the AKAP group, is a polybinding protein and shows activity in the cAMP signal pathway on the basis of its protein kinase binding structure. The cAMP signaling pathway is a well-characterized signal transduction cascade. The cAMP, as a second messenger, activates cAMP dependent PKA. The PKA tetramer has two catalytic subunits and two

regulatory subunits. PKA is involved in many key cellular functions such as cell growth and division, actin cytoskeleton remodeling, ion channel conductivity and metabolism. Controlling the intracellular organization of PKA, gravin is effective in stimulating many of the enzymes within its cellular pathways, such as kinase and phosphatase. The fact that the gravin molecule controls the PKA and PKC molecules contained in the cell cycle highlights the role of this molecule in preventing cancer formation. Signaling pathways regulated by AKAP12 and AKAP12 play a critical role in the development and advance of various cancers (18–20).

Three different isoforms of gravin protein, weighing 305, 287 and 250kDa, have been identified and named as AKAP 12/A, AKAP 12/B, AKAP 12/C. When the distribution of gravin in tissues was examined, it was observed that it was found in fibroblasts, peripheral and central nervous system components, adrenal medulla, somatic layer of Bowman's capsule and in the smooth muscle cells of some organs. It has been located plasma membrane and endoplasmic reticulum of the cell. It takes part in the localization of intracellular signals. Gravin plays a role in the proliferation of endothelial cells and their response to damage. It is also important for maintaining cell integrity. Specific role of gravin include suppression of malignant cancer, particularly aspects of metastatic progression. In some cancer studies, it has been shown that the level of gravin gene expression decreases, and in cancer cell the ability to metastasize increases with the decrease of gene expression level. Recent data describe the direct function of gravin in cytokinesis completion and also play important role as a negative regulator of cell senescence (15).

The chromosomal region of gravin gene is identified as 6q24-25.2. This locus can affect the lung cancer risk. The serum response factor (SRF) regulate gravin expression in this chromosomal structure. It has been reported that this regulatory region is inactivated by hypermethylation in some types of cancer. One of these types of cancer is lung cancer (18-20).

Gravin is a tumor suppressor gene that is a member of the A kinase-stabilizing protein family. It plays a role in the physiology of sperm development, testicular development and neuron development. In additon, it plays a role in the transmission of intracellular signals and the localization of these signals. Its role in oncogenesis has been demonstrated in many experimental studies. It has been shown that gravin expression is decreased in gastric adenocarcinoma, prostate carcinoma, lung adenocarcinoma, childhood acute lymphoblastic leukemia, skin cancer and breast cancer. When demethylating agents are applied in cell culture studies it has been shown that oncogenic features regress (21–24).

Gravin modulates mitogenesis by fixing key signaling proteins (such as PKA and C) and regulating the gene expression involved in apoptosis and cell cycle. It suppresses cancer cell viability and growth by inducing apoptosis via caspase 3, Bax expression upregulation and Bcl-2 expression downregulation (21). Gravin expression has also been investigated in myeloid malignancies. Its expression has been shown to be reduced in AML, KML and MDS. Some studies have shown that gravin expression is decreased in patients with papillary thyroid carcinoma. Gradually, genetic testing of many hepatocellular carcinoma patients began to focus on gravin. Gravin is downregulated in hepatocellular carcinoma tissues as a result of DNA methylation. Gravin has been found to act as a cancer suppressor in hepatocellular carcinoma. Analysis showed that miR-103 binds to the gravin 3'UTR region and expression of miR-103 is associated with gravin (21, 24). Some studies demonstrated that gravin may be a biomarker and a treatment target for several malignancies.

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CHAPTER 18

CELL ADHESION MOLECULES (CAMS) AS TARGETS IN CANCER THERAPY

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1. Introduction

Cancer is a worldwide important disease group and the second cause of the common deaths globally(1). The suppression of the immune system is a considerable feature of cancer, which leads to growth, survival and metastasis of tumour cells(2). The spread of cancer into distant organs in the body is the reason to pursue invasion of tumour cells, exist of cancer stem cells, the invasion of lymphatic blood vessels and the proliferation of other cancer tissues (3). One of the factors that contribute to the maintenance or growth of tumour cells is the presence of various surface receptors that are actively acting on the cell surface as depend on the function of the ligands associated with these receptors (4). These receptors mainly include growth factor and cytokine receptors, tumour necrosis factor receptors and ligands, cell adhesion molecules (CAMs) etc.

Physiological and biochemical activities within the cell are regulated by binding of various signals to their cell surface receptors. These receptors are contributed to carcinogenesis and tumour development. CAMs receptors may able to play an important role in the transformation of the cell to apoptosis or cancer cells (5). CAMs also play a crucial role in mediating cell-cell

interactions and communication between cells and environment (3). The CAMs can be used in the form of a biomarker as a therapeutic target to the identification and diagnosis of these molecules for treatment strategies, in various types of cancer including melanoma, breast, renal, ovarian, gastric, colorectal cancers (6). The use of these biomarkers is become an important for the early diagnosis of the diseases with the occurrence of diseases such as cancer and diabetes caused by mutagenic, carcinogenic agents and various chemicals (7).

2. Cell Adhesion Molecules (CAMs)

Receptor ligand interaction, which is common in all receptors, is the initiation of physiological changes as a result of specific binding of ligand to the receptor (5). These changes, as well as disorders affecting cell-cell and cell-extracellular matrix (ECM) interactions, can consequently lead to various diseases such as cancer (8, 9). Cell adhesion consistently communicates with cell-cell or cell-ECM. Errors in the CAMs trigger the formation of tumour and metastasis. CAMs that have various roles in cell recognition, growth, differentiation, inflammation, migration, metastasis, and invasion of cells are taken important tasks in the growth of cancer cells (Table 1). CAMs are generally divided into four classes according to their functional and structural properties; integrins, selectins, cadherins, and immunoglobulin superfamily (IgSF), also involve proteoglycans, EpCAM, CD44, mucin (Figure 1) (10, 11).

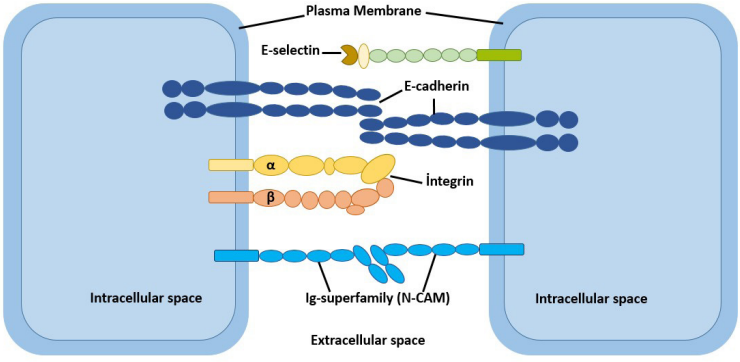

Figure 1. Cell adhesion molecules (CAMs) include selectins, cadherins, integrins, Ig superfamily (IgSF), and others. CAMs are typically transmembrane proteins involved in both cell–cell and cell–matrix interactions.

CAMs have an important task in the binding and interacting of cells with ECM and other cells. These interactions take place via the CAMs that have functions in both cell-cell and cell-ECM components. Thus, CAMs play an important role in regulation of cell signalling, particularly on endothelial cells (12). Cellular processes such as signal transduction, apoptosis, immunity, recognition, and communication are also realized by CAMs. During cancer development, the cell growth and proliferation increases as a result of damage of the CAMs (13). For example, in tumour growth, the tumour cells easily spread into the ECM for tumour cell metastasis in non-small cell lung carcinoma that the E-cadherin is lost (8, 14).

Furthermore, the tumour cells also occur by triggering the transformation of various adhesion molecules in tumour angiogenesis. The members of CAMs such as integrins, selectins, cadherins, IgSF contribute to both cell–cell and cell–matrix interactions in each step of tumour vascularization. CAMs mediate participating in the signal events which arrangement the elongation and the maturation of tumour vessels (12).

This chapter aims to highlight the importance of the role of CAMs as a biomarker and a therapeutic target in various cancer types. To define in earlier stage and to understand these molecules involved in cancer mechanisms, CAMs can be used in the diagnosis and the target strategies of cancer treatment such as tumour angiogenesis, cell migration, metastasis and invasion.

2.1. Integrins

Integrins are the most important cell adhesion family that provide cell- ECM interactions, connecting the cellular cytoskeleton to ECM, and like cellular matrix adhesion receptors. Integrins are type I transmembrane proteins emerged heterodimeric structure in resulting non-covalent binding of an alpha (α) unit and a beta (β) unit. Up to date, 11 beta subunits and 18 alpha subunits had been defined among integrins and giving raises to 24 different integrin heterodimers in mammals. Integrins have the size of alpha subunits between 12-14 kDa and the size of beta subunits 10-12 kDa. The both subunits of molecule are necessary for their functional activities (15, 16,17, 18, 19).

Integrins are significantly take part in cancer cells and inflammatory diseases that is particularly comprise metastasis, cell proliferation, cell adhesion, cell migration, tissue inflammation, dysregulation of cell in ECM and gene expression. Integrins binding ECM components are also transmembrane receptors triggering signal of cascades that coordinate cellular events

throughout cancer development, body homeostasis, and diseases (20, 21). Integrin α3β1 is highly expressed in glioma cells of normal and tumour tissues of the brain. Integrin α3β1-mediated interaction with laminin-5 stimulates adhesion, migration and invasion of malignant glioma cells (22). Integrin β1 subfamily (very late antigen: VLA), associates with various subunit α integrin chains to form receptors for binding ECM proteins. For colorectal cancers, Nigam et al. found a consistent loss of the α2 and β1 integrin subunits in the poorly differentiated adenocarcinomas (23). Carcinoembryonic antigen (CEA) expressions were also preserved but with basolateral accentuation seen in tumours (23). Tumour growth and metastasis in cancer progresses is important for ECM-rich region observed vasculogenic mimicry (VM) formation that can be used as a therapeutic approach for malignant cancer via to carry out inhibition of integrin β1 (ITGB1). ITGB1 is overexpressed in malignant cells and plays a critical role in various cancer phenotypes and tumour metastasis (19). Studies related to a therapeutic metastatic target showed that miR-205 expression inhibits tumour metastasis and growth by down-regulating integrin α5 (ITGA5) in triple negative breast cancer (TNBC) (24). Integrin αvβ3 is highly expressed on endothelial cells for angiogenesis formation in cancers such as breast cancer, glioblastoma, and melanoma. The matrix metalloproteinase-14 (MMP-14), MMP-2 and integrin αvβ3 are targeted as therapeutics. (25). The integrins α3β1, αvβ1 and α6β1 in various cell lines of ovarian carcinomas are important for cancer cell migration, proliferation, adhesion and invasion, and these integrins mediate interactions with ECM components such as collagen, laminin and fibronectin as a therapeutic target for ovarian carcinoma (26). It has been reported that integrin α9 subunit (ITGA9) plays a key role in different cellular processes such as angiogenesis and lymphangiogenesis at enhanced epithelial-mesenchymal transition. The overexpression of ITGA9 inhibits cell proliferation, migration, tumour growth and metastasis in hepatocellular carcinoma (HCC) and it can be used as a therapeutic target in cancer (21).

In summary, the integrins play a major role in cancer cell and their environment interactions. The other main role of integrins is the initiation of signal transduction pathways besides the cell adhesion, survival, proliferation, migration, metastasis and apoptosis. Cell survival signals will transmit if cell-ECM adhesion is appropriated. Therefore, the integrins can promote cell proliferation via signalling pathways such as the focal adhesion kinase (FAK) activation. The up-regulation of integrins facilitates the invasion and metastasis of cancer cells (27). The studies have been carried out to develop the integrin-

targeted therapy strategies for various cancer types. Some anti-integrin drugs such as abituzumab, intetumumab and cilengitide are used in clinical trials (27, 28). For instance, αv, α5, β1, β3, and β5 integrins have improved survival and metastatic characteristics in lung cancer cells. These integrin molecules may be a target as therapeutic biomarker in lung cancer to prevent chemotherapeutics metastasis with understanding anti-cancer approaches, development of anti-cancer drugs (29).

2.2. Selectins

Selectins are other a member of the CAMs interacting with carbohydrate ligands on endothelial and leukocyte cells. Selectins are classified according to different cell types which they are synthesized; leucocyte (L-selectin), endothelium (E-selectin), platelet (P-selectin), and their lengths are 17, 32, 35 amino acids, respectively. All selectins are a single chain transmembrane glycoprotein with a similar modular structure: an extracellular domain, a transmembrane domain and an intracellular C-terminal cytoplasmic tail. The extracellular domain of the selectin molecules consists of three part; the N-terminal carbohydrate recognition domain, Ca^{+2}-dependent lectin domain, an epidermal growth factor (EGF)-like domain and a varying number of short consensus repeats (2, 6 and 9 for L-, E-, and P-selectin, respectively). Selectin ligands, unlike other cell adhesion molecules, can consist of a lipid carrier protein characterized by some carbohydrates, as ligand interactions are a carrier protein. The lectin domain of selectins functions as a glycoprotein, allowing it to bind to glycoproteins of other cells. Thus, selectins play an important role in maintaining of tissue integrity. (11, 30, 31). Selectins enable temporal cell-cell adhesion, leukocytes to recognize endothelial cell vessels in the inflammatory process and cellular regions to which they will migrate (4).

Selectins also mediate adhesion of circulating cancer cells to stimulated endothelial cells and facilitate metastasis. Some studies have shown that selectin plays a major role in the binding to endothelium of circulating cancer cells. E-selectins are calcium-dependent lectin-type transmembrane proteins that are induced in skin, bone marrow endothelial cells and found in inflammatory regions. E-selectin promotes progression and metastasis of breast cancer. E-selectins are overexpressed in tissues such as lung, liver and brain cells. Several studies have highlighted the metastatic importance of E-selectin for the spread of cancer cells (31, 32, 33 34). E-selectin is activated by some signal pathways in cancer cells such as PI3K/Akt pathway, pro-migratory p38 and pro-survival ERK pathways (35). L-selectin is commonly expressed on leucocytes,

granulocytes and monocytes and plays an important role in formation of the cancer (32, 34). The decrease of L-selectin expression reduces metastasis of cancer cells (32). P-selectin is a protein binding the carbohydrate ligand and depending on the presence of calcium ions, expressed on activated platelets and endothelial cells (31, 34). In addition, the higher levels of all selectins were observed in colorectal cancer patients with lymph nodes (stage III) and liver (stage IV) metastases (36). Selectins play the main role in tumour progression including metastases and the results indicate that P-selectin may a more potential target in the prevention and attenuation of metastasis.

2.3. Cadherins

Cadherins are a transmembrane protein family consisting of extracellular cadherin domain repeats that provide Ca^{+2} dependent cell-cell adhesions between extracellular regions of neighbouring cells (37). There are at least 24 cadherin subfamilies. They enable the interaction in cell types of various tissues such as epithelial (E-cadherin), vaso-endothelial (VE-cadherin), neural (N-cadherin) and placental (P-cadherin). E-cadherins have an important role in intercellular adhesion, which can be able to cause invasion and metastasis in epithelial tumour cells. N-cadherins are expressed in smooth muscle, neural tissues, endothelial cells and fibroblasts. P-cadherins are expressed in myoepithelial mammary, lung and skin cells. Cadherin genes, especially E-cadherin, are considered as a tumour suppressor gene. Their reduced expressions lead to dysfunction of the cell-cell adhesion; thus it is trigger neoplastic progression (38). But, the overexpression of N-cadherin is associated with cancer metastasis (39). P-cadherin is important in maintaining normal tissue and may indirectly participate to tumorigenesis, upregulating in some cancers (39). Adherens junctions are known as cadherins located at intercellular adhesion site (junction) of the plasma membrane and interacted with cytoskeleton and cytoplasmic proteins (4, 38).

Cadherins contribute to the spread of malignant tumour cells into the blood or lymphatic circulation due to the loss of intercellular adhesion and they could be associated with invasion in many human cancers. Briefly, cadherins, especially E-cadherin and N-cadherin, function as factors participating tumour invasion, metastasis, angiogenesis and tumour immune response (39). Thus, abnormal expressions of cadherins play a role as markers of tumour prognosis. Restoring cadherins could be potential targets for cancer therapy (13, 40). Nigam et al. reported a decreasement in expression of E-cadherin in 5/5 poorly differentiated

adenocarcinomas (23). Cadherins association with β-catenin is crititical for cell-cell adhesion in epithelial cells. The deterioration of this association leads to an enhancement in malignancy in epithelial cells (41).

2.4. The immunoglobulin superfamily (IgSF) CAMs

The IgSF is a largest family of CAM proteins that associated with the recognition, binding, and adhesion processes of cells. Most of the IgSF members include type I transmembrane proteins with a cytoplasmic tail, a single transmembrane domain, and an extracellular domain (containing one or more Ig-like domains) interacting with many cells (42). The neural cell adhesion molecule 1 (N-CAM1) is the best known a member of the IgSF CAMs. N-CAM1 is generally expressed in various cells and tissues comprising the brain and pancreatic endocrine cells such as skeletal muscle, glia, neurons and natural killer (NK) cells (43). N-CAM1 plays a role in cell-cell interactions throughout the nervous system and many tumours of neuroectodermal derivation (44). NCAMs are continuously expressed in many types of cancers, such as small cell lung cancer, neuroblastoma, glioblastoma, rhabdomyosarcoma, brain tumours, multiple myeloma and acute myeloid leukaemia. It may be a target for antibody-based immunotherapy (45).

Human epithelial cell adhesion molecule (EpCAM), which is a transmembrane glycoprotein, is expressed by normal and neoplastic epithelial cells. In addition to tumour aggressiveness, EpCAM is highly expressed in a variety of carcinomas. An excessive and irregular expression of EpCAM in tumour tissues and stem cells is used as a biomarker with metastasis and poor prognostic characteristics in epithelial cancer cells. Although there is a relationship between EpCAM activity and carcinogenesis, the mechanisms in which EpCAM supports malignancy and its role in cancer progression are not yet fully known (46, 47).

Activated leukocyte cell adhesion molecules (ALCAMs) are cell adhesion molecules that belong to immunoglobulin superfamily, both heterophilic and homophilic, providing cell-cell interactions. ALCAMs cause angiogenesis, metastasis and invasion in various types of cancers, such as colon cancer, oral squamous cell cancer, bladder cancer, oesophageal squamous cell cancer, pancreatic cancer, breast cancer, ovarian cancer, gastric cancer, and melanoma. Alterations in ALCAM expression have been shown to be associated with the prognosis of many cancer patients (48, 49). The overexpression of ALCAM in the patients with non-small cell lung cancers (NSCLC) increases malignancy

(49). ALCAM may use as a biomarker and therapeutic target in both NSCLC and different cancer types.

The gene expression of MUC18 (CD146) and L1CAM, ALCAM (CD166), which belongs to the IgSF, can be used as a prognostic biomarker and therapeutic target due to its role in apoptosis, autophagy, invasion, metastasis and migration of tumour cells for breast cancer (50). Intercellular adhesion molecule-1 (ICAM-1) is also a member of IgSF and expressed in trans-endothelial migration of white blood cells. ICAM-1 expression is play an important role in malignant disease development and is associated with metastatic spreading of lung cancer cells to lymph nodes (51).

CEA family is a significant glycoprotein in cell-cell interaction and expressed in many different cells (52). CEA are discovered as a tumour marker at colorectal carcinoma and are known 12 families of CEA-related cell adhesion molecules (CEACAMs). CEACAMs mediate cancer progression, angiogenesis, inflammation, migration and metastasis (53, 54). CEACAM1 is expressed on normal epithelia from the gastrointestinal tract, endometrium, mammary ducts, etc., as well as T and B lymphocytes, myeloid cells, NK cells. Although expression of CEACAM1 is downregulated in the epithelial cells in the early stages of various solid cancers such as colon, prostate, liver and breast carcinomas, CEACAM1-L form is overexpressed in some cancers such as thyroid, melanoma, NSCLC, gastric, and bladder carcinomas with invasiveness and metastatic spread. So, both downregulation and upregulation of CEACAM1 in various carcinomas seems complex, but CEACAM1 may be a valuable target in prognosis, diagnosis, and treatment of distinct cancer types (54).

Table 1. Some cell adhesion molecules (CAMs) and their roles in the various cancers.

CAMs	Roles	Cancer Type	References
Mel-CAM (MUC18 or CD146)	Metastasis	Melanoma, Breast cancer	55
Immunoglobulin superfamily (IgSF)	Metastasis, Cell adhesion, Immune response	Breast Cancer	50
Activated leukocyte cell adhesion molecule (ALCAM)	Migration, Invasion	Non-small-cell lung cancer (NSCLC)	49
Intercellular adhesion molecule-1 (ICAM-1)	Invasion	Non–small cell lung cancer (NSCLC)	51
Integrin α5 (ITGA5)	Metastasis	Triple negative breast cancer (TNBC)	20, 24
Integrin β1	Invasion, Radioresistance	Laryngeal cancer	58
Integrin subunit α9 (ITGA9)	Cell proliferation, Migration, Tumour growth, Metastasis	Hepatocellular carcinoma (HCC)	21
Integrin subunits α3, α6, αv and β1	Proliferation, Adhesion, Migration, Invasion	Ovarian cancer	26
Integrin subunit α9β1	Invasion, Metastasis	Prostate cancer, Colorectal carcinoma	57
E-selectin	Metastasis	Breast cancer	33
E-selectin	Adhesion, Apoptosis, Metastasis	Colon carcinoma	35
E-selectin	Metastasis, Chemoresistance	Multiple myeloma	58
P-, L- and E-selectin	Metastasis	Colorectal cancer	36
P- and E-cadherin	Metastasis	Breast cancer	59

3. Conclusion

CAMs play an important role in cell-cell or cell-ECM interactions. Errors in these molecules trigger formation of tumour and metastasis. Integrins, selectins, cadherins, IgSF members, and other CAMs molecules will be beneficial to utilize the diagnosis and treatment of many cancer patients. Consequently, CAMs can be used as a biomarker and a therapeutic target in various cancers such as breast cancer, prostate cancer, colon cancer, lung cancer, thyroid cancer etc.

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CHAPTER 19

HEPATITIS E VIRUS IN ANIMAL FOODS

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1. Introduction

Foodborne diseases caused by viruses are an important global health problem today. In recent years, information about foodborne viral infections has increased and it is emphasized that these pathogens reduce economic growth in many countries (1). According to the European Food Safety Authority (EFSA), foodborne viral agents are responsible for 12% of outbreaks (2). However, in the United States, again, foodborne norovirus (NoV) causes about 58% of foodborne illnesses (3). Hepatitis E virus (HEV) is one of the main causes of acute hepatitis worldwide (4).

Hepatitis E virus (HEV) is a foodborne pathogen with a multi-reservoir host. Since HEV is considered a zoonotic pathogen, the pig is currently believed to be the primary reservoir. However, this is not enough to justify the high seroprevalence of HEV in both developing and developed countries (4). Most cases of infection are asymptomatic in animals and therefore this virus is considered to have gone unnoticed. This virus infects humans as a result of consuming contaminated food raw or undercooked (3). It was discovered that virions remain infectious for up to 21 days at 37°C and up to 28 days at room temperature (5). HEV is transmitted by the oral-fecal route (7). HEV infection in immunocompromised patients carries a high risk for the development of chronic hepatitis (4).

[1]**Keywords:** Foodborne illness, Hepatitis E virus, zoonoses, public health

HEV is a positive-sense single-stranded RNA virus belonging to the *Orthoherpesvirus* genus of the *Herpesviridae* family (8,9). Eight different genotypes (gt) (HEV-1-8) of orthoherpesvirus were identified. Genotypes HEV-1 and HEV-2 are transmitted by the faecal-oral route and are mainly associated with waterborne HEV outbreaks in underdeveloped and developing countries (10). These human-specific genotypes are related to inappropriate wastewater management, especially in Asia and Africa (2). HEV-3 and HEV-4 infect animals such as pigs, wild boars, deer, rabbits, cows and goats, and end-host humans (11). However, it has been stated that HEV-3 and HEV-4 are excreted in the milk of ruminants (4,12-13). It is not clear that HEV genotypes HEV-5 and HEV-6 are found in pigs but are human pathogens (14). HEV-7 is also zoonotic, chronic HEV infection has been documented in a liver transplant patient through frequent ingestion of camel meat and milk (15). Recently, however, the genotype HEV-8 has been reported as camel variants (16).

2. Groups at Risk For HEV

2.1. Veterinarians and Occupational Exposure

Veterinarians have an important key role in applying knowledge about zoonoses and their impact on public health (17). An effective food safety service must provide risk-based surveillance, as communicated by European Law (EC No. 625/2017). A meta-analysis showed an increased prevalence of anti-HEV IgG in five occupations, including swine workers, butchers, meat processors, pork retailers, and veterinarians, in all countries. Therefore, they are 50% more likely to be infected with HEV than the general population (18).

The risk of HEV viral seroprevalence was studied in 593 forest workers (including woodcutters, game or fishing keepers, rangers, and controls) and 421 wild boars. As a result of the study, 31% of forest workers and 14% of wild boars proved HEV antibodies. This study is one of the first papers in which scientists have shown that these categories of workers are more exposed to HEV virions (19).

Slaughterhouses play a key role in HEV RNA transmission. Generally, infected animals are asymptomatic or present with a self-limited hepatitis. Therefore, veterinarians cannot identify and suspect positive animals in ante mortem evaluation. These animals can enter the food processing chain as "healthy". Consequently, contaminated meat and liver processing spreads HEV to all slaughter lines (20). In a study, environmental samples and liver samples

were collected from different surfaces in contact with offal and fresh meat at the slaughter line in different pig slaughterhouses. 53% of environmental samples and 34% of liver samples were positive for the presence of HEV RNA (21). Therefore, cross contamination starts from slaughterhouses and comes to the table as foods that have an impact on the health of consumers. People living in industrialized countries are often exposed to the Hepatitis E virus by consuming contaminated food (22).

Other animal species such as goats, rabbits (23) and sheep (24) pose risks to the health of slaughterhouse workers. High titers of anti-HEV IgG were detected in men and women working in rabbit slaughterhouses (43.6% male and 47.2% female workers). While the seroprevalence was 64.1% in workers with a working year of >2, it was 14.3% in workers with a working year of <0.5 (25). Also, goat farmers, shepherds, and sheep milk cheese maker workers reported similar results (24,26).

2.2. Immunocompromised patients

In immunocompromised patients, HEV is usually asymptomatic depending on the genotype (27). Patients experience jaundice with nausea, vomiting, fever, abdominal pain and hepatomegaly in only a certain percentage of cases after an incubation period of 2 to 8 weeks (28).

Immunocompromised individuals such as organ transplant recipients (29), patients with chronic liver disease (30), patients affected by HIV infection (31) and individuals affected by lymphoblastic leukemia (32); these are some of the categories that show a high risk for HEV infection.

Human-to-human transmission of HEV-3 and HEV-4 needing support of blood or blood product transfusions can be mentioned (33). Therefore, some industrialized countries (Ireland, United Kingdom, Japan, Netherlands and Germany) have initiated nationwide HEV RNA screenings of blood donations (34).

High seroprevalence values are also affected by dietary and geographical traditions, namely hunting activities and consumption of game products. In some regions, particularly high prevalence rates (over 30% anti-HEV immunoglobulin) may be explained by local dietary habits and heavy environmental HEV contamination (35). For this reason, developed countries adopt an approach focused on “risk-based decision making”. Molecular screenings of blood, blood products, and foodstuffs for patient categories can be used if there is a characterization for HEV low seroprevalence blood donors (22).

3. Evidence of HEV in Animal Foods

3.1. Meat Products

The first evidence of HEV transmission in humans was described in wild animal meat in Japan. These cases have been associated with consumption of uncooked or undercooked pork and venison (36). In general, contamination originates from the primary production of fresh produce, food processing and water used in food production (30).

Unlike many other foodborne viruses, HEV in meat products can also be localized in the interior of food products. Viremia is responsible for HEV virion spread in several muscles. For this reason, health authorities recommended that they stop using non-heat-treated pork products (37). Little is known about the virulence effect of HEV in food matrices such as ready-to-eat and raw meat products containing pork or liver. Generally, heat treatment eliminates the risk of HEV infection. However, there are few studies on the effect of food processing technologies on viral loads (38).

Traditional and homemade food processing is another important consideration. These are typical in Mediterranean European countries (Italy, Spain, France and Greece) (30). Complete inactivation for HEV may depend on the initial viral load and the exact composition of the food matrix (39).

Little is known about the resistance of HEV under processes such as food processing technologies, fermentation, curing, drying (salami, sausage, etc.), smoking and cooking. Therefore, governmental authorities need to regulate food product labeling to prevent and control the risk of HEV infection, especially for vulnerable groups such as pre-existing chronic liver disease or transplant recipients (22).

In the application of innovative food technologies, the effects of high pressure processing (HPP), lactic acid (LA) and intense light pulse (ILP) for pork liver, ham and sausage were evaluated. Researchers stated that HPP reduced viruses both on food surfaces and in food (40).

3.2. Milk

European experts suggest that milk is a source of risk for HEV infection. Therefore, consumption of unpasteurized and contaminated milk may create a possible HEV infection for consumers (2).

Pasteurization is an important step in the dairy industry. In some cases it cannot neutralize all viral loads (HEV) and it is possible for consumers to

become infected through the ingestion of pasteurized milk. However, boiling milk (100°C for 3 minutes) provides complete sterilization (4).

Contrasting data for HEV positivity can be found between rural and industrialized regions. In rural areas, living in direct contact with different animal species (i.e. cattle, pigs, sheep, goats) on mixed farms and poor hygiene practices contribute to increased anti-HEV IgG seroprevalences (11).

The role of the mammary glands as a source of HEV RNA excretion has also been investigated in humans. High titers of anti-HEV antibodies have been detected in pregnant women through the intake of contaminated water and food (41).

In pregnant women, high steroid hormone (estrogen) levels promote viral replication and it may be possible to isolate HEV RNA from human breast milk during the acute phase of infection (42).

3.3. Shellfish Products

Water used in food processing plants, water used in aquaculture, wastewater, and water used for irrigation of vegetables and fruits can be sources of enteric viruses (i.e. HEV) (30, 43). These viral pathogens reach aquaculture farms. Mollusks accumulate aquatic microorganisms through their diet. It has been reported that HEV can persist for weeks in shellfish (44). Therefore, raw edible seafood is a risk to the health of consumers. On the other hand, applied heat treatments (cooking) can always reduce viral loads (45).

The health of aquatic creatures is definitely related to a correct wastewater management (bioindicators) (46). Consequently, environmental safety has an impact on consumers (47). Aquaculture farms are often located near urban areas, slaughterhouses and meat preparation industries (48) or livestock areas (49). Therefore, wastewater treatment plants are a critical control point. It may be beneficial to implement new surveillance, control measures and structural practices to prevent viral spread and infections. Parallel development of molecular diagnostic tests will increase epidemiological and ecological knowledge regarding HEV circulation (50).

4. Conclusions

Detection of HEV in food products has been studied in meat, dairy and seafood chains. It has also been detected in other food matrices such as milk (cow, goat, sheep and donkey) and in animal samples such as feces and blood. In the future, the World Health Organization (2016) predicts that large numbers

of foodborne hepatitis E infections will continue to affect endemic countries (especially HEV-1, HEV-2 and HEV-4 for African and Asian continents). In the future, the World Health Organization predicts that large numbers of foodborne hepatitis E infections will continue to affect endemic countries (especially HEV-1, HEV-2 and HEV-4 for the African and Asian continents). It is thought that HEV-3 will still be mostly responsible for sporadic infections in North America and Europe. Therefore, official authorities, public health authorities and private producers should implement and improve monitoring activities in different food production chains.

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