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Methodology, Research and Practice

Editor

Prof. Dr. HÜLYA ÇİÇEK

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PREFACE

Health science is a discipline that tries to keep the comfort zones of individuals at the highest level and approaches all people at the same distance without discrimination of religion, language, race and gender. Healthcare professionals do not avoid self-sacrifice to provide this assistance. The service provided in the field of health is teamwork, so all employees bear great responsibilities. People studying or working in the health field are looking for more information on many topics. Our aim in presenting this book is to convey the products and experiences created as a result of the efforts of valuable healthcare professionals to a wide audience. Thus, those currently working in the health sector can benefit from up-to-date information and good practices that can be applied in their organizations. Because knowledge and love grow when shared.

In addition to the fact that health employees have been in a very busy working environment in recent years, the COVID-19 pandemic, which has affected the whole world since 2020, has made our living conditions difficult. This situation increased the burden of health workers, they had to make extra efforts to solve the public health problems. Despite this, the colleagues in our book shared their knowledge and experience with us and increased our chances of integrating with various branches of health science. With this aspect, the content of the book will guide many people. We wish to shed light on new studies that will contribute to humanity and our country by joining hands in health science, to scientists who work not only for themselves but for all humanity. So, I would like to thank our team of authors who supported our book and everyone who contributed to its publication.

Editor
Prof. Dr. HÜLYA ÇİÇEK

CHAPTER I

NEUROENDOCRINE TUMOR CASE WITH HYPERCALCEMIA

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1.Introduction

Neuroendocrine tumor (NET) are tumors originating from the neuroendocrine system anywhere in the body. They are rare tumors that occur with different clinical pictures due to their localization and the hormones they secrete, and may have an aggressive course, although they are mostly benign (1, 2). Widespread lymph node which may lead to clinical manifestations in these tumors lymphoproliferative diseases are also miscible (3). In this phenomenon, a neuroendocrine tumor of unknown primary who presented with hypercalcemia was discussed in the light of the current literature.

2. Case report

A 48-year – old male patient was admitted to our emergency clinic with complaints of weakness, fatigue, weight loss and thirst. In the last 2 months, the complaint of gradually increasing fatigue and weakness as well as unintentional loss of 8 to 9 kg was noted. In the emergency room, urea was measured as 98 mg/dl, creatinine 1.5 mg/dl and calcium 22 mg/dl in routine biochemistry. The patient, whose general condition was moderate, conscious and oriented, was admitted to the Endocrinology clinic due to hypercalcemia. The patient was started with 4000 cc /

day isotonic fluid and furosemide ampoule 60 mg / day. Along with it, methylprednisolone ampoule 40 mg / day was added. The patient's complaints regressed the day after his hospitalization, and his control calcium levels gradually decreased. Parathyroid pathology was eliminated in the patient with parathyroid hormone: 1.48 pg / ml and vitamin D: 4.55 ng / ml, and abdominal ultrasonography was requested due to the possibility of malignancy which is the second most common cause of hypercalcemia.

Abdominal ultrasonography showed a 85x140 mm pancreas extending along the paraaortic line in the midline along the left upper quadrant and a marked vascularized mass lesion whose intermediate plan could not be clearly identified.

Magnetic resonance imaging of the whole abdomen revealed a 14x11x9 cm hypointense mass in the left upper quadrant, pushing the pancreas to the right and inferior, the left kidney posteriorly and the stomach superiorly. Lymph nodes, the largest of which was 30x22 mm in size, were observed around the celiac trunk and SMA(Figure 1). Thorax tomography and brain tomography were performed on the patient. No mass lesions and lymph nodes were detected.

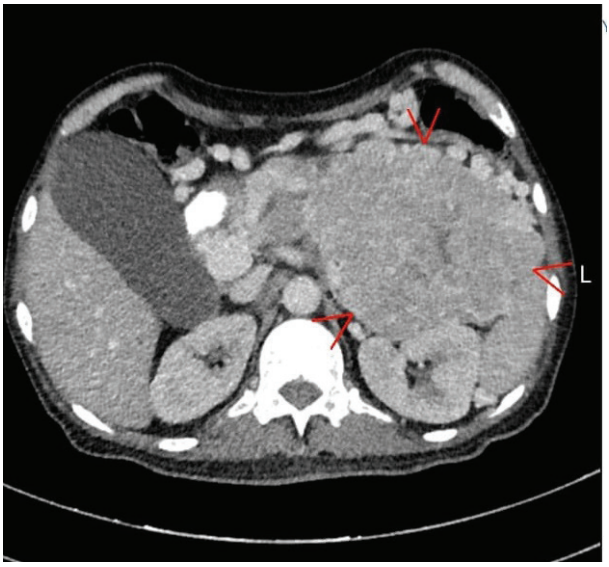

Figure 1: Radiological appearance of neuroendocrine tumor..

The patient was consulted with interventional radiology for biopsy of the intra-abdominal mass. Biopsy results were evaluated as synaptophysin CD56 Pan CK: Diffuse strong positive, chromogranin A PAX-8: Patchy weak positive, CK20: Very rare positive: PAX8 positive and pancreatic primary low-grade neuroendocrine tumor(Figure 2).

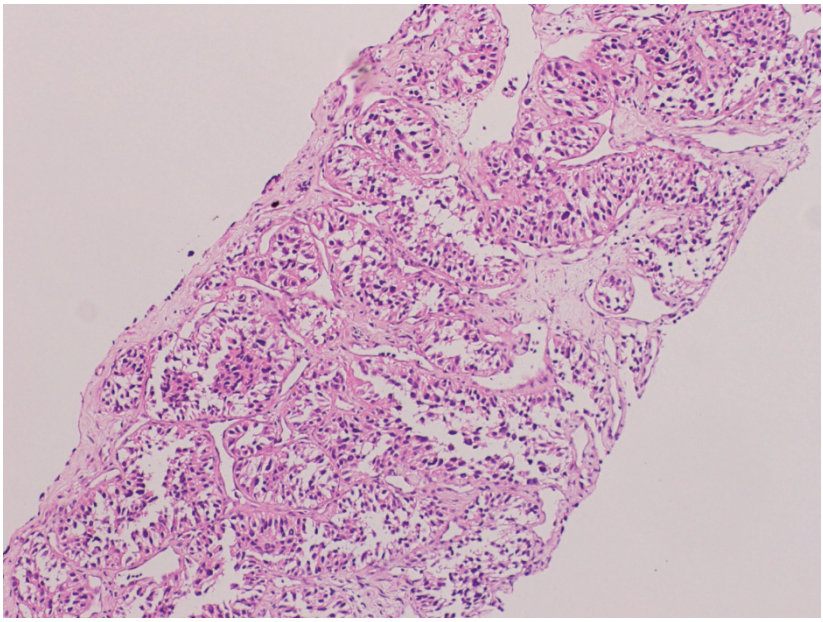

Figure 2: Neuroendocrine tumor microscopic appearance stained with hematoxylin-eosin

Later, Ga 68 DOTATATE whole body positron emission tomography was performed on the patient. Increased uptake (SUV max: 17.1) and increased Ga68-DOTATATE uptake (SUVmax: 15.3) in lymph nodes around the peripancreatic and celiac trunk was observed in the pancreas extending on the paraaortic line in the left upper quadrant of the abdomen, and the left kidney and a mass lesion with irregular contours and soft tissue density, whose intermediate plans could not be clearly identified. The patient was discussed at the oncology, general surgery and endocrinology council, and with the diagnosis of neuroendocrine tumor, lanreotide was started at 90 mg / month and Zolendronic acid

was continued at 4 mg / month. Surgical intervention was not considered with these findings.

3.Discussion

The incidence of neuroendocrine tumors is 1~2 / 100,000 and the incidence of women in reproductive age increases and the incidence increases in both sexes with age. The age of diagnosis is 54 years in the rectum, and 64-66 years in NET's of lung and small intestine origin (4, 5). The age difference can be evaluated as a result of the delay in diagnosis.

Endocrine cells are found throughout the mucosa of the gastrointestinal tract, and endocrine tumors show common phenotypic properties due to their production of some bioactive products. The term neuroendocrine is named because these tumors express neural cells related proteins such as synaptophysin, neuron-specific enolase and chromogranin A .Gastroenteropancreatic neuroendocrine tumor (GEP-NET) cells originate from the cells of the diffuse endocrine system that they phenotypically resemble (1,2).

Gastroenteropancreatic neuroendocrine tumors (GEPNET) are rare tumors with a wide spectrum of clinical course. Factors determining the biological behavior of these tumors are complex and multifaceted. Some of these parameters are the location of the tumor in the gastrointestinal tract, the diameter of the primary tumor, and the presence of localized or distant metastases (6, 7). GEPNETs are classified according to localization, diameter, depth of invasion, proliferative activity and function (1, 4). GEPNETs are divided into 4 separate classes. Muscularis propria invasion and / or metastasis determines malignancy in GEPNETs. Generally, tumors limited in the stomach and small intestine smaller than 1 cm, colon, rectum and appendix smaller than 2 cm in the mucosa and submucosa are benign (5,8).

In patients with symptomatic GEP-NET, nonspecific complaints such as abdominal pain, nausea, vomiting, weight loss, gastrointestinal blood loss, hypercalcemia can be seen. Sometimes cases are presented with carcinoid syndrome, which occurs with the effect of hormones

secreted by the tumor (6, 9). These patients typically have symptoms such as watery diarrhea, flushing, bronchospasm, and tricuspid regurgitation. Carcinoid syndrome is usually associated with liver metastasis of the primary tumor. In this case, the serotonin synthesized by the metastatic tumor is mixed into the blood without being metabolized, and typical carcinoid syndrome findings emerge. Sometimes, other clinical syndromes may occur depending on the main bioactive substance produced in cases with GEP-NET (5,10). In this case, symptoms of weakness, fatigue and weight loss are observed.

The distribution of GEP-NETs according to organs is 38% in the small intestine, 19% in the rectum, 15% in the appendix, 10% in the colon, 9% in the pancreas and 7% in the stomach, and 2% of it is stated as the other (6). The most common organs in the study conducted on 25.531 patients with carcinoid tumors; It was evaluated as 38% small intestine and 34% rectum (11). In a single-center study by Shaka and Raghavan (2019), the most common involvement site was the pancreas (34.8%); rectum and stomach were found with a rate of 20.2% and 14.0% (11). It is seen that the frequency in the places of involvement can vary according to the geography and racial characteristics. Pancreatic involvement is seen in this case. It is similar to the results in the literature.

In a multidisciplinary single-center study conducted by Tang et al on 233 patients with NETs, the male sex ratio was found to be 52.8% and the female gender ratio to be 47.2% (12). In another study, this rate was 56% male and 44% female. The presence of a male gender in this case confirms the information that GEP-NET is more common in male gender (6).

In GEP-NETs, diagnosis is made with the help of biochemical markers, endoscopic methods, conventional and functional imaging methods and pathology (4, 5). Diagnostic methods were used in this case and the correct diagnosis was made in this direction. When other cases are examined, it has been emphasized that biochemical markers and imaging methods attract attention in diagnosis (2,4).

Pancreatic Neuroendocrine Tumors constitute 1-2% of all pancreatic tumors and more than 90% are hormonally silent. The prognosis of non-functional PNETs is worse than functional ones, possibly related

to the delay in diagnosis. In recent years, the number of non-functional PNETs with incidental diagnosis has been increasing and the optimal management of tumors smaller than 2 cm is controversial. The incidence of insulinomas, which are the most common functionally, is 0.5 / 100,000, and they are generally less than 2 cm in size and have low malignancy potential. Other functional PNETs are 60-90% malignant. Functional NETs are shown in detail in Table 1 (1,4). Non-functional PNETs also release hormones such as chromogranin A-B, Pp, α-human chorionic gonadotropin (hCG) and β-hCG, but they do not cause a specific symptom. They cause symptoms related to mass effect or metastasis due to the increase in size. Although symptoms such as abdominal pain, jaundice, weight loss, fatigue and bleeding 15 are seen most frequently, it is diagnosed incidentally at a rate of 10-15%. Non-functional PNETs are often well differentiated, but may be metastatic at the time of diagnosis due to delay in diagnosis. Especially those larger than 3 cm are usually metastatic at the time of diagnosis (2,10). In this case, it was found that the general condition of the patient was good and there was no metastasis.

Broad population-based data support that smoking, alcohol, and hypergastrinemic syndromes are risks for the development of NETs (5). As can be seen sporadically, hereditary syndromes pose a risk for NETs. In this case, a NET case with hypercalcemia is described (6,10). When the literature is evaluated; It is stated that hypercalcemia is also an important indicator in determining the NET diagnosis, but there are a limited number of case studies (1, 2, 6, 7). With this case report, it can be said that evaluating patients in terms of hypercalcemia is important for NET.

4. Conclusion

Neuroendocrine carcinomas with hypercalcemia are rare tumors with a poor prognosis with a tendency to liver metastasis. It is important to diagnose neuroendocrine carcinoma by differential diagnosis with clinical and immunohistochemical findings in order to determine the correct treatment protocol and prognosis. In the presence of a tumor with hypercalcemia, it is important to keep in mind neuroendocrine carcinoma, although it is rarely observed, since the reported case will

contribute to the development of appropriate treatment protocols for other cases and to predict the prognosis.

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CHAPTER II

ANATOMY, PATHOLOGICAL PHYSIOLOGY AND SURGICAL TREATMENT OF HYDROCEPHALUS

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1. ANATOMY OF CEREBRAL VENTRICLES:

1.1 The Ventricles Of The Brain:

The central nervous system is hollow; it develops from a neural tube whose cavity persists. The innerside of the cavity is lined throughout with ependyma. The brain formation seems to require the presence of the cerebro-spinal fluid (CSF), which is produced within this cavity. Most of the CSF is produced within the ventricles (1).

The ventricles of the brain are the lateral, third, and fourth ventricles (fig1). The two lateral ventricles communicate through the inter-ventricular foramina (foramen of Monro) with the third ventricle. The third ventricle is connected to the fourth ventricle by the cerebral aqueduct (aqueduct of Sylvius).

The fourth ventricle in turn is continuous with the narrow central canal of the spinal cord and, through the three foramina in its roof (the 2 lateral foramina of luschka and the middle foramen of Magendie), with the subarachnoid space. Also, the central canal of the spinal cord has a small dilatation at its inferior end, which some authors refer to as the terminal ventricle (1).

1.1.1 Lateral ventricle:

Is a C-shaped cavity lined with ependyma, lying with in the cerebral hemisphere. There are two lateral ventricles located within each cerebral hemisphere. The lateral ventricle may be, divided into a body, which occupies the parietal lobe and from which anterior, posterior, and inferior horns extend into the frontal, occipital, and temporal lobes, respectively. The lateral ventricle communicates with the cavity of the third ventricle through the inter-ventricular foramen. This opening, which lies in the anterior part of the medial wall of the ventricle, is bounded anteriorly by the anterior column of the fornix and posteriorly by the anterior end of the thalamus (1). Each lateral ventricle contains about 7-10 ml of cerebrospinal fluid (CSF). This fluid is produced in the choroid plexus of the lateral ventricle and normally drains into the third ventricle through the interventricular foramen (2).

The choroid plexus of the lateral ventricle lies on the medial wall of the ventricle in an undulating fashion. It is a vascular fringe composed of pia mater covered with the ependymal lining of the ventricular cavity.

The choroid plexus is, in fact, the irregular lateral edge of the tela choroidea, which is a double fold of pia mater situated between the fornix superiorly and the upper surface of thalamus. It ends at the junction of the body and the inferior horn of the lateral ventricle where the choroid plexus tapers into the choroid fissure (2). The choroidal artery lying within the choroidal fissure provides the collateral arterial blood supply to the choroid plexus.

1.1.2 Third ventricle:

Is a slit-like space. It lies in a sagittal plane. Much of the lateral wall is occupied by the thalamus, a rounded mass of gray matter that bulges convexly into the ventricle, the cavity of the third ventricle is lined with ependyma, continuous through the interventricular foramen with that lining the lateral ventricles and through the aqueduct with that lining of the fourth ventricle. As in all ventricles, the lining of ependyma reaches the surface pia mater to allow for invagination of the choroid plexus. In

the third ventricle this place is a narrow roof (1). The choroid plexuses of the third ventricle are formed from the tela choroidea situated at the roof of the ventricle. The vascular tela choroidea projects downward on each side of the midline, creating the ependymal roof of the ventricle.

The blood supply of the tela choroidea and therefore also of the choroid plexuses of the third and lateral ventricle is derived from the choroidal branches of the internal carotid and basilar arteries. The venous blood drains into the internal cerebral veins, which unites to form the great cerebral vein. The great cerebral vein joins the inferior sagittal to form the straight sinus (2).

1.1.3 Cerebral aqueduct (Aqueduct of sylvius):

The cerebral aqueduct is a narrow channel about 3⁄4 inch (1.8 cm) long that connects the third and the fourth ventricles (fig1).

It is lined with ependyma and is surrounded by a layer of gray matter, called the central gray. The direction of flow of CSF is from the third to the fourth ventricle, there is no choroid plexus in the cerebral aqueduct.

1.1.4 The fourth ventricle:

The substance of the midbrain surrounds the aqueduct and the substance of the lower medulla surrounds the central canal. Between the two, however, the substance of pons and upper medulla lies ventrally and the central canal is expanding posteriorly into a cavity known as the fourth ventricle, which is roofed by fine transparent lining made of ependyma and pia matter (superior medullary velum) (1). It is continuous above with cerebral aqueduct and below with the central canal of spinal cord. It possesses lateral boundaries, a roof and a rhomboid-shaped floor.

The tent shaped roof project into the cerebellum. The lateral recesses extend laterally around the sides of medulla and open anteriorly as the lateral opening of the fourth ventricle, or the foramina of Luschka. The median aperture in the roof of the fourth ventricle is the foramen of Magendie. It is through these openings that CSF enters the subarachnoid space.

The choroid plexus of the fourth ventricle is T shaped; the ventricular part of the T is double. It is suspended from the inferior half of the roof of the ventricle and is formed from the highly vascular tela-choroidea.

The tela choroidea is a double fold of pia mater that projects through the roof of the ventricle and is covered by ependyma. The horizontal part of the T extends into the lateral recesses of the ventricle on each side. The blood supply to the plexus is from the posterior inferior cerebellar arteries (1).

1.1.5 Central canal of the spinal cord and medulla oblongata:

The central canal opens superiorly into the fourth ventricle. Inferiorly, it extends through the inferior half of the medulla oblongata and through the entire length of the spinal cord. In the conus medullaris of the spinal cord, it expands to form the terminal ventricle. The central canal is closed at its lower end, is filled with CSF, and is lined with ependyma. The gray commissure is the gray matter tissue surrounding the central canal along the spinal canal. There is no choroid plexus in the central canal (2).

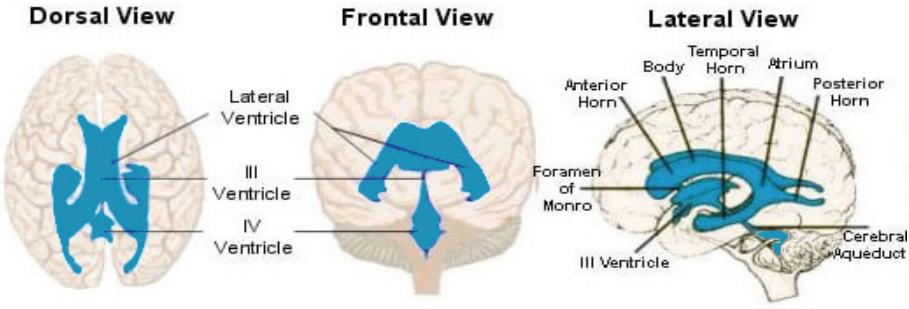

Figure (1.1) anatomy of the ventricles of the brain

2. PHYSIOLOGY OF CEREBROSPINAL FLUID (CSF):

CSF is a clear, colorless fluid. It contains inorganic solutes similar to those in the blood plasma. Its glucose content is about half that of blood

and there is only a trace of protein. Only few cells are present and these are lymphocytes (0-3 cells/mm^3).

The total volume of CSF in the subarachnoid space and within the ventricles is about 130ml (2). The subarachnoid space extends caudally around the spinal cord and ends in lumbosacral dural sac where is surrounds the cauda equina. The volume of CSF in the lumbar sac is about 30 ml (2).

3. FUNCTION OF CEREBROSPINAL FLUID (CSF):

Function of CSF is multiple: CSF bathes the tissues and from a mechanical stand point, it serves to protect the brain. Moreover, the CSF is in direct communication with extra cellular space of the brain and helps deliver, circulate, and clear the various substrates of brain metabolism, metabolic products, hormones, and neurotransmitters (2).

The close relationship of the fluid to the nervous tissue and the blood enables it to serve as a reservoir and assist in the regulation of the nervous system contained within craniospinal thecal sac (1). In addition, the CSF compartment provides the clinician access to the nervous system for laboratory analysis and pressure measurements (1).

4. FORMATION OF CEREBROSPINAL FLUID (CSF):

The major portion of CSF is produced by non-neural structure in the brain called “choroid plexus”. A choroid plexus is a collection of blood vessels with ion pump that promote movements of water from blood into the ventricles. These vessels have holes in their walls large enough to allow passage of water, ions (sodium and potassium), and small molecules (sugars and small proteins) through them while larger protein molecules (like albumin and immunoglobulin) and cells (red and white blood cells, platelets) cannot pass through the choroid plexus and remain in the blood (3).

Smaller portions of CSF are produced by blood vessels of meningeal and ependymal lining of the CSF chambers and still smaller portions by the blood vessels of the brain and spinal cord.

In summary, CSF formation at the choroid plexus occurs in two stages: passive hydrostatic filtration of fluid across the highly permeable capillary endothelium and a regulated secretion across the single-layered choroidal epithelium. The choroidal epithelium forms a fluid barrier since tight junctions are expressed at the apical cell membrane (3). The rate of choroidal CSF formation is rather insensitive to osmotic and hydrostatic pressure changes in the CSF and therefore relatively independent of changes in intracranial pressure and plasma osmolarity. Hence, water transport across the choroid plexus epithelium is not a simple osmotic diffusion but a mechanism controlled by membrane transporters within the epithelium. Differential expression of aquaporins and transporters at the basolateral (in contact with the plasma) and apical (in contact with CSF) membranes play critical roles in CSF secretion. Due to its high AQP1 expression, the apical membrane has high water permeability. In contrast to this, the basolateral membrane lacks significant AQP1 expression (3). At the apical membrane a K^+/Cl^- cotransporter is co-localized with the Na^+/K^+ -ATPase. Together, these transporters expel water from the cell into the CSF space.

The sodium concentration of CSF is similar to plasma levels at 134-150 mmol/L compared to potassium at 2.7-3.9 mmol/L being slightly lower than normal plasma concentrations (4). In most adults the rate of CSF production is between 400 to 600 cc per day. The normal adult ventricular system contains only approximately 125 to 150 cc of CSF, the daily rate of production is three to four times and therefore in only a few hours with no absorption, normal production (1/3 cc per minute) will lead to significant volume and pressure increases with potential pathophysiologic consequences including coma and death (1).

5. CEREBROSPINAL FLUID CIRCULATION PATHWAYS:

After production at the choroid plexus the CSF moves around within the ventricles and then out of the ventricular system into the subarachnoid space around the base of the brain, then down around the spinal cord and roots of the cauda equina in the lower thecal sac (fig2).

After reaching the bottom of the sac the fluid then circulates back up in the subarachnoid space continuing up over the surface of the brain and into the venous dural sinus drainage channels (3). It is believed that CSF takes one to two hours to reach the basal cisterns, 3 to 4 hours to reach the sylvian fissure and 10 to 12 hrs to spread over the cerebral subarachnoid space. By 24 hrs it starts to be cleared into the superior sagittal sinus (10).

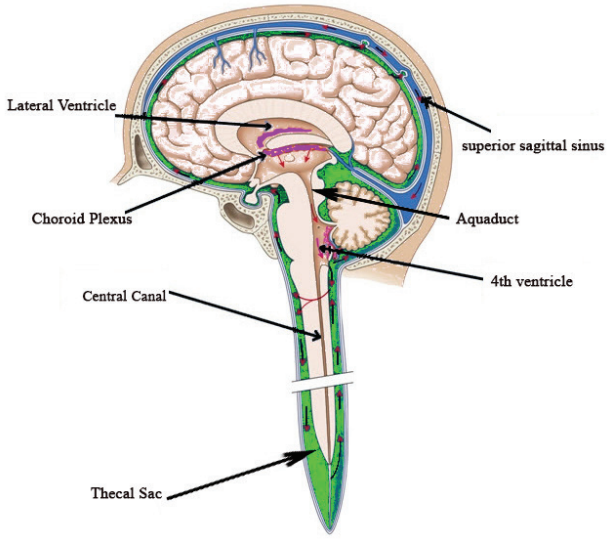

Figure (2): Circulation of CSF in the craniospinal axis.

6. CEREBROSPINAL FLUID ABSORPTION:

CSF is re-absorbed through microscopic channels between the subarachnoid space over the brain and the dural venous sinuses (3), especially the superior sagittal sinus through the arachnoid villi that project into the dural sinuses (fig2). The arachnoid villi tend to be grouped together to form elevations known as arachnoid granulations. these arachnoid granulations increase in number and size with the age. The absorption of CSF into the venous sinuses occurs when the CSF pressure exceeds that in the sinus. Some of the CSF probably is absorbed directly into the veins in the subarachnoid space and some possibly escapes

through the perineural lymphatic vessels of the cranial and spinal nerves (2). CSF formation is relatively insensitive to pressure while on the other hand, absorption of CSF increases as intracranial pressure increases, (3).

7. NORMAL CEREBROSPINAL FLUID PRESSURE:

In children and babies CSF pressure is low. In infants it is estimated to be 40 to 50 mms of water and in children from 40-100 mms of water. In the older age group, it remains constant of about 150 mms of water or 15 mm of mercury. Pressures above 200 mm of water or 20 mm of mercury are considered abnormal. The CSF pressure is usually about 40-50 mm of water above the intracranial venous pressure. Ventilation and cardiac contractions lead to regular fluctuations in the CSF pressure. CSF pressure falls with inspiration and rises during expiration, a variation of about 40 mms of water, with cardiac contraction there is a variation of about 20 mms of water with ventricular systole (5).

8. HYDROCEPHALUS

8.1. Definition of Hydrocephalus:

Hydrocephalus is an abnormal expansion of cavities (ventricles) within the brain caused by the accumulation of CSF (5). Hydrocephalus, as defined in pathophysiologic terms, may be regarded as an imbalance of CSF formation and absorption of sufficient magnitude to produce a net accumulation of fluid with in the cerebral ventricles (6).

8.2. Pathophysiology Of Hydrocephalus:

The pathologic effect of ventricular enlargement include:

- Atrophy of the white matter.
- Spongy edema of the brain surrounding the ventricles.
- Fibrosis of choroid plexuses.
- Stretching and denuding of the ependymal epithelium.

- Formation of ventricular diverticula.
- Fenestration of the septum pellucidum.
- Thinning and elongation of the interhemispheric commissures (6).

Atrophic process in hydrocephalus involves primary destruction of axons, a secondary loss of myelin, chronic astrogliosis. Neurons are selectively spared, presumably because the gray matter enjoys a more luxuriant blood supply. This may explain why the thickness of cerebral mantle is not a reliable prognostic criterion in patients with hydrocephalus (6).

8.3. Classification Of Hydrocephalus:

Hydrocephalus can be classified as communicating and non-communicating hydrocephalus. Both these types of hydrocephalus are, in essence, obstructive, although at different sites (7).

8.3.1 Communicating hydrocephalus (non-obstructive): caused by lesion that obstruct the subarachnoid space, there is a free flow of fluid out of the ventricles up to the point of obstruction, for example obstruction by white blood cells and other debris in infection, by tumor cells from cancer or by red blood cells following hemorrhage into the subarachnoid space. CSF absorption may be insufficient to keep up with production and an excess of CSF can result (CSF circulation blocked at the level of arachnoid granulation) hydrocephalus.

8.3.2 non-communicating hydrocephalus (obstructive): when the ventricles do not communicate through their foramina or aqueducts, CSF backs up and the volume in the ventricle proximal to the blockage increases (7), as is the case in obstruction of the aqueduct of Sylvius. The most common cause of obstruction of one of the interventricular passage ways is a mass, such as tumor (7).

Etiologies of aqueduct stenosis (AqS):

- A congenital malformation: hydrocephalus may be associated with Chiari malformation or neurofibromatosis.
- Aquired:

- Due to inflamation (following hemorrhage or infection)
- Neoplasm: especially brain stem astocytomas.
- Quadrigeminal plate arachnoid cyst (7) (fig 3c)

In infancy AqS is a frequent cause of congenital hydrocephalus (up to 70% of cases). Patients with congenital AqS usually have hydrocephalus at birth or develop it within 2-3 months. Congenital AqS may be due to an X-linked recessive gene. 4 types of congenital AqS described by Russell:

- forking: multiple channels (often narrowed) with normal epithelial lining that do not meet, separated by normal nervous tissue.
- periaqueductal gliosis: luminal narrowing due to subepindymal astrocytic proliferation (fig 3d).
- true stenosis: aqueduct histologically normal (7).

In aduldhood aqueductal stenosis may be an over looked cause of "normal pressure hydrocephalus". It is unknown why some cases of aqueductal stenosis remain occult and manifest only in adulthood (fig 3d).

8.4. Hydrocephalus May Arise In Three Ways:

a) Obstruction of CSF pathways: as in following infections and subarachnoid hemorrhages.

b) Over secretion of CSF: as in choroid plexus papilloma, whereby large amount of CSF formation exceed the absorption capacity of the arachnoid villi.

c) Impaired venous drainage: can lead to hydrocephalus (not well established) (6)

9. CLINICAL FEATURES OF HYDROCPEHALUS:

Hydrocephalus causes symptoms and signs by two major mechanisms;

Distortion of normal anatomic relationships between brain structures and increase in intracranial pressure.

9.1.Signs And Symptoms Of Active Hydrocephalus;

9.1.1 In young children:

- Cranium enlarges at a rate more than facial growth.
- Irritability, poor head control.
- Fontanelle full and bulging.
- Enlargement and engorgement of scalp veins: due to reversal of flow from intracerebral sinuses due to increased intracranial pressure.
- Macewen's sign (cracked pot sound on percussion over dilated ventricles).
- 6th nerve palsy.
- Setting sun sign (upward gaze palsy, from pressure on region of supra pineal recess).
- Hyper active reflexes.
- Irregular respiration with apneic spells.
- Splaying of cranial sutures (seen on plain skull X-ray) (7).
- The scalp is often thin and glistening.
- Trans illumination of the head is usually positive if the cerebral mantle is less than 1,0 cm in thickness and the patient is under 9 moths of age (8).

9.1.2 In older children/ adults with rigid cranial vault:

Sudden obstruction of the CSF pathways can be followed within hours by acute dilatation of the ventricles proximal to the blockage (9). If the cranial sutures are closed, the clinical syndrome is characterized by a rapid and severe rise in intracranial pressure, including: papilloedema, Nausea, vomiting, headache, gait changes, up gaze and/or abducens

palsy (8). Less often, episodes of transient or sustained blindness can occur as a result of transtentorial herniation and entrapment of the posterior cerebral arteries against the free edge of the tentorium. There is generally a varying degree of decorticate or decerebrate posturing, slowing of the pulse and respirations, and an elevation of the systolic and diastolic pressures. Unless treatment is instituted death ensues promptly (9).

9.1.3 Signs And Symptoms Of Chronic Hydrocephalus:

Features indicative of chronic hydrocephalus (as apposed to acute hydocephalus) are:

- Beaten copper cranium on plain skull X-ray. By itself, does not correlate with increased ICP, however when associated with other sighns below, does suggest increase intracranial pressure. May be seen in craniosynostosis.
- Third ventricle herniating into sella (seen on CT or MRI).
- Erosion of sella turcica which sometimes lead to empty sella, and erosion of the dorsum sella.
- The temporal horn may be less prominent on CT than in acute hydrocephalus.
- Macrocrania: by convention, OFC (occipital-frontal circumference) greater than 98th percentile.
- Atrophy of corpus callosum: best appreciated on sagittal MRI (fig 3c).
- In infants:
    - Sutural diastasis (skull X-ray).
    - Delayed closure of fontanells.
    - Failure to thrive (8)

Clinical syndrome of hydrocephalus characterized by bifrontal or generalized headache, vomiting, papilloedema or optic atrophy, failing mental function, behavioral disturbances, and memory loss.

Unilateral or bilateral abducent palsy, weakness of upward gaze. Disturbances of gait and motor function.

Endocrine abnormalities including infantilism, adiposogenital dystrophy and precocious puberty, due to compression of the pituitary gland by ballooning and thinning of the floor of the third ventricle

10. CT SCAN AND MRI FINDINGS IN HYDROCEPHALUS:

- Severe dilatation of the bodies of the lateral ventricles and increased height of the ventricles (10).
- The corpus callosum is thinned and bowed forming an arch (my fig) (10).
- Sulcal effacement (11).

Dilatation and rounding of the temporal horns may be the earliest manifestation of ventricular obstruction but are not consistently presentin all cases (fig 3). These signs can be seen well before enlargement of the bodies of the lateral ventricles are obvious (12).

Enlargement and ballooning of the third ventricle often noted, in sagittal projection. However, the roof of the 3rd ventricle often flattened by markedly enlarged lateral ventricular bodies (fig 3c).

The fourth ventricle is enlarged in communicating hydrocephalus, and it is normal or small in non-communicating hydrocephalus.

Periventricular edema (fig 3a), seen as hyperinsity in T2WI and hypointensity on T1WI in the periventricular white matter of the frontal, temporal, and occipital horns is often present in acute phase of hydrocephalus but not in the chronic stages of hydrocephalus (12).

CSF flow MRI of the aqueduct, allows flow velocity to be quantified using phase conrast imaging. In hydrocephalus CSF velocity may reach 5 to 10 cm/sec (10) at the cerebral aqueduct (31).

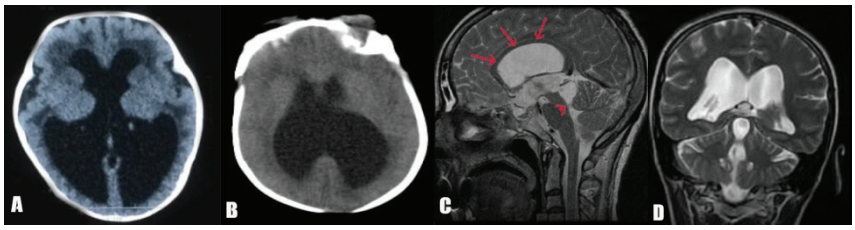

Figure (3): CT scan and MRI findings in Hydrocephalus.

a. Hydrocephalus in a 3-month old baby born with septooptical dysplasia. Absence of corpus callosum and periventricular edema are notable on the CT scan.

b. CT scan shows gyral affecement in a baby due to hydrocephalus. Gyral effacement is indicatif of severe incereased intracranial pressure
c. Non-communicating hydrocephalus is seen on the MR images of an 8-year old child diagnosed with arachnoidal cyst inside the cerebral aqueduct.

d. Late presenting hydrocephalus in a 68 years old adult patient presenting with acute deterioration of ataxia, memory loss and slurred speech. Patient had been on followup for a clincally silent and radiologically diagnosed hydrocephalus and aqueduct stenosis for 20 years before suddenly becoming symptomatic.

11. TREATMENT OF HYDROCEPHALUS:

The physiologic objective in the treatment, whether medical or surgical, of hydrocephalus, is restoration of the balance between CSF production and absorption.

11.1. Medical treatment of hydrocephalus: hydrocephalus remain a surgically treated condition. Medical treatment with diuretic therapy may be tried in premature infants with bloody CSF (as long as there is no evidence of active hydrocephalus) or where surgical treatment is not possible. Acetazolamide (a carbonic anhydrase inhibitor) seems to lower

CSF production at the choriod plexus level and can be given at 25 mg/kg/day orally in divided doses and increased 25 mg/kg per day untill 100 mg/kg/day is reached and continued up to 6 months. Weekly followup with ultrasound or CT scan should be performed and ventricular shunt should be inserted if progressive ventriculomegaly occurs.

11.2. Options of surgical treatment

Normal sized ventricles is not the goal of therapy. The goal is optimum neurological function (which usually requires normal intracranial pressure) and a good cosmetic result (11).

11.2.1. Choroid plexectomy: described by Dandy 1918 for communicating hydrocephalus, may reduce the rate but does not totally halt CSF

Production (27). Endoscopic cauterization of the choroid plexus was originally described in 1910 by VL L'Espinase, a urologist from

Chicago. He used a small rigid cystoscope to cauterize the choroid plexus (13).

11.2.2. Eliminating the obstruction: opening a stenosed sylvian aqueduct often carries a higher morbidity and lower success rate than simple CSF diversion with shunts, except perhaps in the case of tumor (12).

11.2.3. Endoscopic third ventriculostomy (ETV).

Indications

- Obstructive hydrocephalus
- An option in managing shunt infection (as a means to remove all hardware without subjecting the patient to increase ICP)
- An option for patients who developed subdural hematomas after
- Shunting (shunt is removed before the third ventriculostomy is performed)
- Slit ventricle (overdrainage) vsyndrome (11).

11.2.4. Shunting: Creation of a diversionary CSF flow channel is effective in reestablishing the balance between production and absorption in the majority

Of hydrocephalus patients. Ventriculoperitoneal shunts are the most commonly used technique (7). Types of shunts that can be used are:

- Ventriculoperitoneal (V-P) shunt.
- Ventriculo-atrial (VA) shunt.
- Torkildsen shunt (shunts ventricle to cisternal space).
- Lumboperitoneal (shunt).
- Miscellaneous: various distal projections.
- Used historically or in patient who have had significant problems with
- Traditional shunt locations (e.g. peritonitis with (V-P) shunt, subacute bacterial endocarditis with vascular shunts).
- Ventriculopleural shunt.
- Shunt from ventricle into gall bladder.
- Shunt from ventricle to ureter or bladder (cause electrolyte imbalances due to losses through urine) (14).

12. VENTRICULOPERITONEAL SHUNT

(V-P) shunting is the most popular technique for CSF diversion (fig4). It is relatively simple, it is suitable for patients of all ages with hydrocephalus from any cause and complications are easy to manage. The contraindications are few and include and active abdominal infection and diffuse peritoneal adhesions with obliteration of the peritoneal cavity. The approach to the ventricular system and placing the tip of ventricular-catheter in the lateral ventricle must be remote as possible from the choroid plexus. This can be achieved through a frontal (koher's point) or posterior parietal burrhole (keen's point) where the frontal horn is the proper target for the catheter insertion.

The burrhole should be 2-3 cm from midline (In infants the mid papillary line may be used to adjust for scale (7)) and 1 cm anterior to coronal.

Suture (fig 5). And the catheter is directed towards the ipsilateral inner aspect of the pupil and pointed back slightly towards the external auditory canal. A 5-6 cm ventricular catheter should be used when done through the frontal route (7) in an adult.

Figure 4: V-P shunt device

The standard posterior parietal burr hole site (Keen's point) is 3 cm behind and 3 cm superior to the pinna (ear). Positioning the burr hole slightly too high can be tolerated (7).

The abdominal incision is a vertical incision, just 5 cm to the right of the umbilicus. Abdominal wall is opened in layers until the peritoneum is identified and opened in order to introduce the peritoneal catheter (15).

The advantages of using peritoneal cavity in shunt operation is that:

a) Potentially life threatening infections are rare comparing to shunts in the venous system.
b) A large amount of tubing can be placed intra peritoneal to minimize the need for elective lengthening.
c) Placing intraperitoneal shunts is relatively easier and less time consuming comparing to other types of shunts.

12.1 Procedure Of VP Shunt:

The hair is shaved in preparation for shunting. After induction of general anesthesia, a small incision is made either over the front part of the skull

(just behind the hairline) or toward the back of the skull (above and behind the ear) (fig5). A pocket beneath the scalp is created using various elevators towords the back of the incision to create space fort he valve.

The skin is retracted away, after which a drill is used to place a small hole in the skull. An opening in the dura mater is then made and a thin, flexible catheter is passed through the opening into the ventricle. It is important to note the squirt of CSF out of the catheter to make sure the ventricle is penetrated.

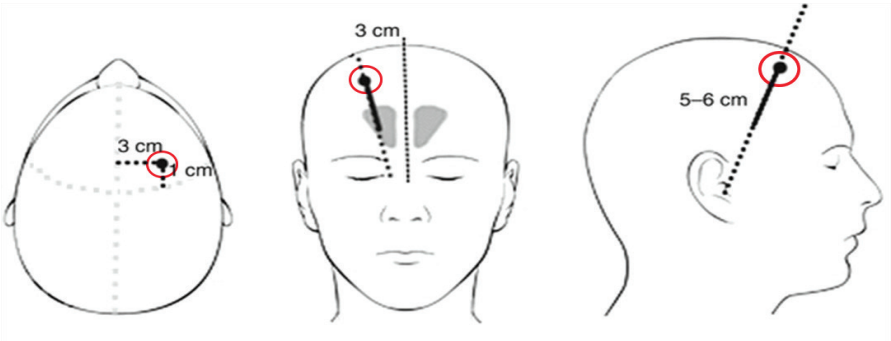

Figure (5): site of entry into the lateral ventricle.

This catheter is then attached to a valve (which controls the flow of the CSF). A small incision is then made in the lower abdomen 5 cm lateral to the umbilicus and the anatomical layers external abdominal fascia, rectus abdominis, internal abdominal fascia and peritonium are opened to introduce the distal catheter into the peritoneal cavity where CSF will be drained and absorbed. Then a tunnel is done under the skin from the abdominal cavity up toward the scalp incision with means of a long, thin tunnelizator. The long abdominal tunneling catheter (distal catheter) is pulled up through the tunnelizator and is connected to the valve inside the scalp incision. Sometimes a small incision is made directly behind the ear in order to assist with the tunneling of the distal catheter. The incisions are then closed prior to the termination of the operation.

12.2 Contra Indications Of CSF Shunt Insertion:

- Ventriculitis.

- Other inadequately treated infections.
- Acute intra ventricular hemorrhage.
- Hydrocephalus due to treatable obstructive lesion.
- Futility on the basis of extreme brain pathology (i.e., hydroncephaly).
- Asymptomatic, non progressive hydrocephalus.
- Ventriculomegaly without elevated intracranial pressure (14).

12.3 Complications Of Ventriculo-Peritoneal Shunt:

a) **Obstruction:** Most common type of shunt malfunction is that of the proximal portion of the shunt. In 1988 Al-bright et al demonstrate a better survival for frontal shunts: At 5 years 55% of frontal shunts continued to function as compared to only 33 percent of parietal shunts (16). The ventricular catheter is the most often infected part (17).

The proximal catheter can also be blocked by brain debris or blood in the ventricular system.

Also in certain cases pathologic processes such as tumor tissue can enter and block the ventricular tip (14). Distal shunt malfunction may occur due to shunt infection. The presence of an abdominal pseudocyst detected on abdominal ultrasound or CT scanning should be considered a shunt infection until proven otherwise (14). Distal slit valves located at the end of peritoneal tubes may occlude with debris or the tip of the peritoneal catheter may migrate into an area where absorption is limited (my fig6a) (14).

b) **Infection:** Shunt infection continue to disappoint neurosurgeons all around the world with an incidence of 2-8% of postoperative shunt infection (17,18). Over all, between 5 and 15% of all shunts can be expected to become infected over the lifetime. 70% of infections are diagnosed within one month after surgery and close to 90% by six months. Shunt infections can be presented with signs of meningitis and ventriculitis, as well as with external signs showing redness along the path of the shunt. In addition, signs of septicemia or peritonitis can be seen, depending on

the type of shunt. Distal shunt malfunction frequently accompany shunt infections. The most common agents are staphylococci, but gram positive bacilli, and entero bacilli can also contaminate the shunts (18).

c) Disconnection at a junction, or break at any point.

d) Hardware erosion through the skin, usually only in debilitated patients (especially infants with enlarged heads and thin scalp from chronic hydrocephalus, who lay on one side of head due to elongated cranium).

e) **Seizures:** There is = 5.5% risk of seizures in the first year after placement of a shunt which drops to = 1.1% after the 3rd year. Seizure risk appears higher with frontal catheter than with parietal (19). Shunt infection resulting in ventriculitis increases the incidence of seizure in myelomeningocele population (20).

f) **Extraneural metastases of certain tumors (e.g. medulloblastoma):** This is probably a relatively low risk.

g) **Intra-ventricular hemorrhage:** may occur during introduction of ventricular catheter, or may occur later after removal of obstructed shunt due to adhesion to choroid plexus (9).

h) **Extra-cerebral fluid collection:** In certain patients following shunting, relief of intra-ventricular pressures reduces ventricular size so that the cortex withdraws from the inner calvarium creating a vacum effect in the subdural space creating subdural collections over over the cortical surface (fig6c).

This is a major concern in the delayed treatment of patient with congenital hydrocephalus or of any patient with a considerable degree of atrophy in addition to symptomatic hydrocephalus (14). Temporary closure or revision of shunt valve may be necessary to treat this complication.

i) **Subdural hematomas:** Sub-dural hematomas may occur in shunted patient following relatively trivial trauma. In the shunted patient, the presence of small extra-cerebral spaces leads to stretching of cortical veins draining to the venous sinuses. Even insignificant trauma can cause tears in these veins (fig6c).

j) **Over drainage syndrome:** Most commonly occurs in children who have been shunted very early in life with low pressure valve or in adults treated primarily for normal pressure hydrocephalus. Patients complain of positional headache which is worse when erect and is relived

by lying down. CT scan will usually show small or slit ventricles. Treatment of this condition is to upgrade the valve to a higher pressure system.

k) **The slit ventricle syndrome:** is the presence of slit-like small ventricles on CT scan or MRI in the presence of an intraventricular shunt. Typically affects small children and can lead to elevation of intra-cranial pressure which may be as high as 500 to 600 mm H2O, in the face of small ventricles. This condition occur as a result of the "drying out" of the calvarial contents that occurs in a chronically shunted child. There is a very little CSF space over the convexities. Total extra-cellular water in the brain is probably diminished along with the reduction in size of all CSFcisterns. Concomitantly the ventricular walls collapse on the catheter while loosing its elasticity due to gliosis. Any event which subsequently elevates CSF pressure even for a brief periods, such as a viral infection or temporal shunt occlusion, will result in an intra-cranial pressure rise that is not buffered by extra-ventricular CSF displacement (14). The incidence of asymptomatic slit ventricles is relatively common 60% (11) while symptomatic slit ventricle syndrome occurs infrequently in approximately 6-12% of shunted children (11).

l) Other complications:

- Intestinal obstruction (fig6b).
- Volvulus.
- Hydrocele.
- Tip migration: Into secrotum, perforation of (viscus, stomach, bladder…) more common with older spring-reinforced (raimondi) shunt tubing or migration
- Through the diaphragm
- Intestinal stangulation (14).
- CSF ascites: In rare cases however, the peritoneum simply cannot absorb the CSF delivered to it and ascites develops without loculation (14).
- Ureter obstruction by shunt catheter is a rare complication and can be relived by shortening the peritoneal catheter (21)

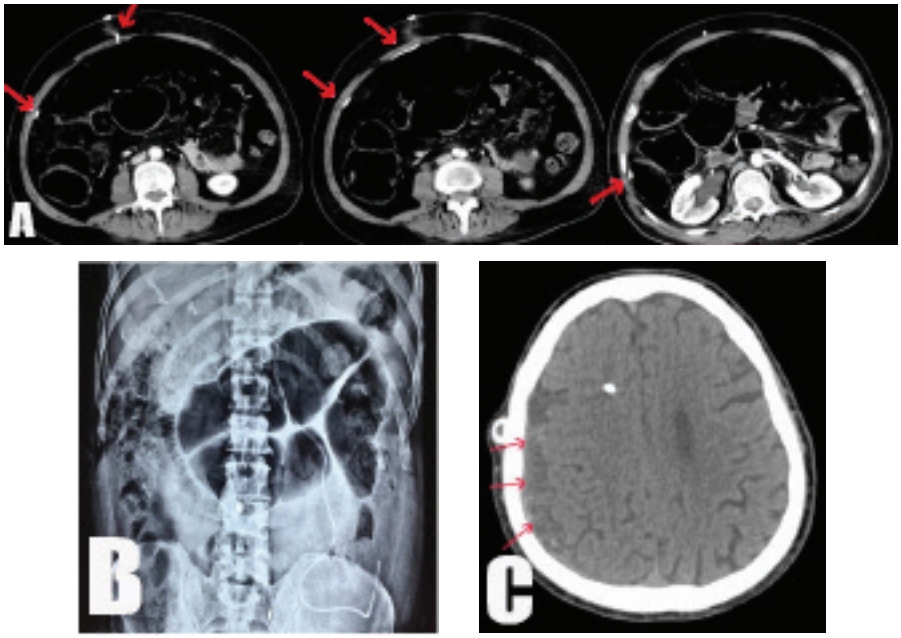

Fig 6:
a. Migration of abdominal catheter. This patient showed signs of malfunctioning of VP shunt 10 days after shunt surgery. CT revealed a marginal trajectory of the intraperitoneal tip.
b. Ileus causing malfunction of the lower catheter of a VP shunt due abdominal distention and increased intraabdominal pressure.
c. Subdural hemorrage. 2 months after VP shunt surgery this patient developed frontal headache. CT scan revealed subdural subacute hematoma on the right side.

13. ENDOSCOPIC THIRD VENTRICULOSTOMY (ETV)

The past few decades have witnessed the resurgence of endoscopic third ventriculostomy in neurosurgery. Dandy was the first to do a third ventriculostomy in a patient in 1922 and a year later, in 1923, Mixtar carried out the first endoscopic procedure in neurosurgery using a small ureteroscope and performing a third ventriculostomy procedure endoscopically (22).

In the pre-shunt era, this procedure was one of the most frequently performed surgical procedures in the management of hydrocephalus. However, due to high complication and mortality rates, the procedure was gradually abandoned and replaced with a new surgical technique, shunting. Technical problems such as insufficient illumination, poor lenses, and the fact that scopes were not equipped with cameras were at least partially responsible for the poor outcomes in that time. These issues were some of the main reasons the procedure was set aside. Decades later, Guiot (1963) and Vries (1978) reinvigorated the procedure in neurosurgery by publishing their endoscopic third ventriculostomy (ETV) results with zero mortality and low complication rates (23,24). Also, technological advancements in this field, such as more powerful light sources and illumination, and miniature-size video cameras and optic systems, helped to produce thinner and smaller endoscopes. High rates of shunt-related complications and clinical problems in hydrocephalus patients also prompted neurosurgeions to find better ways to manage hydrocephalus. As a result, ETV started to regaine its popularity in neurosurgery in the 1990s as large number of series with promising results were being published. The goal of ETV is to provide free flow of cerebrospinal fluid (CSF) between the ventricular system and the basal cisterns. This is done by fenestrating the transclucent mambrane of tuber cinereum at the floor of the third ventricle between the mamillary bodies and the infundibular recess. When this is done, the CSF in the ventricular system circulates through the prepontine cistern, reaches the cortical subarachnoid space, and is absorbed by the arachnoid villi. Comparing to shunt placement, ETV offers a more natural physiological solution to hydrocephalus. It is associated with lower complication rates, avoids implantation of foreign material, and eliminates shunt-related complications such as overdrainage. As a result of these benefits, ETV is now accepted as a mainstay treatment modality for obstructive hydrocephalus.

13.1 Endoscopic System And Instrumentation

Endoscopic surgical systems have undergone revolutionary changes in the last two decades. Neuroendoscopic systems (fig 8,9,10,11) can be

divided into two main categories: rigid and flexible endoscopes. These have different indications for use, and each has its own advantages and disadvantages. In rigid endoscopes, the view angles vary from 0 to 120 degrees. Those with 0-30 degree view angles provide appropriate optical and anatomical orientation for straightforward cases. The outer diameters of rigid endoscopes are usually 3.8-6.2 mm, but may be larger or smaller depending on the endoscope used. The main advantages of rigid endoscopes over flexible endoscopes are better image quality, wider and multiple working channels, stability, and adaptability to stereotactic frames. The disadvantages of these instruments are larger diameter and limited maneuverability. Flexible endoscopes are thinner and less traumatic than rigid endoscopes.

Their outer diameter is 2.3- 4.6 mm, and their main advantage is superior maneuverability. The main disadvantages of these scopes are narrower working channels and poor image quality.

The neuroendoscopic armamentarium has expanded continuously during the last decade. The most widely used and specially designed neuroendoscopic instruments are probe-perforators, Fogarty catheters, biopsy and grasping forceps, scissors, mono- and bipolar cauteries, suction tips, and laser wires (24). Although there are many specially designed neuroendoscopic tools, most straightforward ETV procedures can be performed with a few basic tools.

13.2 Indications for endoscopic 3rd ventriculostomy

The classic indication for ETV is noncommunicating hydrocephalus, in which the patient typically presents with dilated lateral and third ventricles, and a normal fourth ventricle. However, today there is a much wider spectrum of indications for this procedure, including normal-pressure hydrocephalus. Some of the main reasons for this extensive range are increased capability of neuroendoscopic systems due to major improvements in the field; improved expertise of surgeons, increased numbers of reports with favorable long-term results; and increased numbers of shunt-related problems with high social and personal costs.

Today, the indications for ETV are somewhat subjective. Some surgeons prefer to use this method even if the success rate of ETV in that specific patient group is only 20-30%. The rationale behind this is offering the patient a chance at a shunt-free life. Although there is consensus on good outcome after ETV in patients with late-onset hydrocephalus, there is serious debate about other indications, such as ETV in newborns, or patients with myelomeningocele. Some authors believe that the ETV success rate is low for patients who have previously had shunts because their subarachnoid spaces are presumed to be obliterated. In contrast, other researchers have reported good success in these cases, and are convinced that this patient group should be managed by shunt removal and ETV (71,77). The patient group with myelomeningocele and hydrocephalus is also controversial. Most authors have reported poor outcome after ETV in these individuals, and have attributed this result to obliterated and abnormal CSF pathways, deformed ventricular anatomy, and a thickened and obstructive massa intermedia. On the other hand, Warf et al reported relatively high success rate in this patient group when ETV is combined with choroidal plexus cauterization (28). The importance of the age at the time of ETV has also been widely discussed. Some researchers have reported poor results in newborn and infants, and have emphasized the negative effect of young age on outcome, whereas others disagree with this explanation (25,26). Cinalli et al. reported no difference in results between children younger than 6 months old and an older pediatric age group, and concluded that the age of a child is not a contraindication for ETV procedure (27).

13.3 Indications for endoscopic third ventriculostomy:

13.3.1 Strong Indications:

- Delayed-onset aqueduct stenosis
- Congenital aqueduct stenosis
- Obstructive hydrocephalus caused by pineal and posterior fossa tumors

- Obstruction of the foramina Magendi and Luschka
- Shunt malfunction in a patient with obstructive hydrocephalus
- Shunt malfunction in older patients with spina bifida 13.3.2 Weaker Indications:
- Neonates with aqueduct stenosis
- Myelomeningocele
- Communicating hydrocephalu
- Normal-pressure hydrocephalus

13.4 The main contraindications for ETV are;

- History of radiotherapy,
- Significantly distorted ventricular anatomy,
- Abnormally narrow prepontine space due to tumor or vascular lesion,
- Ectatic basilar artery or vascular lesions on the floor of the third ventricle,
- Prematurity,
- Continuing intraventricular hemorrhage or infection involving the ventricles/meninges.

13.5 Preoperative Evaluation

Appropriate patient selection criteria and appropriate indications are prerequisites for good surgical outcome with ETV. Careful assessment with preoperative magnetic resonance (MR) imaging is critical in order to avoid complications during surgery and achieve a good outcome. The anatomical details of related structures must be carefully evaluated, including the size of ventricles and foramen of Monro; the anatomy and location of the basilar artery and its relationship with the floor of the third ventricle; the width of the prepontine space, and the aqueductal anatomy. Also, a preoperative MR flow study should be obtained as a baseline. The surgeon should take all these features into account before deciding to perform ETV and estimating the potential for success with this procedure. Drake described some clinical and radiographic features

that favour good outcome with ETV and may be useful for predicting outcome Table below (29).

Clinical Features:

1.Cause of hydrocephalus in high or intermediate success group (see above)

2.Age>6 months at time of hydrocephalus diagnosis

3.No prior radiotherapy

4.No history of hemorrhage or meningitis

5.Patients previously shunted

Radiographic Features:

1.Clear evidence of ventricular non-communication
- *1.1*-Obstructive pattern of hydrocephalus
- *1.2*-Aqueductal anatomic obstruction
- *1.3*-Lack of aqueductal flow void on T2 MRI

2.Favorable Ventricular Anatomy:
- *2.1*-Width of foramen of Monro sufficient to accomodate endoscope (rigid >7mm & flexible> 4mm)
- *2.2*-Thinned floor of third ventricle
- *2.3*-Downward bulging floor, draped over clivus
- *2.4*--Basilar artery posterior to mamillary bodies

3.Absence of structural abnormalities:
- *3.1*-AVM or tumor obscuring floor of third ventricle
- *3.2*- Enlarged massa intermedia
- *3.3*- Insufficient space between mamillary bodies, basilar artery, and clivus
- *3.4*-Basilar artery ectasia

Table (1.1):

13.6 Surgical Technique

The patient is placed in supine position and the head is elevated to 20-30 degrees with slight flexion of the neck. This is done to prevent postoperative pneumocephalus and reduce the risk of subdural hematoma. An incision is made in the scalp and a burrhole is drilled on or just in front of the coronal suture on the mid-pupillary line. In a study by Kennar et al, the optimal entry point for ETV was found as 8mm anterior to the coronal suture and 28 mm lateral to the midline (30). After a burr-hole of approximately 1cm diameter is created, the dura is opened in cruciate fashion and a peel-away cannula (12F) or rigid sheath (7 mm), depending on the endoscopic system used, is introduced into the frontal horn of the lateral ventricle

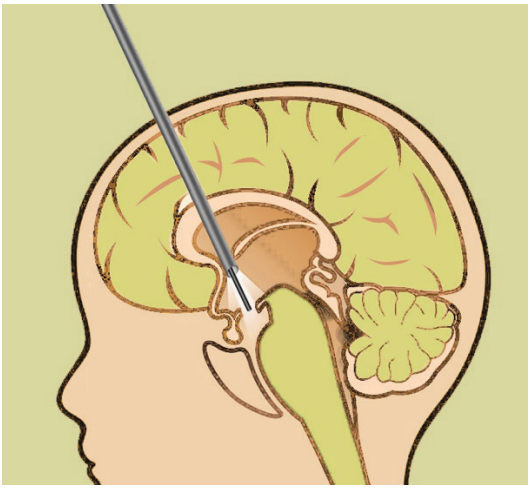

Figure (7): diagrammatic representation of trajectory of the endoscope through the foramen of Monro during ETV.

The endoscope is then passed through the cannula into the frontal horn. The Foramen of Monro is located by following the choroid plexus, anterior septal, and thalamostriate veins, and the endoscope is passed through this opening and placed into the third ventricle (fig7). In normal subjects, the mean sagittal diameter of the foramen of Monro is 2.9 mm and the vertical diameter is 5.1 mm (31). This foramen is usually noticably

enlarged in hydrocephalic patients, and the endoscope can usually pass through easily without injuring the fornix. Once the endoscope is in the third ventricle, the infundibular recess, tuber cinereum, mamillary bodies, massa intermedia, aqueduct, and posterior commissure can be observed from anterior to posterior direction. The optic recess, lamina terminalis, and suprapineal recess can be seen if the instrument is a wide angled rigid or flexible endoscope (fig9,10). Success with ETV is closely related to the surgeon's knowledge of third ventricle anatomy, as the ventricular system can be navigated and worked on through the use of anatomical landmarks. The mamillary bodies are bright white-yellow rounded structures in the floor of the third ventricle, and can be seen just after the scope enters this cavity. If the endoscope is maneuvered anteriorly and superiorly upon entry, the small pink-red infundibular recess (color due to vascularity of the hypothalamic portal system) can be observed. The tuber cinereum is a triangular and often transparent area between the mamillary bodies and the infundibular recess, and it includes the arcuate nucleus of the hypothalamus. In hydrocephalic patients, the tuber cinereum is usually very thin and translucent, and the dorsum sella, clivus, and basilar artery can easily be seen beneath it. Fenestration is performed at the tuber cinereum midway between the infundibular recess and the intermamillary point (fig12).

Ideally, the site of fenestration should be away from the basillary tip. Normally, the mean distance between the infundibular recess and mamillary bodies is 6mm (range,3.5-9mm). The mean distance between the basillary artery and the infundibular recess in the normal setting is 10.5±2.3 mm, whereas the corresponding distance in hydrocephalus patients is 12±3.7 mm (32). If the ventricle floor is translucent, the basilar artery may be seen and fenestration is performed distant from it. It is also critical to fenestrate at the above-mentioned midpoint, because more lateral fenestration may cause a third nerve injury. Fenestration of the floor of the third ventricle may be performed using a blunt probe, Fogarty catheter, the endoscope itself, special scissors, a coagubtor, or a number of other instruments, depending on the surgeon's preference. We use an angled blunt probe designed for this purpose, and angle the tip of the probe toward the dorsum sella so as not to injure the basilar

artery during fenestration. As mentioned above, the floor of the ventricle is usually quite thin in patients with hydrocephalus, and can be easily punctured with a blunt probe. However, in some cases it may be relatively thick, and the surgeon may prefer to use coagulation or sharp fenestration techniques in these cases. However, using coagulation to fenestrate the floor may damage vascular structures below and may cause thermal injury to the hypothalamus.

After puncturing the floor of the third ventricle, the fenestration is enlarged using a 3F Fogarty catheter (fig8-12). The catheter is passed through the puncture hole, its balloon is inflated, and the catheter is then withdrawn to enlarge the hole. Using this method, a fenestration of 5-6 mm diameter is created. The Fogarty catheter may injure vascular structures and the third cranial nerve below, and should not be advanced into the prepontine space too far. The proximal end of the balloon should be visible to the surgeon. Once this enlarged passageway is formed, the endoscope is inserted into the prepontine space to explore the basilar artery and its tributaries, the pons, the dorsum sella, and the clivus.

It is not uncommon to observe a second membrane, often connected to the Lilliquest membrane, in the prepontine space. The main purpose of this exploration is to ensure there is no other membrane obstructing free CSF flow in the prepontine space. If there is such an obstructing membrane, it must also be fenestrated with a blunt probe and enlarged with a Fogarty catheter, as described above. After exploring the prepontine space, the endoscope is withdrawn into the third ventricle and the pulsations of the floor with "flapping" of the edges of the newly created opening as CSF flows through which indicates a patent venreculostomy. Observing some bleeding during fenestration, especially if the floor is thick and vascular. However, this is easily stopped by irrigating the field with Ringer's lactate for awhile. Another way to stop hemorrhage from the edges of the new opening is to inflate the Fogarty balloon just at the level of the opening so that it compresses the edges. The inflated balloon should be kept in place for 15-30 seconds. When the procedure is complete, the endoscope is withdrawn slowly, exploring the third and lateral ventricles to ensure there is no active bleeding. A piece of Gelfoam® is placed in the burr-hole and the scalp is closed in standard

fashion. Some surgeons leave a ventricular drain in place after ETV. The purpose of this is to measure intracranial pressure (ICP) and be able to drain CSF if necessary.

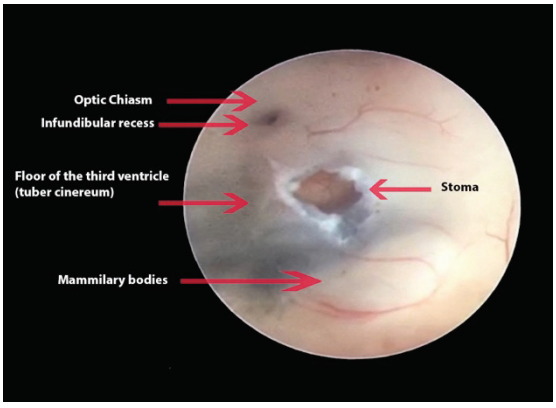

Fig 12. Creation of a passage (stoma, fenestration) at the base of the third ventricle.

13.7 Potential Problems

Although ETV is a straight forward procedure, there are a number of potential problems. Most of these relate to variations in third ventricle anatomy (33). Thick and opaque third ventricular floor is one of the most frequently encountered variations, with an approximate frequency of 16% (33). Another significant detail in preoperative MRI assessment is the the distance between the pons and clivus in prepontine space. If this distance is smaller than 4 mm, a fully inflated 3F Fogarty catheter balloon may compress the basilar artery and pons. In these cases the fogarty should be inflated less than usual. Other anatomic variations relate to the nature of the ventricle floor. The floor of the third ventricle may be steep because the upper level of the dorsum and infundibular recess are elevated compared to the mamillary bodies. Puncturing a steep ventricle floor can be very difficult. It can also be challenging to puncture a floor that is unusually resistant. If the floor is stretched excessively during puncturing attempts, postoperative diabetes insipidus and fever related to hypothalamic injury may develop. In addition, it may

not be possible to visualize the basilar artery and dorsum if the floor is thick and opaque, and this increases the risk of vascular injury during puncturing. Basilar artery injury is most serious potential complication of ETV, and this can be lethal. The location of the basilar artery should be clearly established both pre- and peroperatively, fenestration should be performed anterior to this vessel, and cautery should not be used to perforate the floor. Hypervascular ventricular floor is another potential problem in ETV, and may cause significant bleeding during fenestration. Although it is not common, spontaneous fenestration of the floor of the third ventricle may also be seen. These fenestrations are usually small and partial; thus, standard fenestration with a 3F Fogarty catheter should be created even if the surgeon notes spontaneous fenestrations in the floor during the procedure. Another potential problem during ETV is upward bulging of the ventricle floor. The floor can herniate upward and obliterate the third ventricle, making it very challenging to find the fenestration hole again and continue the procedure (34). Dilation of the infundibular recess may also cause problems during surgery. The anterior third ventricle may herniate into the sella in these cases, and fenestration may unintentionally create an opening into the sella. As mentioned above, careful preoperative MRI assessment is important to avoid unwanted problems. Knowing the basilar artery anatomy and location are also very significant factors for planning and performing successful ETV. Missing an ectatic or anteriorly placed basilar artery during preoperative MRI evaluation can lead to catastrophe. It should be noted that the basilar artery may be found more anterior to the mamillary bodies than normal in up to 12.9% of patients, especially in older individuals. Finally, in some cases, the ventricle anatomy may be completely disrupted with almost all anatomical landmarks absent (31). These cases are especially challenging, and the surgeon's experience is most important determinant of successful outcome.

13.8 Postoperative Evaluation

Ventricle size often does not change after ETV. Reports state that only 16-33% of patients have smaller ventricles after this procedure (35,36).

Although observations of flapping of the edges of the fenestration site during the procedure implies patency of the ventriculostomy and free CSF flow, this sign alone is not very reliable. Findings indicating clinical improvement are considered more valuable for assessing the success or failure of ETV. Clinical findings such as resolution of papilledema, normalization of ICP, relaxation of the fontanelles, and stable head circumference indicate a successful procedure. Several objective tests can also be used to evaluate success. Per- or postoperative flow studies performed with radiopaque or radioisotope materials may also be useful for assessing patency after ETV. Another option is to leave an external ventricular drain in place and monitor normalization of ICP postoperatively. However, it is important to remember that ICP may remain high for the first few days post-surgery (adaptation period), and this does not indicate failure. Today, MR flow studies are the most widely used and reliable postoperative tests for assessing success of ETV. These studies provide detailed information on the subject's CSF flow Dynamics. Flow-sensitive cardiac-gated cine phase-phase contrast MR images are used for quantitative and qualitative CSF flow studies, and this is one of the most frequently used methods for assessing patency in these cases (31,32).

13.9 Complications

As noted above, the most serious complication of ETV is basilar artery injury. Although very rare, this can lead to pseudoaneurysm or even death. Injuries that occur during floor puncture are more common. These include damage to the hypothalamus, pons, cerebral peduncle, and third cranial nerve. The most frequent surgical complication in ETV is bleeding, and this usually occurs due to injury of the ependymal vessels or choroid plexus. To avoid these complications, it is very important to remember that significant neurovascular structures may be very close to the endoscope during the procedure, even if they are not directly in view.

Table 1.2 shows approximate rates of various complications of ETV based on published series (23).

Neurological deficit	2.2%	Extraparenchymal hemorrhage	2.3%
Hemiparesis / plegia	0.4%	Intraventricular hemorrhage	1.8%
Herniation syndrome	0.1%	Subdural hematoma	0.3%
Fornix injury	0.1%	Epidural hematoma	0.1%
Brainstem injury / cranial nerve deficit	1.3%	Basilar artery injury	0.1%
CSF leakage	0.2%	Mortality	0.1%
Hypothalamic impairment	1.2%		
Asymptomatic Intrapar7 Hematoma	0.5%	Overall complication rate	9.4%
Intracranial infection	3%	Complication range in series	4.4-34.4%

Table 1.2: Complication rates in endoscopic ventriculostomy [23]

13.10 Outcome Of Endoscopic 3rd Ventriculostomy

Successful ETV is defined as improvement of clinical findings after the procedure with no need for shunt placement. Rates of success with this procedure vary considerably, depending on patient age and the type and etiology of hydrocephalus. Overall success rates with ETV in different groups has been given in Table 1.3 (23).

Cause	
Pineal/Tectal tumors	84%
Nontumoral aqueductal stenosis	77%

Other obstructive mass lesions	71%
Myelomeningocelel	70%
Intraventricular hemorrhage (adults)	62%
Normal-pressure hydrocephalus	57%
Slit ventricle syndrome	50%
Posthemorrhagic hydrocephalus (neonates)	8%
Age	
Age>2 years	78%
Age<2 years	54%
Age<1 years	26%
Previous shunt surgery	
Previously shunted	68%
Never shunted	65%

Table 1.3: Success Rate of Endoscopic Third Ventriculostomy in Different Patient Groups [23]

A meta-analysis done by Pople et al. in 2001 documented the highest ETV success rates in patients with hydrocephalus related to aqueductal stenosis, spina bifida, and mass lesions in the tectum, pineal region, and posterior fossa (23).The lowest rate was in patients with a history of central nervous system infection. These investigators calculated an overall success rate of 65-75% with ETV. One of the most controversial subjects related to ETV outcome is the success rate in infants. Cinalli et al. reported that the long-term success rate with ETV in infants younger than 6 months was 72% which is similar to the rate in adults (27). In contrast, Javadpour et al. documented a success rate of 21% in infants (38). The rate reported by Buxton et al. who investigated ETV in 19 premature babies of mean age 8.9 weeks, was 32% (37). These discrepancies show how variable success rates with ETV can be. Classifying success in relation to etiology may be helpful for selecting surgical candidates. Drake and Iantosca devised the following system based on this rationale (29).

High Success Rate (>75%)
Acquired aqueductal stenosis
Tumoral mass
Medium Success Rate (50-70%)
Myelomeningocele
Shunted adult
Congenital aqueductal stenosis
Cystic lesions
Arachnoidal cysts
Dandy-Walker syndrome
Shunted patients
Slit ventricle syndrome
Shunt infection
Shunt malfunction
Low success rate (<50%)
Myelomeningocele
Never shunted, newborn
Post-hemorrhagic hydrocephalus
Post-infectious hydrocephalus

Table (1.4): success rates in ETV

If a patient continues to exhibit persistent headache, increased ICP, and bulging fontanelles without clinical improvement, or if CSF leakage from the burrhole is observed after ETV, it is highly possible that the procedure has failed. In addition to technical problems, failure may be due to inappropriate indication for ETV. The most common reasons for failure in the early postoperative period are presence of a second membrane in the prepontine space, obliterated subaraclmoid spaces, and insufficient circulation or absorption of CSF. The most frequent cause of late failure is sealing of the fenestrated floor due to fibrosis, and the procedure should be repeated in these cases (27).

Another noteworthy issue is the need for extensive follow-up of these patients. One study showed that the patency rate in patients who have undergone ETV decreases over time to 44% at 10 years post-surgery (23). Thus, long-term radiologic followup should be done in these cases, and the procedure should be repeated if necessary.

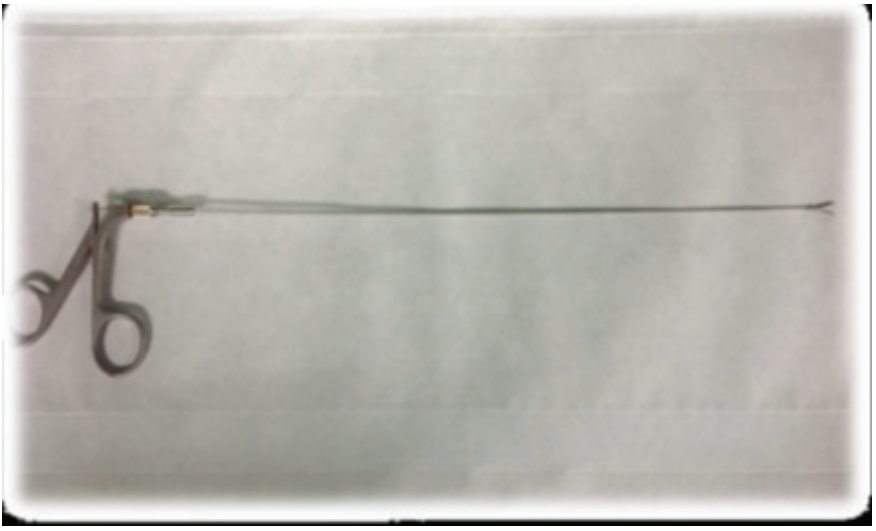

Figure (8): ffenestration forceps used to perforate the floor of the 3rd ventricle

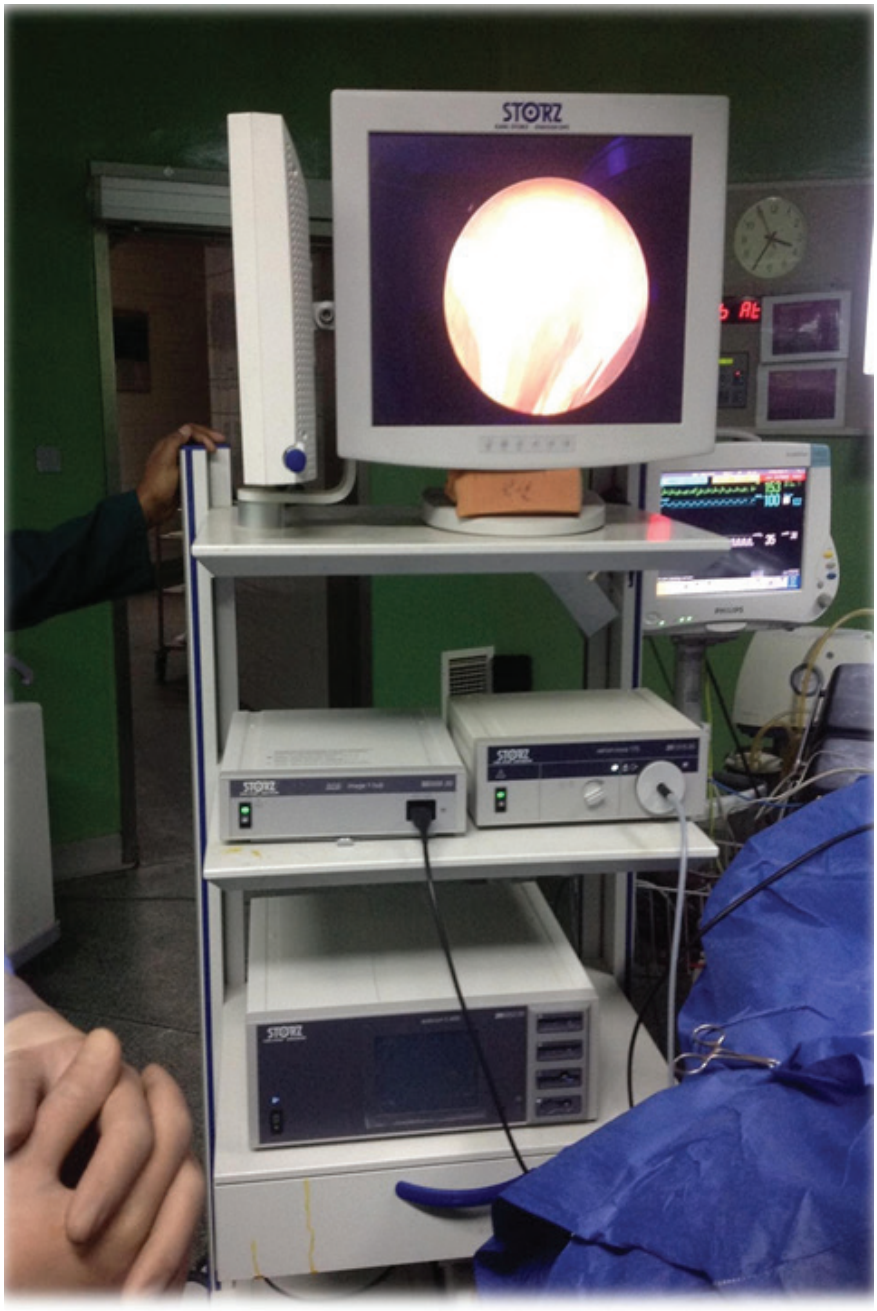

Figure (11): The monitor, light source and the recording device of the endoscope system

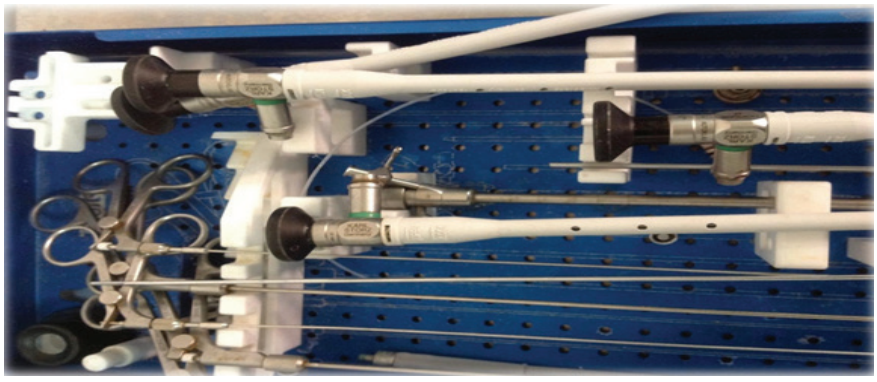

Figure (8): The instruments used in ETV

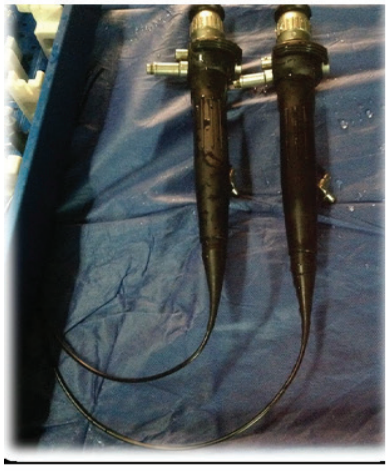

Figure (9): The flexible endoscope

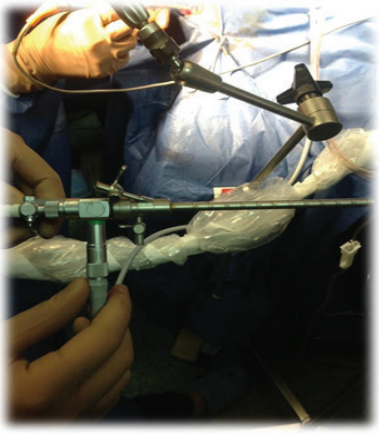

Figure (10): The rigid endoscope

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CHAPTER III

OPTHALMIC ARTERY ANEURYSMS

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1. Introduction

Aneurysms that arise from the ophthalmic artery (OAT) are particularly uncommon and complex compared with other aneurysms originating from the circle of Willis. OAT aneurysms are generally diagnosed incidentally. Symptomatic appearances are usually because of mass effect and present with exophthalmus or progressive visual disturbance (1). Clinical admission with subarachnoid hemorrhage (SAH) due to such an aneurysm is an extremely rare event when considered with the other intracranial aneurysms (2). The complex vascular anatomy of clinoid and ophthalmic segments of the internal carotid artery (ICA) and its branches and its intimate relationship to the optic nerves, the cavernous sinus and the anterior clinoid process (ACP) make it challenging to fully dissect and visualise these aneurysms and achieve sufficient proximal control. Understanding the detailed anatomy of the clinoidal ICA and the precise preoperative assessment of the origin of these aneurysms is therefore a crucial aspect of their management.

1. Microsurgical Anatomy of the Ophtalmic Artery

The ICA is divided into four segments : the C1 or cervical segment begins from common carotid artery bifurcation and terminates at the entrance of the carotid canal; the C2 or petrous segment runs inside the

carotid canal and terminates where the artery gets into the cavernous sinus; the C3 or cavernous segment runs inside the cavernous sinus and terminates where the artery runs through the dura mater making the top of the cavernous sinus; and the C4 or supraclinoid segment extends from where the artery enters the subarachnoid space and ends at the bifurcation into the anterior (ACA) and middle cerebral arteries (MCA).

ICA C4 segment accesses the subarachnoid space by passing the medial edge of the anterior clinoid process and beneath the optic nerve. It runs posterior, superior, and moderately lateral to the lateral edge of the optic chiasm and bifurcates into the ACA and MCA just beneath to the anterior perforated substance at the medial margin of the sylvian fissure.

The ophthalmic artery is the most proximal branch of the C4. Ninety-two percent of the ophthalmic arteries originate from the ICA just below the optic nerve in the subarachnoid space, superior to the dural roof of the cavernous sinus, and run anterolaterally beneath the optic nerve to enter the optic canal and orbit. The remaining 8% of the ophthalmic arteries arise from the ICA within the borders of the cavernous sinus (3). Ophthalmic artery originating from the middle meningeal artery is also reported (4). Absence of the ophthalmic artery is rare.

The ophthalmic artery is divided into three segments based on the site of the anatomical localization. These segments are; intracranial segment (preforaminal segment) extends from its junction with the internal carotid artery to the access of the optic canal , intracanalicular segment courses within the optic canal and intraorbital segments. The length of the intracranial segment of the ophthalmic artery is variable. Harris reported in a cadaveric study that, in 14% of the cadavers, there is no intracranial segment of the ophtalmic artery and the artery immediately enters the optic canal; in the remaining 86% of the cadavers, length of the preforaminal segment varies between 2.00 mm and 7.0 mm (mean 3.0 mm) (3). Drilling the anterior clinoid process both intra or extra-durally facilitates to expose the origin of the ophthalmic artery. Dividing the falciform ligament and drilling the anterior clinoid process both achieve early optic decompression and adequate dissection of the aneurysm neck during ophthalmic aneurysm surgery. Exposing the origin of the is also important to avoid the clip compromise of the ophthalmic artery.

2. Microsurgical Anatomy of the Anterior Clinoid Process

The anterior clinoid process is a posteromedial extension of the lesser wing of the sphenoidal bone like a peninsula. ACP has three extensions in continuity with the adjacent part of the sphenoidal bone. The lesser wing of the sphenoidal bone has two portions. Anterior portion forms the roof of the optic canal and posterior portion forms the base of the optic canal. This portion also forms the supero-medial roof of the superior orbital fissure. The posterior portion of the lesser wing is called optic strut. Clinoidal segment of the ICA courses just medial and below the ACP. The shallow trace of **ıca** can be visualized at the medial border of the ACP. The tip of the ACP can project posteromedially as a bony bridge and for the clinoidal foramen. This variation is an absolute contraindication for clinoidectomy because it can jeopardize the ICA during drilling the ACP. Tentorium, anterior and posterior interclinoid dural folds attach ACP. Falciforme ligament covers the ACP, runs above the optic canal and optic nerve and continues with the dura of the planum sphenoidale. Sphenoidal sinus air cells may continue to the medial edge of the ACP and overlooking this anatomical variation can cause cerebro-spinal fluid (CSF) fistula.

3. Microsurgical Anatomy of the Distal and Proximal Dural Ring

The complex relationship between the dura covering ACP and the surrounding bony, vascular and neural structures is one of the most complex patterns in comprehending the anatomy of this region and its orientation in surgical applications. The dura lining at this region has two parts; the distal (upper) dural and proximal (lower) rings. The distal dural ring lines between optic strut laterally and diapragma sella medially just below the optic nerve. The proximal dural ring lines between optic strut laterally and carotid sulcus medially just above the oculomotor nerve. The lateral part of the proximal dural ring is also called carotidooculomotor membrane. The interdural space contains large venous channels and termed as clinoid venous plexus.

4. Microsurgical Anatomy of the Ophtalmic Artery Aneurysms

Aneurysms arising from the ophthalmic segment of ICA are classified as ophthalmic, superior hypophyseal, cave and variant aneurysms. OphA aneurysms arise from the superior (dorsal) surface of the ICA in direct relation to the OphA and distal to its origin. When viewed from laterally, the cavernous (C3) and intracranial (C4) segments of the ICA have two apparent bendings that create a S-shape, and together these parts are named the carotid siphon. The aneurysm arises at the second curve of the siphon of the ICA and projects superiorly along the route of blood flow around the curve. The medio-lateral projection of the ophthalmic aneurysms depends on the origin of the ophthalmic artery. The optic nerve is commonly shifted superiorly and medially, with its superolateral aspect compressed in contact with the falciform ligament. Superior hypophyseal artery aneurysms arise from the inferomedial surface of the ICA and projects medially. The relationship between the origin of the aneurysm and the distal dural ring determines the complexity and geometric shape of the ophthalmic aneurysms. If the aneurysm is superior to the distal ring, the involvement of the carotid cave will not be possible and the aneurysm will be less complex. Exposure of the neck of this aneurysm may be improved by the drilling of the anterior clinoid process, removing the roof of the optic foramen to enable mobilization of the optic nerve, and by dividing the falciform process. Cutting the distal dural ring is usually required for appropriate clipping. For proper clipping, dividing the distal dural ring is generally needed. The perforating arteries, which arise from the ophthalmic segment of the ICA, are usually located on the medial side of the artery, so the risk of injury to the perforating arteries is very low.

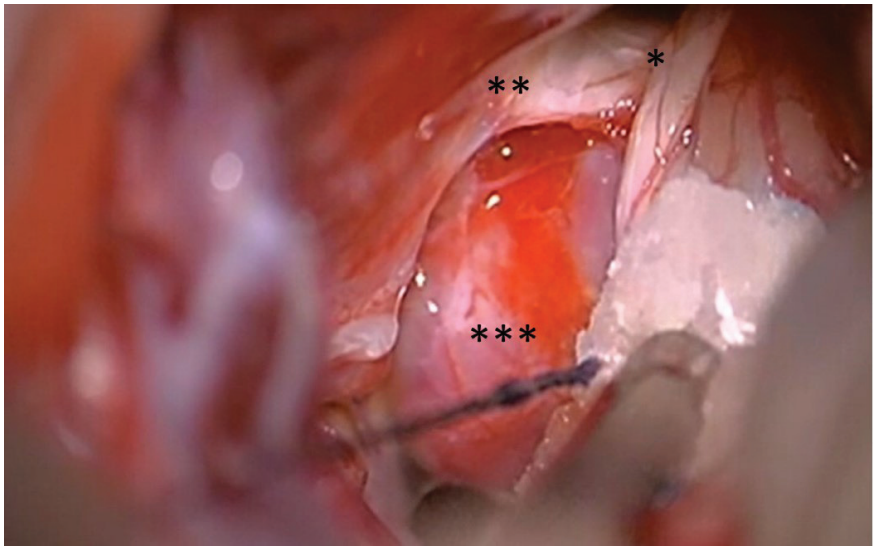

Figure 1: Intraoperative visualizing of the olfactory (*), optic (**) nerves and the ophthalmic artery aneurysm (***).

5. Surgical Technique Approach

Pterional approach with 20 degrees laterally rotation for improving the visibility of the clinoidal area is the standart approach for ophthalmic artery aneurysms.

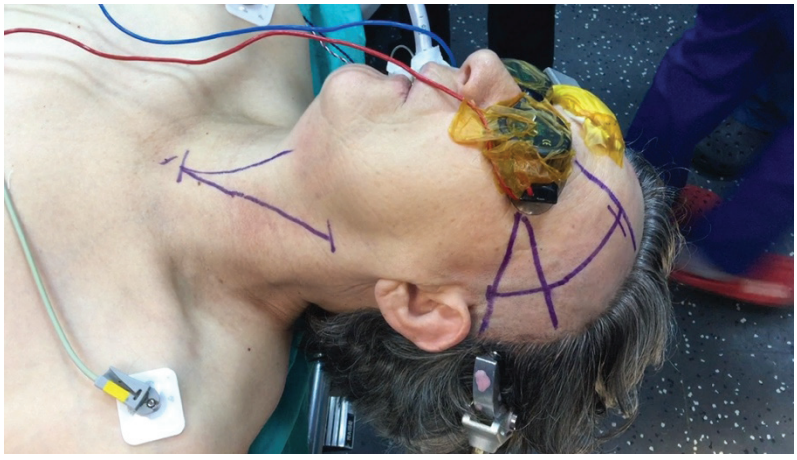

Figure 2: Head position and skin incision for ophthalmic artery aneurysm surgery. Neck is prepared for proximal controlling of the ICA

6. Neck Preperation for Proximal Controlling of the Aneurysm

Proximal controlling of the aneurysms, which is a requirement for aneurysm surgery, can be performed either by preparing the ICA at the neck or by transcavernous approach for the ophthalmic artery aneurysms, and one of these two strategies should be applied according to the surgeon's experience.

7. Extradural or intradural removing of the ACP

An anterior clinoidectomy can be performed extradurally (Dolenc approach), but the intradural drilling of the ACP is preferred because it visualizes the aneurysm and allows immediate clipping if the aneurysm ruptures prematurely.

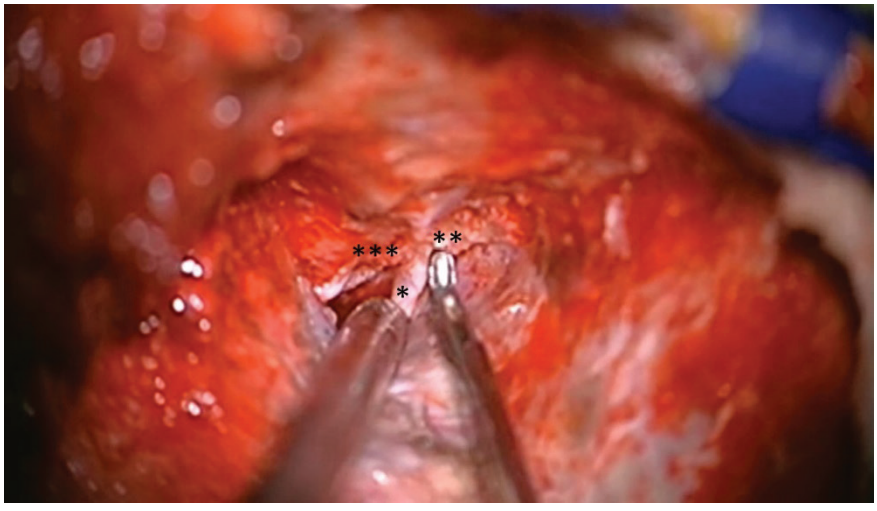

Figure 3: Extradural drilling of the ACP. Demonstration of the optic nerve (*), optic canal (**) and the optic strut (***).

8. Intraoperative Diagnostic Tools

Intraoperative angiography is the most useful intraoperative diagnostic tool during ophthalmic aneurysm surgery. However, alternative diagnostic tools for intraoperative angiography have been developed due to their

expensiveness, lack of presence in each center and difficulty of use. The most effective of these intraoperative tools is Indocyanine video angiography (ICG-VA) and has a high specificity and sensitivity to evaluate the aneurysm remnant, the parent and the perforating patency of the artery intraoperatively (5).

In addition to these two methods, micro-Doppler ultrasonography and dome puncturing after clip application should be used to evaluate aneurysm.

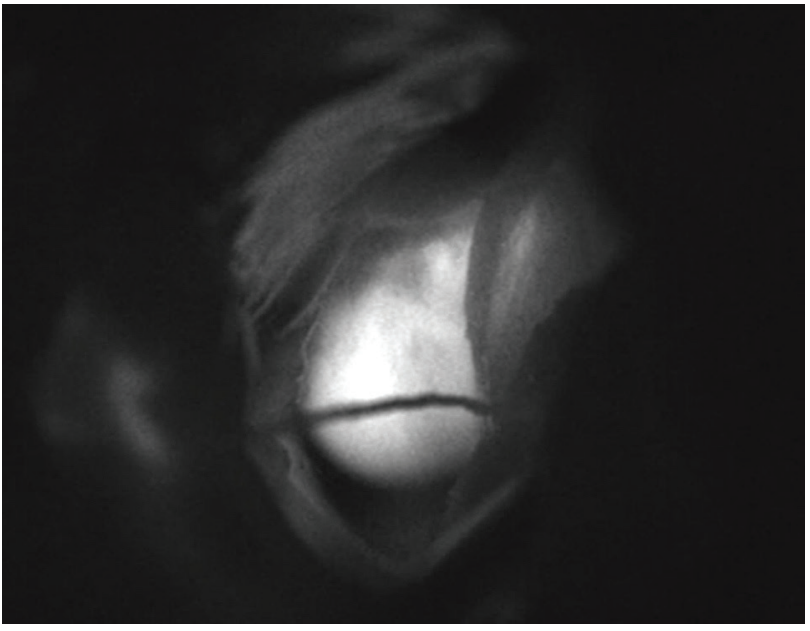

Figure 4: Aneurysm observation after ICG injection.

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CHAPTER IV

MIGRAINE: AN UPDATE ON CLINICAL DIAGNOSIS AND MANAGEMENT

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1.Introduction

Migraine is characterized by recurrent attacks of headache affecting the people during the most productive periods of their lives. The underlying pathophysiology is not clearly established yet but the activation of the trigeminovascular system seems to play the major role with contribution of the genetic and environmental factors (1-3). Patients with migraine are thought to be underdiagnosed and undertreated with a high socioeconomic burden on society (4,5). Although the development of novel treatment modalities led to better management of the patients, the lack of cure of the disease keeps up the interest in researchers

2.Epidemiology

Migraine can begin at any age but most frequently starts during puberty. The initial attacks usually occur before 30 years of age. During childhood, there is a small preponderance of males but after adolescence period, it affects women more than men with a ratio of 3:1 (5,6). The exact prevalence is not known because most people with rare headache attacks

do not consult the physician. But it is thought to affect approximately 18.2% of female patients and 6.5% of male patients (1). It can rarely start in older people. Secondary headache disorders should be excluded in people with late onset headache disorders. Up to 90% of patients have a positive family history, so it is thought to have a genetic basis (5).

3.Pathophysiology

Although studied extensively, the pathophysiology of migraine is not well understood. But it is widely accepted that it is a complex brain network disorder with overlapping phases involving cortical, subcortical and brainstem regions with a support of genetic basis and environmental factors (2,3,5).

Four phases of migraine are defined.; prodromal phase, aura phase, headache phase and postdrome phase (1). Patients can experience these phases seperately or they can overlap each other. The prodromal phase starts before the headache and and it may persist during the headache phase. Activation of hypothalamus and talamus are the main mechanisms of prodromal phase (5,7). Some studies had demonstrated increased blood flow in the hypotalamus in the early stages of migraine attacks (1). One-third of patients with migraine experience the aura phase which is caused by cortical spreading depression (2). Cortical spreading depression was first identified by Laeo in 1944. It is a slowly propagating wave of depolarization of cortex at a rate of 2-5 mm/min.and it is followed by hyperpolarization in cortical neurons and glia (1,2,7). The depolarization leads to local ionic shifts and release of some neurotransmitters. Extracellular increase of potassium and intracellular increase of sodium, chloride and calcium leads to neuronal swelling (2,5). Some aminoacids and neurotransmitters are released which helps the propagation of cortical spreading depression. Glutamate increases the production of nitric oxide and plays an important role in cortical spreading depression as an excitatory neurotransmitter. Vasodilatation lasting for one or two minutes and increase in regional cerebral blood flow occurs. This is followed by a long period of hypoperfusion. These changes are called as spreading hyperemia and spreading oligemia (2). Their role in migraine

aura and headache physiology is unclear. Cortical spreading depression is accepted as the main pathophysiological mechanism of aura phase but its association with headache phase is not clearly demonstrated (1,5).

Headache phase is explained by neurovascular theory in which the trigeminovascular system plays the key role (1,2,7). Nociceptive fibers of the trigeminal ganglion release inflammatory mediators. The most important mediators are calcitonin gene-related peptide (CGRP), substance-P and vasoinhibitory peptide. They initiate signals along the trigemino-vascular pathway. The trigeminal cervical complex has direct connections with important brain centers such as thalamic, hypothalamic, basal ganglia and brainstem nuclei and its activation leads to cascade of events resulting in headache phase (1,2).

The postdromal phase is mostly unreported by the patients and is least studied by the researchers. It may be continuation of the same pathology or a seperate entity. It is thought to be due to persistent activation of diencephalon and brainstem during and after the pain stmuli (1).

4.Genetics

Migraine is known as a hereditary neurovascular disorder (3,5). Family history of the patients points to the genetic predisposition of the disease (5). Migraine with aura and migraine without aura are polygenic variants. Small changes in many genetic loci cause the two different forms of migraine (1). The heritability of these common migraine forms thought to be between 30 and 60%. (1). The most clear association with genetics was observed in patients with familial hemiplegic migraine which is a rare form of the disease (1,3,5). Familial hemiplegic migraine is a monogenic autosomal dominant disorder. The prevalence of hemiplegic migraine, including both the familial and the sporadic forms is reported as 0.01%. Three main gains were identified for familial hemiplegic migraine. FHM1 (CACNA1A) is the first identified gene for familial hemiplegic migraine which is present on chromosome 19p13. It encodes the voltage-gated calcium channel. Animal studies showed that female sex hormones can act as modifiers of CACNA1A. This may be the reason for the female predominance of the migraine patients. Spinocerebellar ataxia type 6

and episodic ataxia type 2 are associated with heterozygous mutations in CACNA1A. The second identified gene is FHM2 (ATP1A2). It is located on chromosome 1 and encodes the K/Na-ATPase channel. This mutation has an autosomal dominant inheritance pattern presenting various clinical symptoms like seizures, fever, mental retardation and recurrent coma. The third identified gene is FHM3 (SCN1A) which encodes the voltage-gated sodium channel and presents on chromosome 2. It is present on 2q24.3. SCN1A mutations are also commonly reported in epilepsy syndromes (1,3).

5.Hormonal factors

The prevelance of migraine is equal in both sexes before puberty. But after menarche, it becomes three times more common in women (1,6). It is a disease of women of reproductive age. Menstrual periods can trigger the attacks in some patients. Menstrual migraine attacks may occur exclusively during menstruation or may be throughout the cycle with being more frequent or more intense during the cycle (6,8). Estrogen withdrawal is thought to modulate these changes. The use of oral contraceptives may worsen the pre-existing migraine or de novo migraine attacks may begin after a patient starts using oral contraceptives. Estrogen levels rapidly increses and stays high in pregnancy (8). Approximately, 70% of women report remission during pregnancy although it may worsen or remain the same in some patients (6, 8). Two thirds of women report decrease in migraine attacks in menapause whereas in a minority of patients it may begin after menapause (6).

6.Classification

The diagnostic criteria of the International Headache Society (IHS) have been accepted as the standard classification all around World (1,9). The International Classification of Headache Disorders 3rd edition is the last revised criteria of IHS (Table 1). It defines and classifies all known headache disorders. If a patient fulfills the criteria for more than one type, all should be coded (9).

Table 1: Classification of migraine types using the International Classification of Headache Disorders, 3rd edition.

Migraine types	
1.1 Migraine without aura	
1.2 Migraine with aura	1.2.1 Migraine with typical aura 1.2.1.1 Typical aura with headache 1.2.1.2 Typical aura without headcahe
	1.2.2 Migraine with brainstem aura
	1.2.3 Hemiplegic migraine 1.2.3.1 Familial hemiplegic migraine 1.2.3.1.1 Familial hemiplegic migraine type 1 1.2.3.1.2 Familial hemiplegic migraine type 2 1.2.3.1.3 Familial hemiplegic migraine type 3 1.2.3.1.4 Familial hemiplegic migraine, other loci 1.2.3.2 Sporadic hemiplegic migraine
	1.2.4 Retinal migraine
1.3 Chronic migraine	
1.4 Complications of migraine	1.4.1 Status migrainosus
	1.4.2 Persistent aura without infarction
	1.4.3 Migrainous infarction
	1.4.4 Migraine aura-triggered seizures
1.5 Probable migraine	1.5.1 Probable migraine without aura
	1.5.2 Probable migraine with aura
1.6 Episodic syndromes that may be associated with migraine	1.6.1 Recurrent gastrointestinal disturbance 1.6.1.1 Cyclic vomiting syndrome 1.6.1.2 Abdominal migraine
	1.6.2 Benign paroxysmal vertigo
	1.6.3 Benign paroxysmal torticollis

Migraine without aura and migraine with aura are the two most common types of migraine (1,8,9). The diagnostic crtieria are different for migraine with aura and migraine without aura (Table 2). At least five attacks lasting for 4-72 hours are required for the diagnosis of migraine without aura whereas two attacks are enough for the diagnosis of migraine with aura. Unilateral location, pulsation, moderate or severe pain intensity and aggravation by physical activity are the main characteristics of migraine without aura. At least one of the symptoms of nausea or photophobia and phonophobia should accompany (4,8,9).

Approximately 15-20% of the patients with migraine have migraine with aura (1,4,8). In the diagnosis of migraine with aura, there should be at least one of the fully reversible aura symptoms including visual, sensory, speech, motor, brainstem or retinal symptoms (8,9). Most of the patients with migraine with aura also have attacks of migraine without aura. Both of the diagnosis should be coded in these patients. Over 90% of patients migraine with aura report visual aura. Fortification spectrum or a zigzag figure are the most common auras (1,9). Adolescents may report bilateral visual symptoms. Sensory disturbances are the second most common auras which usually affects one part of the body, face or tongue (9). Studies have shown that patients with one of these aura types occasionally present other aura types. Therefore, they are all classified as migraine with aura. If the patients demonstrate one of visual, sensory and/or speech symptoms, then it is coded as migraine with typical aura (9). Typical aura with headache is described as headache with or without migraine characteristics preceded by typical aura. Patients may not experience headache during or after the aura phase. These patients are coded as typical aura without headache. If the aura symptoms originate from the brainstem, then it is classified as migraine with brainstem aura (9).

Dysarthria, vertigo, tinnitus, hypacusis, diplopia, ataxia and decreased level of consciousness are the aura symptoms arising from the brainstem. There should be no motor or retinal symptoms in patients with brainstem aura. Hemiplegic migraine is used for patients with migraine reporting motor weakness as an aura symptom (3,9). It can be familial or sporadic. For fulfilling the diagnostic criteria for familal hemiplegic migraine, at least one relative should have a diagnosis of hemiplegic migraine.

Headache usually occurs in these patients. Typical aura symptoms or brainstem symptoms can frequently accompany. Gene mutations should be demonstrated for the diagnosis of familial hemiplegic migraine (1,3,9). If patients with hemiplegic migraine do not have first- or second-degree relatives having hemiplegic migraine, the diagnosis of sporadic hemiplegic migraine is suitable for them. Secondary causes should be ruled out in these patients. Retinal migraine is a rare type of migraine. The aura of retinal migraine is characterized by reversible, monocular, positive or negative visual phenomena such as scintillations, blindness or scotoma. It should be confirmed by either visual field examination or the patient's drawing of a monocular field defect. The differential diagnosis should be made from hemianopia and other causes of transient monocular blindness (9).

Chronic migraine is described as a headache occuring on fifteen or more days per month for more than three months with at least eight days per month having characteristics of migraine headache with or without aura. The headache of chronic migraine can be as migraine-like or tension type-like headache, because the characteristics of chronic headache may vary from day to day. Headache diary can be helpful for the diagnosis of these patients. It may overlap with medication-overuse headache (4,8,9).

Table 2: Diagnostic criteria of migraine without aura and migraine with aura.

Migraine without aura	Migraine with aura
A-At least five attacks fulfiiling criteria B-D. B-Headache attacks lasting 4-72 hours (when untreated or unsuccessfully treated) C-Headache at least has two of the following four characteristics : 1-unilateral location 2-pulsating quality 3-moderate or severe pain intensity 4-aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs) D-During headache at least one of the following: 1-nausae and/or vomiting 2-photophobia and phonophobia E-Not better accounted for by another ICHD-3 diagnosis	A-At least two attacks fulfilling criteria B and C. B- One or more of the following fully reversible aura symptoms: 1-visual 2-sensory 3-speech and/or language 4-motor 5-brainstem 6-retinal C-At least three of the following six characteristics: 1-at least one aura symptom spread gradually over ≥5 minutes 2-two or more aura symptoms occur in succession 3-each individual aura symptom last 5-60 minutes 4-at least one aura symptom is unilateral 5-at least one aura symptom is positive 6-the aura is accompanied, or followed within 60 minutes by headache. D-Not better accounted for by another ICHD-3 diagnosis.

ICHD-3: International Classification of Headache Disorders, third edition.

Complications of migraine is another type of migraine and status migrainosus, persistent aura without infarction, migrainous infarction and migraine aura-triggered seizures are subtypes of it (8,9). A migraine attack unremitting for more than 72 hours with debilitating pain or associated symptoms is accounted as status migrainosus (8,9). Medications or sleep can cause remissions of status migrainosus for up to 12 hours. Patients diagnosed as migraine with aura can have typical auras except one or more aura symptoms persisting for more than one week with no infarction on the neuroimaging. These patients are accounted as persistent aura without infarction (9). If the one or more aura symptoms persist for more than 60 minutes with an ischemic infarction in the appropriate territory demonstrated by neuroimagimg, it is diagnosed as migrainous infarction (9). It is mostly reported in posterior ciirculation and in young women. Patients may have additional symptoms of the infarction. Increased risk of ischemic stroke is reported in patients with migraine with aura, but the underlying pathophysiology of this comorbidity is unclear. Migraine and epilepsy are both paroxysmal neurologic disorders. Epileptic attack occuring in a patient with migraine with aura during or within one hour after the migraine attack is diagnosed as migraine-aura triggered seizures. It is a rare phenomen and sometimes referred as migralepsy (9).

Sometimes it is not possible to make a definitive diagnosis of migraine (4,9). These patients are categorised as probable migraine. Probable migraine can be coded for both migraine with aura and migraine without aura. It is used for migraine headache attacks fulfilling all but one criteria (9). These patients should be counted as migraine. Because early treated attacks or mild migraine attacks may not have all the characteristics of migraine but usually respond to migraine treatments.

Episodic syndromes that may be associated with migraine are mostly reported in childhood and consists of three subtypes named as recurrent gastrointestinal disturbances, benign paroxysmal vertigo and benign paroxysmal torticollis (8,9). Motion sickness or some sleep disorders may also coexist in these patients. Recurrent gastrointestinal disturbance is described as at least five attacks including one or more of abdominal pain, discomfort, nausea or vomiting (9). It consists of cyclic vomiting syndrome and abdominal migraine (8,9). Normal gastrointestinal

examination is mandatory. The diagnostic criteria of cyclic vomiting syndrome requires at least five attacks of intense nausea and vomiting lasting for more than one hour and occuring at least four times per hour. The cyclic nature of the disease requests complete freedom between the episodes. Abdominal migraine is defined as at least five attacks of abdominal pain accompanied with two of the four symptoms of anorexia, nausea, vomiting or pallor. The patients should have normal physical examination and organic causes should be ruled out. It is seen mostly in children and they do not report headache during the episodes. But they will have a tendency to develop migraine headache later in life. Benign paroxysmal vertigo is defined as recurrent attacks of vertigo which are maximal at onset. One of the symptoms of nystagmus, ataxia, vomiting, pallor and fearfulness is required (9). Benign paroxysmal torticollis is the recurrent attacks of head tilt to one side. At least one of the symptoms of pallor, irritability, malaise, vomiting or ataxia should be reported. It is usually encountered in infants and small children (9).

Some patients may also report prodromal phase or postdromal phase. Prodromal phase starts before the migraine headache and headache follows in about 72 hours. Postdromal phase is mostly igonored by the patients. The symptoms of the prodromal phase are various combinations of fatigue, mood swings, irritability, phonophobia and food cravings. Difficulty in concentration, tiredness, mood changes, reduced appetite and muscle weakness are the most important symptoms of postdromal phase (5,1).

7.Diagnosis

7.1.History

Accurate history taking is the main issue in the diagnosis of migraine (1). It is useful to begin with when and how the headaches begin. The location, characteristics, severity, duration and frequency of the headache should be clarified. The triggering or the exacerbating factors should be asked. The presence of associated symptoms, aura, prodromal or postdromal phases should be ascertained (4). Current and previos medications should

be sought. Asking about the patient's medical history, family history and social history and encouraging the patients for keeping a headache diary would be helpful for the diagnosis (1,4).

7.2.Physical Findings

Patients with migraine usually have normal physical and neurological examinations between the attacks. The major aim of the examination is to exclude the other causes (4). During the attack, there may be distention of the scalp vessels and the blood pressure may be raised. Patients experiencing migraine with brainstem aura may have dysarthria, ataxia or decreased level of consciousness during the headache attacks. Patients with motor aura or familial hemiplegic migraine reveals various degrees of motor weakness. The visual complaints of the patients with visual aura are subjective. No impaired vision can be found. The fully reversible, monocular visual phenomena of the patients with retinal migraine should be confirmed by clinical visual field examination (9).

7.3.Laboratory and Neuroimaging Findings

The diagnosis is based on the history of the patients. There is no specific investigation for the diagnosis of migraine (1). In patients with repeated migraine attacks, the visual evoked potentials may be slowed down. Cranial CT or MRI attacks may reveal signal changes which are thoght to be due to edeme of the affected region. They resolve in a few days. Cerebral infarction must be demonstrated by neuroimaging methods for patients with migrainous infarction. Cranial CT or MRI are mostly used for the exclusion of other structural causes (4,1).

8.Treatment

When a diagnosis of migraine is made, we should tell the patient that it is a benign condition and can be controlled or at least alleviated. We should also mention that there is not a structural cause.

8.1.Avoidance of Triggering Factors

The importance of the avoidance of the triggering factors should be strongly emphasized (1,4,5,8). Nifedipine, vasodilators, indomethacine, theophylline and reserpine can cause headache. So there may be a need for the modification of the medications of the patients. Estrogens and oral contraceptives can also cause headache in some individuals (1,6,8). Reduction of caffeine and alcohol intake are helpful for most of the patients (8). Smoking should be stopped. Avoidance of fasting and bad sleeping habits should also be adviced (4). Dietary factors can rarely trigger the migraine headache (1,4,5,8). Foods containing monosodium glutamate, nitrites, tyramine, phenylethylamine and octopamine are reported to cause migraine attacks in some patients. So the patient should not take these foods if they precipitate the pain. Some strong odors may cause attacks in some patients which requires avoidance of the use of smelling items. Stress is an important triggering factor for most of the patients. Telling simply to avoid stress may not be meaningful for many of the patients. They may need the help of a psychologist (1,5,8).

8.2.Pharmacotherapy

Pharmacotherapy can be administered as symptomatic treatment and/or prophylactic treatment.

8.2.1.Symptomatic Treatment

Symptomatic treatment aims to relieve the pain, nausea and vomiting. It is more useful to start as early as possible in the development of an acute attack (4,8). If there is an recognised aura, patients can take the drug during the aura phase. Oral preperations can be less effective when the attack is fully developed. There is no benefit in using the oral preparations when the patient begins vomiting. Simple oral analgesics such as acetaminophen should be preferred for starting the symptomatic treatment (1,10). Non-steroidal anti inflammatory drugs or analgesic combinations should be second-line drugs (1,8). Combination with caffeine or anti-emetic drugs

such as metoclopramide or trimethobenzamide can be helpful for some patients (8). Ergot preparations are still important in the symptomatic treatment of migraine attacks despite some side effects (8). They should be cautiously used in patients with hypertension, cerebral or peripheral vasoconstriction, tachycardia and medication overuse headache. They are contraindicated in patients with coronary artery disease, uncontrolled hypertension, mitral stenosis, ischemic cerebrovascular disease, renal or hepatic impairment and pregnancy. Triptans can be preferred for moderate or severe cases (4,8,10). They are highly selective 5-HT receptor agonists. Some forms of triptans can be administered orally, intranasally or by subcutaneous injections. They are contraindicated in patients with peripheral vascular or cerebrovascular disease, uncontrolled hypertension, prinzmental angina, basilar and hemiplegic migraine and pregnancy (1,8,10). Opiods such as meperidine, morphine, tramadol or neuroleptics such as chlorpromazine, prochlorbenazine or haloperidol can also be used in severe cases or in patients that can not use the other symptomatic treatments (8).

8.2.2.Prophylactic Treatment

Prophylactic treatment aims to reduce the frequency, duration and severity of the headache attacks (1,11) Preventive migraine agents are used daily. They should be considered for patients who have two or more headache attacks or four or more headache days per month (8). If the patient can not the use the symptomatic treatment agents because of the contraindications, side-effects or the ineffectiveness of the drug or in some special circumstances like headache producing disability, the prophylactic treatment can also be admisinistered (4,8). The therapeutic effects starts after two months and at least six months is required for the full therapeutic effects. For the efficient prophylactic therapy, there should be at least 50% reduction in the condition within three months (8). Administering the prophylactic treatment also reduces the risk of developing medication overuse headache.

Beta-adrenergic blockers are the most frequently used drugs for the prophylactic treatment of patients with migraine. Propranolol, nadolol,

atenolol and metoprolol are all shown to be effective. They should be used with caution in patients with hypotension, bradycardia, depression, diabetes mellitus and thyrotoxicosis. They are contraindicated in patients with asthma (4,8). Verapamil, flunarizine and diltiazem are the calcium channel antagonists that can be used as a prophylactic treatment. They can prevent vasoconstriction. Therefore they can be preferred in patients with familial hemiplegic migraine, basilar migraine, hypertension, Raynaud's phenomenon, angina and asthma (4,8). Some of the antiepileptic drugs also serve as preventive treatment of migraine headache. Topiramate, valproic acid, gabapentin and pregabalin and zonisamide are the anticonvulsants that are used in migraine prophylaxis. Lamotrigine can be preferred in patients with prolonged aura (8,11). Methysergide and methylergonovine are the serotonergic agents which are shown to be effective in prophylactic treatment of migraine. Amitriptyline is an effective and most commonly used antidepressant in migraine prophylaxis (8,11). The efficacy of serotonin reuptake inhibitors and other antidepressants is not clearly demonstrated (8).

Calcitonin gene-related peptide has become a target for both symptomatic and prophylactic treatments. Exogenous administration of CGRP to patients with migraine can cause acute and delayed headache attacks. CGRP receptors are found in both central and peripheral neurons. Erenumab, fremanezumab and galcanezumab are the three new approved CGRP monoclonal antibodies for the prevention of migraine in adults (2,5,8).

If the pharmacologic treatments fail, the patient should be referred for other treatment modalities. OnabotulinumtoxinA injection can be used with high-quality evidence in patients with chronic migraine who does not respond to other prophylactic treatments used for at least six months. It is effective and well-tolerated. It should be administered to at least 31 injection sites across seven specific head and neck muscles. Treatment should be repeated at three-month intervals (4,8,11). The pharmacological block of the greater occipital nerve with local anesthetic agents such as lidocaine or bupivacaine is reported to be effective for the prophylaxis of chronic migraine. Most of the studies suggested that combination of steroid and local anesthetic agents have no extra benefit

(8,12). Neurostimulation of the supraorbital nerve, vagal nerve, occipital nerve and transcranial magnetic stimulation can be used for very severe or treatment refractory cases (4,8,11,13).

9.Conclusions

Migraine is a complex neurological disorder involving a series of abnormal neuronal networks affecting multipl cortical, subcortical and brainstem regions with contributing effects of the genetic and environmental factors (2,5,7). Patients with migraine have a reduced quality of life with impact of the disease on work or school activites and on social life. It also has a high substantial economic burden on society (4). It is evident that migraine brain differs from the non-migraine brain and migraine is more than a headache. Accurate history taking is the most important part of the diagnosis since there is no other objective diagnostic criteria. With the help of new treatment options, it became a treatable type of headache for most of the patients. A better understanding of the issues behind migraine will lead to better management of this disorder which is often overlooked and undertreated.

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CHAPTER V

METASTASES OF BREAST CANCER TO THE GASTROINTESTINAL TRACT

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1. Introduction

Breast cancer is the most common malignancy in women worldwide with a lifetime risk of 1:10. Early diagnosis and surgical treatment are effective in the management of the disease. Breast cancer is considered as a manageable disease since there has been a remarkable improvement in the diagnosis and treatment of the disease in the last fifty years. However, in more than 30% of cases, metastases occur following surgical treatment, chemotherapy, radiotherapy, and hormonal therapy. Breast cancer often metastasizes first to the axillary lymph nodes, with the incidence of distant metastases being bones, lungs, central nervous system, liver, and skin, respectively. While metastasis from breast carcinoma to the gastrointestinal (GI) tract is rare in the clinic (1), its incidence has been reported in the range of 8% to 35% in autopsy series (2,3). In most series, it has been reported that lobular breast carcinoma has a higher propensity to metastasize to the GI tract (4). The literature on GI tract metastases of breast cancer appears to be limited, mostly consisting of case reports (5). The most common incidence of rare extrahepatic GI tract metastases is colon and rectum, followed by stomach, and then small intestine (6). In this study, the diagnosis and treatment of a case of invasive ductal breast cancer that metastasized to the small intestine and cecum, which is very

rare in the literature, is presented. A detailed literature review of breast cancer metastases to the GI tract is also presented.

2. Case Report

Mechanical bowel obstruction in a 77-year-old female patient caused by a very rare GI tract metastasis from breast cancer is presented in this study together with literature review on metastases of breast carcinoma to the GI tract. Written informed consent was obtained from the patient for the presented study. The patient was diagnosed with breast cancer approximately 6 years ago, and right modified radical mastectomy was performed with the pathological diagnosis of invasive ductal carcinoma. Afterwards, the patient received systemic chemotherapy and no recurrence was observed during the follow-up period. During the post-operative routine oncological follow-up, the patient applied to our clinic with the complaint of abdominal pain lasting for 10 days. In the examinations, masses causing obstruction were detected in the terminal ileum-caecum junction of the patient and an emergency operation decision was made. During the exploration, tumoral lesions were observed in the caecum and jejunal segment that obstructed the passage. The patient underwent right hemicolectomy and partial small bowel resection operation. The pathological examination of the postoperative specimens was reported as invasive adenocarcinoma consistent with metastatic breast carcinoma in submucosal location under the small bowel mucosa.

3. Breast Cancer Metastases to Gastrointestinal Tract

The most common type of cancer observed in women is breast cancer. The sites of metastasis of breast cancer are often bone, lung, skin, soft tissue, brain, and liver. Metastasis of breast carcinoma to the GI tract has been rarely reported (7). About 75% of all metastases of breast cancer occur within the first five years of the disease being diagnosed at an early stage. This was found to be particularly true for hormone

receptor-negative disease. However, it has been found that metastases can occur over a longer period of time, sometimes even up to thirty years later, which is more common in hormone-positive disease. Breast cancer usually metastasizes to the axillary lymph nodes, bone, lung, liver, and brain. Usually, metastatic spread of any type of cancer to the GI tract is considered a rare phenomenon. Despite being infrequent, metastasis of breast cancer to the GI tract occurs in descending order in the stomach, colon, and rectum. Metastasis to the small intestine, on the other hand, is extremely rare (8).

Early diagnosis of intestinal metastasis from breast carcinoma is difficult because the symptoms are often nonspecific. Sometimes, as the tumor causes intestinal obstruction, patients may present with abdominal pain, diarrhea, or acute abdomen such as intussusception or appendicitis (9-11). Malignancy is a common cause of bowel obstruction, while adhesion, strangulated herniation, and foreign body ingestion are other causes of obstruction observed in small bowel (12). In cancer patients, small bowel obstruction is usually caused by peritoneal carcinomatosis or postoperative adhesion, although obstruction after tumor metastasis to the small intestine is rare. Among these, lobular breast cancer and melanoma are the primary malignancies that most frequently metastasize and cause small bowel obstruction (13).

The literature consists of single cases or case series, since metastasis of breast cancer to the GI tract is very rare. Although metastasis of primary breast cancer to the small intestine is very uncommon, it has been discussed worldwide since 1964 (14). In the literature on GI metastasis from breast cancer, only 17 cases were reported in a study including the period from 1988 to 2005 (15), only 14 cases were reported in another study covering the years from 1985 to 2000 (16), and a study reviewing the period from 1964 to 2016 found 38 cases (17). Invasive ductal breast carcinoma (90%) has a higher prevalence than lobular breast cancer in women, but lobular breast cancer tends to be more metastatic and metastasize to the GI tract more than ductal cancer (18). Differences in the patterns of metastases from ductal and breast carcinoma have been reported in various clinical and autopsy case series (4, 19, 20). GI and peritoneal metastases from lobular breast carcinoma was found to

have higher prevalence.In a study covering the period 1973-1990, in which 2605 cases, including 359 lobular carcinomas and 2246 ductal carcinomas, it was reported that metastasis to the GI tract was 4.5% in lobular carcinoma and very low with 0.2% in ductal carcinoma (4). In a study including the period from 1995 to 2008, it was reported that in 8 cases where breast carcinoma metastasized to the GI, the histology of most tumors was lobular carcinoma (21). In another study of Mayo Clinic consisting of 1150 cases including GI metastases of breast cancer in the period 2000-2013, it was found that GI metastases from ductal carcinoma were seen in only 12 cases. Seven of these metastases were found in the peritoneum, two in duodenum, one in stomach, one in colon, and one in rectum; and no metastases from ductal breast carcinoma to the esophagus, small intestine, ileum, and jejunum were reported (22). Metastasis from breast cancer to caecum was reported in a single case report (23).

4. Conclusion

Metastasis of breast cancer to the GI tract is extremely rare. Such a metastasis is more common in lobular breast carcinoma than in ductal invasive carcinoma. The number of reported cases of GI metastasis from breast cancer in the literature is limited. Only one case of breast carcinoma metastasis to the caecum, as presented here, has been reported in the literature. In conclusion, even long after the diagnosis of primary cancer in a patient with a history of breast cancer, the complaint of abdominal pain and the detection of any lesion in the GI tract should be carefully evaluated in differential diagnosis and metastasis should be considered. Even if the diagnosis and treatment of the primary tumor were made many years ago, GI metastases are possible, and oncologists should take this into account for patients who have been affected by breast cancer and developed GI symptoms. Adequate diagnostic procedures should be carried out as soon as possible without delay to obtain an accurate cytohistological diagnosis that allows an adequate treatment for patients.

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CHAPTER VI

MECHANISMS OF FORMATION OF ADAPTATION

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1. Introduction

As the cell evolved through environmental interaction, it was able to continually find ways to evolve by adapting to its changing environment. Environmental factors play a primary role in cell evolution in the life organization of a cell. The cell may be under the influence of agents that damage the DNA naturally or artificially in the environment. Organisms have developed many defense mechanisms to minimize genotoxic damage from the environment. Numerous mechanisms developed with the evolution of the cell continually perceive the cell's compatibility with its environment. It provides activation and/or inhibition of some specific metabolic processes that maintain cell viability. One of these defense mechanisms is the search for adaptation. Adaptation seeking is when a small amount of stress causes a rise in resistance to bigger amounts of stress. This situation is called adaptive response.

2. What Is Adaptive Response?

Adaptive response (AR) can be defined as a phenomenon in which the living cell, after being exposed to minimal stress, will respond with a high

resistance when faced with higher stress (1). In other words, adaptive response; the first exposure of the cell or living thing to non-toxic low dose genotoxic chemical agents, ionizing or non-ionizing radiation, and then making it resistant to damage to be caused by the applied toxic doses (2).

The non-toxic dose is called the adaptation dose (AD), while the toxic dose is called the challenge dose (CD). The challenge dose of mutagens causes significant damage to cells and organisms. Understanding the biological mechanism behind the AR might lead to improvements in risk management and cancer therapy assessment (radiation and chemotherapeutic agents) (1).

3. Adaptive Response Generation Methods

An adaptive response can be created in many different ways. In this section, three different methods will be discussed, respectively chemical agents, ionizing radiation, or non-ionizing radiation. The AR caused by ionizing radiation and chemical mutagens has been well documented in the literature by in vitro and in vivo studies. However, the adaptive response created by non-ionizing radiofrequency fields is less common in the literature.

3.1. Adaptive Response Created by Chemical Agents

The AR caused by chemical agents was demonstrated in Escherichia coli in 1977 by Samson and Cairns. In this study, after administration of non toxic doses of N-methyl-N-nitro-nitroso guanidine (MNNG) (1 mg/ml), the application of high-dose MNNG (100 mg/ml) caused bacteria to become more resistant to both cell death and mutation (3). It was determined that a low dose of a genotoxic the chemical agent was applied first, and then the toxic dose of the genotoxic substance was administered, and the damage to the living cell was less than expected. In this way, the cell has become resistant to damage to the toxic dose of the chemical agent applied (1,4-8).

The effect of AR in meiotic cells of Poecilocerus pictus, which was first exposed to an adaptive dose (ethyl methanesulfonate, 0.03 M) and then to a challenge dose (ethyl methanesulfonate, 0.12 M), was investigated. The adaptive response has occurred and cells have become resistant to chromosomal abnormalities (9). The AR induced by quercetin reduced the chromosomal abnormalities caused by high dose quercetin, hydrogen peroxide, and mitomycin C in V79 cells (10).

The AR of Drosophila larvae to three different alkylating agents such as N-nitroso-N-ethylurea, methyl methanesulfonate, and ethyl methanesulfonate was investigated. The number of mutant clones in the cells of the wing discs of Drosophila larvae was decreased by adaptive response generation (11).

3.2. Adaptive Response Created by Ionizing Radiation

Radiation from radon emissions, cosmic rays, and radioactive isotopes in food and water exposes humans to low doses (2.4 mGy on average). It is also exposed to occupational, medical, and research radiation sources. A medical CT scan's effective dosage is roughly 10 mGy. The organism activates its adaptation mechanisms against such attacks released by natural and artificial sources (12). Ionizing radiation dosage, measured in Gy or Sv (1 Gy=1 Sv, such as X-rays, -radiation). Low doses are those that are less than 100 mGy, moderate doses are those that are between 0.1 and 1 Gy, and high doses are those that are greater than 1 Gy, according to the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (13). In humans, epidemiological studies have demonstrated that cumulative doses of ionizing radiation exposure up to 100 mSv do not result in an increased incidence of cancer or adverse health effects (14).

Radioadaptive response induction by x-rays was demonstrated by Hillova and Drasil in 1967. The increased radioresistance after the low dose radiation applied made the cell more resistant to higher stress (15).

Olivieri et al. demonstrated the AR produced by ionizing radiation in human cells in 1984 (16). When cells are treated to very low levels of X-rays (1 cGy) and then exposed to a higher dose (1 Gy), chromosome

breakage is reduced by about half. Adaptation induced by low dose radiation (LDR) causes less damage with higher doses, as it is induced by the chromosome breakage repair mechanism. In this mechanism, it has been shown by a series of experiments that poly (ADP-ribose) polymerase inhibitors play a major role in the AR (17).

Ionizing radiation is classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC). Although the adaptive response mechanism generated by ionizing radiation has been thoroughly investigated, it is still unclear whether it will be beneficial given that ionizing radiation poses a risk to humans even at low doses (18,19).

Environmental stimuli such as environmental conditions, nutrition, chemical agents, and various diseases lead to epigenetic changes. In addition, ionizing radiation causes epigenetic changes as well as genetic mutations. Ionizing radiation causes epigenetic modifications in DNA and chromatin structure, which alter gene expression without modifying the DNA sequence (20). There is very little information in the literature about the possible role of ionizing radiation on the epigenetic mechanisms of AR (21). In the human B lymphoblast cell line (HMy2.CIR), chronic low dose γ-irradiation increased cell proliferation and clonogenicity. In addition, it has been demonstrated to be involved in the AR induced in B lymphoblast cells by increasing genomic DNA methylation in HMy2. CIR (22).

Low dose ionizing radiation has been found to promote the repair of DNA breaks in a variety of cell types and models, making the organism more resistant to cytogenetic damage (23-27), but other studies have found that low dose ionizing radiation has no effect on DNA repair (28,29). In research evaluating the protective mechanisms of LDR in mice with type 1 diabetes model, it was shown that LDR can decrease the causes of kidney damage by stimulating Akt phosphorylation and upregulating the expression of Nrf2 (30). The LDR exposure has been demostrated to significantly prevent kidney damage caused by type 2 diabetes (31).

Adaptive response formation, survival and apoptosis by the TUNEL method were investigated as a result of low ionizing radiation and then

high dose ionizing radiation given to SA-NH murine sarcoma cells. While an increase in survival of SA-NH cells was observed by 20-40%, a decrease of 20-40% was detected in apoptosis examined by the TUNEL method. The study also showed that this survival depends on the adaptive response's ability of cells to activate NF-kB (32).

3.3. Adaptive Response Created by Non-Ionizing Radiation

Radio-frequency (RF) fields in the 3 kHz–300 GHz band of the electromagnetic spectrum are used in technologies such as mobile phones, wireless, internet, and radar which are indispensable parts of our daily lives today. In addition, RF fields are used in medical imaging, diagnosis, and treatment. Biological changes that occur in tissue by electric or magnetic fields of RF radiation that are not directly related to temperature are defined as non-thermal effects (33).

The adaptive response created by non-ionizing radio-frequency fields was first demonstrated by Sanino et al in 2009. Human lymphocytes were first exposed to low dose radio frequency fields, and then a high dose genotoxic agent, mitomycin-C (MMC), was administered. Pretreatment of RF radiation has been shown to significantly reduce genotoxic damage. This study demonstrated that RF radiation has the ability to induce an adaptive response (34). Although RF radiation is not genotoxic, it is stated that it causes oxidative damage. It is thought that the oxidative stress factors may have triggered events such as the DNA repair mechanism (2).

Exposure of animals to non-ionizing radio-frequency delivered as an adaptation dosage can cause "stress" that can generate unnoticeable DNA damage. RF field exposure can activate cell defense systems by stimulating signal transduction pathways. Thanks to the generation of cell-protective processes, it provides the ability to resist harm caused by treat to high doses (2).

In 2011, the effects of non-ionizing radio-frequency radiation were classified as Group 2B by the IARC. Based on the analysis of the available scientific evidence, it was concluded that exposure to radio frequency

fields may induce possible carcinogenic damage to humans (35). Some researchers re-updated this list; Group 2A: considers it should be changed as probably carcinogenic to humans (36).

The AR effect of human lymphocytes caused by RF field exposure in the G0, G1, and S phases of the cell cycle was investigated. In the study, the cell cycle was exposed to 900 MHz radio frequency (SAR 1.25 W/kg) adaptive dose (AD) for 20 hours in the G0, G1, and S phases of the cell cycle separately and then treated to 100 ng/ml MMC high dose (CD). While it did not show an adaptive effect in the G0 and G1 phases of the cell cycle, there was a significant decrease in the number of micronuclei in the S-phase. These findings indicate that the timing of RF field exposure is significant for eliciting an adaptive response (37).

Mice were irradiated with 900 MHz RF field at a power density of 120 mW/cm^2 for 4 hours a day for 1, 3, 5, 7, and 14 days, and then the mice were exposed to a high dose of 3 Gy gamma-radiation. Single strand breaks and alkali-labile base damage were analyzed in the DNA of leukocytes by the alkaline comet method, which is a primary DNA damage detection method. Three, five, seven, and fourteen days prior to exposure to the RF field in mice, the adaptive response was induced and the damage induced by gamma rays was reduced (38). Mice were treated to RF fields with a power density of 120 $\mu W/cm^2$ for 14 days as an adaptive dose, and then 8.0 Gy γ-radiation was applied at a lethal dose. The survival rate in mice treated to only 8.0 Gy lethal dose was 18%, but the survival rate in adaptive dosed mice was up to 43% (39). Mice were treated to a radio-frequency field for five days before receiving a lethal dosage of 8.8 Gy gamma radiation on the sixth day. After 6 days, 80% of balb/c mice treated to radio frequency field + 8.8 Gy survived, while 60% of mice treated to 8.8 Gy alone survived. On day 12, this rate was 60% for radio frequency + 8.8 Gy, while only 10% of mice treated to 8.8 Gy radiation survived. By activating the adaptive response, it enhanced the survival rate of mice that had been pre-exposed to radio frequency field and then exposed to a high dosage of radiation (40).

HL-60 cells were treated to radio-frequency field at a power density of 12 uW/cm^2 for 1 hour/day for 3 days and then administered with doxorubicin. It was investigated whether RF fields can show adaptive

response in cancer cells. The findings revealed that pre-exposure to a radio frequency field might protect cells from the harmful effects of doxorubicin. As a result, the findings show that RF fields can activate an AR in HL-60 cells (41).

Although the AR mechanism has been convincingly demonstrated in vitro, risk assessments in multicellular organisms remain questionable. Therefore, in vivo studies will reduce the uncertainty on both cancer and non-cancer diseases. The question that comes to mind is whether the adaptive response caused by RF fields emitted by wireless technologies, which is one of the inevitable technologies of today and our future, can affect the results of therapeutic (radiotherapy and chemotherapy) applications.

While there is no consensus among scientists about the effects of current wireless technologies and discussions are ongoing, the effects of the increasing use of high frequencies with 5G and future 6G technology on the environmental and adaptive response have been little studied, raising public concerns about their possible effects (42).

4. Molecular Mechanism Of Adaptive Response

We are exposed to various radiation sources such as RF, electromagnetic fields (EMF), microwave radiation, ionizing radiation, and chemical agent which are basic parts of today's life. The oxidative stress induced by these factors activates various molecular mechanisms in cells associated with adaptive responses.

AR can be observed in cells, organs, and mammals using a variety of biological harm indicators after exposure to different stress factors.

The adaptive response has been shown in bacteria, plants, alga, in vitro human/animal cells, and in vivo animal models, where minimal stress renders them resistant to high doses of genotoxic damage (16,43-51). Although the adaptive response has been convincingly demonstrated in cell culture, doubts remain regarding its effects and risks in multicellular organisms.

Methods such as oxidative stress, micronuclei, apoptosis, sister chromatid exchanges, single and double-strand breakage, gene expression

alterations, antioxidant balance, survival, and chromosomal aberration were utilized to try to explain the induction of AR in several various organisms and its mechanism.

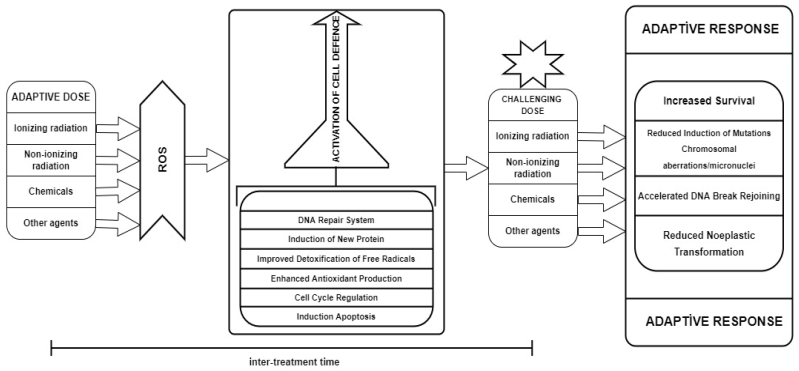

Figure 1: Probable mechanism of adaptive response (adapted from) (1).

Various mechanisms have been suggested to describe the occurrence of the adaptive response. Among these, it is thought to play a key role in cell defense with the activation of signaling pathways, antioxidant protection for more effective detoxification of free radicals, and increasing the regulation of DNA repair enzymes (1,52).

Reactive oxygen species can act with molecules including lipids, DNA, and proteins or they can generate compounds that can react with DNA. Free radicals, also known as ROS, cause oxidative stress by damaging cell components. ROS can also cause base destruction, DNA-protein crosslinks, DNA-DNA crosslinks, and single- and double-stranded breaks (1).

Depending on the type and duration of chemical or physical exposure, defense mechanisms in the cell such as cell survival/death pathway, antioxidant response (SOD, CAT), immune/inflammatory response, DNA damage repair (PARP-1, p53), endoplasmic response to stress, autophagy, and unfolded protein response may be activated.

More information is needed on the adaptive response mechanism to explain the health risks of chemical agents, ionizing and non-ionizing radiation at low natural or industrial exposure levels, and their association with carcinoma or non-cancer diseases (53).

The interval between the first and second treatments is crucial for adaptation to occur. If these exposures follow each other too quickly, the second exposure can be fatal, as there is no acceptable duration for a protective AR to be initiated. The timing between two exposures depends entirely on the compound used. The organism will respond with various defensive systems to low term and high term adaptation. A low term adaption can be described as an adaption that takes place over a short period of duration. High term adaptation refers to changes that are visible over long periods of time (transcriptional regulation) or even generations (genomic and epigenetic) (54).

Previous studies have also shown that the adaptive response does not occur immediately after exposure, so the adaptive response requires a certain time gap between the adaptation and the challenge dose to become active (2,55). There is research showing that the time between adaptive dose and challenge dose for AR formation can be 20 minutes (50), 4-6 hours (56,57). This time interval is likely to differ according to the physical factor (chemical agents, ionizing radiation, or non-ionizing radiation i.e.), cell, tissue, and organism used to generate the adaptive response.

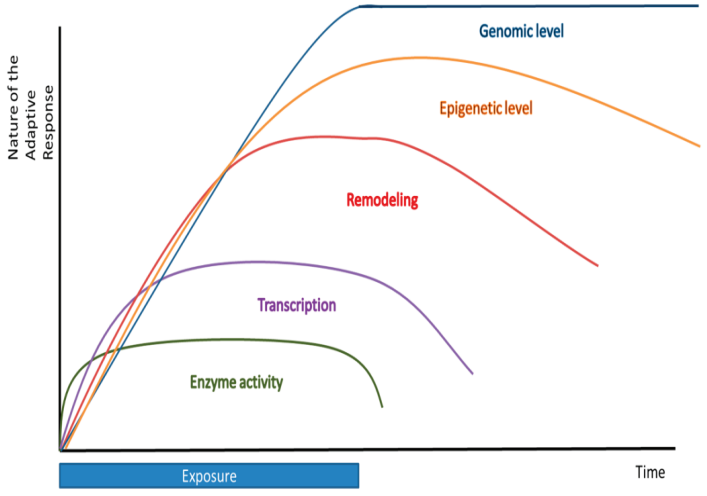

Figure 2: Defense mechanism responses of the organism against short and long-term adaptation (54).

When researching adaptive response mechanisms, it's important to look at them not just in terms of dosage or substance, but also in terms of duration.

At the molecular level, the adaptive response includes oxygen species (ROS), DNA damage response, and signaling molecules such as autophagy, apoptosis, necrosis, the unfolded protein response that play a role in cell survival. In addition, it contributes to the adaptive response mechanism by inducing cell differentiation or proliferation, controlling immune reactions or inflammatory reactions, and inducing the excretion of toxicants through transporters. Finally, it activates distant cells through bystander or abscopal effects, resulting in adaptive response in other cells (53).

5. Conclusion

The effects of adaptive response on humans are controversial. Because of the low amount of chemical or physical exposures, the scarcity of occurrences in people, and the difficulty of verifying their long-term effects, they are difficult to detect.

With an understanding of the possible effects on humans, benefits to humanity and the environment can be revealed by providing better risk estimates, revision of radiation protection standards and possible therapeutic advances.

Improved understanding of hormetic reactions will offer up new options for illness therapies aiming at improving human adaptability. Developing our capacity to adapt can help us cope with environmental changes like oxidative stress, and antioxidant balance which might otherwise lead to disorders including heart disease, malignancy, and autoimmune disorders.

The knowledge we gain about adaptive response will open new ways for disease treatments targeted at improving our adaptability. Increasing our talent to adapt to environmental changes will make human beings more resistant to factors that can lead to diseases such as immune diseases, metabolic diseases, and cancer.

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CHAPTER VII

THE EFFECTS OF COVID-19 ON PENILE ERECTION

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Introduction

Erectile dysfunction (ED) is defined as a permanent disorder in initiating and maintaining adequate erection for satisfactory sexual performance. ED affects physical and psychosocial health status and has significant effects on the quality of life of the patient and his/her partner (1). In addition, there is evidence that ED is a precursor to future coronary artery and peripheral vascular diseases (2).

Epidemiological studies have shown that ED has a high prevalence and incidence. In the Massachusetts Male Aging Study, the general ED prevalence was 52% in men aged 40-70 who did not stay in an institution in Boston, USA, and 69.2% in a study conducted in Turkey (3,4).

1. Physiopathology of erectile dysfunction

The physiopathology of erectile dysfunction consists of vasculogenic, neurogenic, anatomical, hormonal, drug-related and/or psychogenic components. In most cases, ED physiopathology consists of a psychogenic component rather than an organic component (1).

2. Vasculogenic

Vasculogenic ED is the most common etiological cause of organic ED. ED may be the precursor of another underlying vascular disease (5). The

common factor in the pathogenesis of cardiovascular diseases and erectile dysfunction is endothelial dysfunction (6). In another study, the presence of ED was shown to increase the risk of cardiovascular disease by 48% and the risk of coronary artery disease by 46% (7). Smoking is an independent risk factor for ED. In an experimental study, smoking has been shown to reduce nitric oxide synthase (NOS) activity due to oxidative stress (8).

Erectile dysfunction is 3 times more common in diabetic patients. The mechanisms that explain ED caused by diabetes are endothelial cell dysfunction, decreased neuronal NOS, decreased eNOS activity, oxidative stress, increased glycation end products, decreased elastin, and decreased VEGF (9). Hypercholesterolemia and obesity are risk factors for ED. It was found that NOS activity decreased in those who were fed a high cholesterol diet (10).

3. Neurogenic

10-19% of erectile dysfunction cases are of neurogenic origin. Conditions affecting the spinal cord, cavernous nerve or pudendal nerve, which have a place in erectile physiology, may cause neurogenic ED (10). Periventricular nucleus and hippocampus are important centers for erection in the central nervous system. Diseases such as stroke, brain tumors, Parkinson's disease, and multiple sclerosis that affect these centers can cause ED (10).

Spinal cord lesions also lead to ED (10,11). In the European urology guideline, the incidence of ED after radical prostatectomy is 25-75% and the rate of return of erection is 20-25% (1).

Erectile dysfunction is more common after pelvic radiotherapy and brachytherapy due to prostate cancer compared to the normal population (1).

ED is more common in chronic kidney patients (1).

4. Hormonal

Both hypothyroidism and hyperthyroidism lead to ED and ejaculation disorders by disrupting the hypothalamus-pituitary-gonadal axis (12).

Prolactin inhibits GnRH secretion and reduces androgen levels. Therefore, drug-induced hyperprolactinemia and pituitary adenoma are among the causes of ED (10).

- Diabetes Melllitus, Metabolic Syndrome
- Hypogonadism • Hyperprolactinemia
- Hyper- and hypothyroidism
- Hyper- and hypocortisolism (Cushing's disease, etc.)
- Panhipituitarism and multiple endocrine diseases

5. Drug-related ED

Drug side effects constitute 25% of ED cases (13). ED-related drug groups consist of antihypertensives, antidepressants, antipsychotics, anti-androgens and addictive drugs (1).

- Antihypertensives (e.g. thiazide group diuretics, beta blockers, etc.)
- Antidepressants (selective serotonin reuptake inhibitors, tricyclics)
- Antipsychotics (e.g., neuroleptics, etc.)
- Antiandrogens (GnRH analogues and antagonists, 5 alpha reductase inhibitors)
- Drugs that are addictive (e.g. alcohol, heroin, cocaine, cannabis, methadone, synthetic drugs, anabolic steroids, etc.)

6. Psychogenic

Stress, anxiety, and depression can cause ED. Again, irregularities in relationships, marriage problems, cultural factors, feeling of sexual weakness may be precipitating factors. Performance anxiety has been shown to be the most common cause of psychogenic ED (14).

7. Trauma

ED may occur due to vasculogenic, neurogenic and/or psychogenic causes secondary to traumas. The incidence of ED can be seen up to 62% after penile fracture and pelvic fracture (15,16).

Effects of covid-19 on penile erection

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has been on the agenda of the world for more than two years (17). Covid 19 findings are due to "*hyperinflammation*" that occurs as a result of "*cytokine storm*". IL-6 levels were found to be high in these patients with erectile dysfunction (18). As a result, micro thrombi and diffuse intravenous coagulation (DIC) occur. Since it is a new disease, we are just learning about most virus-related effects. One of the curiosities is whether the disease will have negative effects on sexual performance in men or its effects on sexual performance (19).

The causes of erectile dysfunction in men with COVID-19 can be listed as follows:

- Vascular effects (endothelial dysfunction)
- Psychological effects
- Deterioration of general health condition
- Hypogonadism (Low testosterone)
- Impairment of lung hemodynamics

1. **Vascular effects (endothelial dysfunction):** The erection event is closely related to the cardiovascular system), a healthy cardiovascular system is required for a healthy sexuality. Covid causes excessive inflammation in the body and consequently thrombi. In other words, there is a serious inflammation in the cardiovascular system. As a result, the vessels carrying blood to the penis are also damaged from this situation, and erection problems occur in Covid patients as a result of insufficient blood flow to the penis (20).
2. **Psychological effects:** Erection is closely related to psychological factors. For a normal erection and sexual intercourse, a life free from stress is important. Increased stress, anxiety and depression in people due to the pandemic also negatively affect people's normal sexual life (21).

3. **Deterioration of general health condition:** Sexual life and reproductive system are closely related to general body health. Since infection with Covid-19 will negatively affect people's general health conditions, erectile dysfunction or sexual problems are inevitable in these patients (22).
4. **Hypogonadism**: Studies have shown that the testes of patients with Covid-19 infection are also negatively affected and damage occurs in the testicles (23). As a result of Covid-19 infection, leydig, sertoli and spermatogonia cells are negatively affected (24,25,26) . Age is another important factor for both COVID-19 and erectile functions. COVID-19 infection is more severe in elderly patients. Therefore, sexual performance is affected more when elderly patients have COVID-19 than young people.

Numerous studies have shown that testosterone levels are low in COVID-19 patients. Low testosterone (hypogonadism) causes sexual performance deficiency in COVID-19 patients (27).

To put it briefly, erectile dysfunction, that is, sexual performance inadequacy or impotence, is high in male patients with COVID-19, especially in elderly patients. This can be summarized as psychological causes, endocrine causes (hypogonadism), impaired lung functions and cardiovascular causes due to increased inflammation (endothelial dysfunction).

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CHAPTER VIII

ENDOVASCULAR RECANALIZATION OF FEMOROPOPLITEAL OCCLUSIONS AND ANTITHROMBOTIC MEDICATION

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1. Introduction

Peripheral artery disease (PAD) is the third most common atherosclerotic disease after coronary artery disease and stroke, affecting approximately 200 million people worldwide (1, 2). PAD is determined as a partial or complete obstruction of ≥ 1 peripheral artery (1). PAS links with disability, morbidity, and mortality (1). The well-known risk factors of PAD are smoking, Type 2 diabetes mellitus, age, hypertension, dyslipidemia, and obesity (3). The symptoms of PAD can be varied according to disease severity. It can be asymptomatic in the early stage of the disease. However, the major clinical presentation of PAD is intermittent claudication (4). Intermittent claudication is a type of ischemic pain that occurs with exercise and reveals with rest (4). Intermittent claudication may be an indicator of the severity of PAD (5). However, because intermittent claudication is so relative, its correlation with disease severity is controversial. Thus to obtain a more quantitative objective indicator, the ankle-brachial index (ABI) is developed. ABI is the calculation of the ratio of systolic blood pressure at the ankle versus at the arm (6). An ABI ≤ 0.90 is a useful tool to identify PAD with serious stenosis (6).

The femoropopliteal segment includes the superficial femoral artery (SFA) and popliteal artery (7). PAD affects most commonly

the femoropopliteal segment (8). SFA being trapped in the adductor canal during exercise may be a predisposition for PAD. Chronic total femoropopliteal occlusion is the most common cause of intervention (9, 10).

2. Endovascular Treatment

2.1. Indications

According to ACC/AHA/SIR guidelines, endovascular treatment indicates in patients who have a significant disability due to intermittent claudication or critical limb ischemia (11). Endovascular treatment is recommended for femoropopliteal lesions with angiographic 50-75% stenosis. However, in addition to these angiographic criteria, translesional pressure gradient measurement can be performed to determine the hemodynamic effect. The pressure gradient greater than 10 mmHg before and after the vasodilator is accepted as a treatment criterion (8). ABI ratio <0.90 is identified as abnormal, 0.71-0.90 as mild obstruction, 0.41-0.70 as moderate, and when ABI is below 0.40 it is identified as severe obstruction (8). The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II (TASC II) classifies lesions according to their localization and severity (12). Endovascular treatment is recommended for Type A and B of the TASC II. Surgery may be performed the Type C, but if occlusion is longer than 20 cm that is Type D, surgery is recommended for treatment (12). The figure shows endovascular treatment of femoropopliteal artery chronic total occlusion.

2.2. Accessing Target Lesion

Recent developments in endovascular devices have positively affected the feasibility and results of endovascular treatment for femoropopliteal PAD. There are two approaches for accessing target lesions in the endovascular recanalization of femoral-popliteal occlusion. The

most common accessing way is the contralateral retrograde approach (13). The contralateral retrograde approach is started puncturing the common femoral artery, then accessing aorta-iliac bifurcation to past the contralateral iliac artery. This crossover approach has some disadvantages. Crossing to the contralateral side can sometimes be challenging at the iliac bifurcation level. In addition, the effectiveness of manipulations to pass the chronic occlusion may decrease due to decreased support. After passing the occluded segment, loading a balloon, atherectomy device, or stent can be challenging and can cause access loss due to the very acute angle of the iliac bifurcation. To avoid an access loss, using a long sheath is beneficial. However, the crossover approach provides a comfortable working area. Another approach for accessing target lesion (occluded segment) is the ipsilateral antegrade approach. This approach includes ipsilateral SFA or CFA puncture. The antegrade approach poses some advantages that are shorter tools and good support catheter and microwire. The disadvantage of the antegrade approach is the puncturing of SFA and the uncomfortable working area. Puncturing SFA under ultrasound guidance is useful. Another approach is the ipsilateral retrograde technique.

The ipsilateral retrograde technique includes popliteal artery puncture. In this approach, unlike the other two approaches, the patient lies in the prone position, not the supine position. The advantages and disadvantages of the ipsilateral retrograde technique are similar to the ipsilateral antegrade approach. Moreover, obese patients with respiratory distress may not tolerate prolonged prone positions. Oxygenation via a mask or nasal cannula can reduce respiratory stress in patients.

2.3. Percutaneous Transluminal Angioplasty

Percutaneous transluminal angioplasty (PTA) is the procedure of inflating the balloon, which is selected in size to cover the lesion, from the arterial lumen to provide adequate clearance in the lesion area. It is based on the idea that atheroma plaques in the target lesion are mechanically compressed into and along the artery wall. PTA was first described by Andreas Grüntzig in 1974 to open femoral artery stenosis.

The technical success rate for PTA has been reported 95%, with primary patency rates of 87% at 1 year, 80% at 2 years, 69% at 3 years, and 55% at 4 and 5 years (14). Primary patency rates of PTA decrease in the TASC II category from A to C. The primary patency rate is 87% in TASC II A, 69% in TASC II B, and 67% in TASC II C (14). Although, PTA is the first-line endovascular treatment option, it poses some disadvantages. PTA provides a temporary recanalization due to a lack of scaffolding. Moreover, target artery dissection occurs particularly when high calcium deposition is present in the target lesion. High restenosis/re-occlusion rate is another disadvantage of PTA (15).

Drug-coated balloons (DCB) contain an anti-proliferative drug (paclitaxel etc) to be released to the target lesion during angioplasty. Paclitaxel DCBs improve primary patency rates up to 3 years, reduce restenosis rates in femoropopliteal disease (16). However, there are concerns about using Paclitaxel DCBs in infrapopliteal arteries. It is stated that the use of paclitaxel DCBs in the infrapopliteal arteries for the treatment of critical limb ischemia increases the risk of death and amputation (17).

2.4. Stenting

Stents are permanent scaffolding in the vessel lumen. There are two types of stents in terms of expansion style; self-expandable and balloon expandable (18). Self-expandable stents are made of nitinol and these are bare stents (18). Nitinol is a nickel/titanium alloy that has shape memory (18). The self-expandable stents have an im-proved radial force and easy distensibility. For these reasons, they are one of the most using stents for femoropopliteal lesions (19). However, the major concern of stenting for femoropopliteal lesions is stent fracture. Stent fracture can be occurred due to high mobility, external pressure, and strong thigh muscles. For this reason, stenting through joint points should be avoided. The other risk factor for stent fracture is primary lesion features. TASC II C and D lesions associat-ed with high stent fracture risk (20). The cumulative primary and secondary patency rates at the 12th and 24th months after bare self-expandable stents are 85.6%, 83.1%, respectively (21).

Other types of stents are covered stents (as known as stent-grafts or endoprosthesis) and drug-eluting stents (DES). Covered stents have an expandable polytetrafluoroethylene (PTFE) on both the inside and outside. PTFE inhibits the growth of intimal hyperplasia and stent-grafts promise longer stents patency, theoretically (22). Long-term primary patency rates of covered stents are reported at 63%-81% (23). Another advantage of covered stents is the lack of risk for atheromatous plaques passing through the stent cells. The disadvantage of covered stents is that stent thrombosis and acute limb ischemia occur more rapidly when covered stents fail. Drug-eluting stents (DESs) are self-expandable nitinol stents with a loaded anti-proliferative agent. Anti-proliferative agent realizes slowly to avoid endothelium proliferation for obtaining long-term stent patency. The primary patency of DESs has reported a 78.8% rate at 1 year (24). The major concern of the DESs is about anti-proliferative agents' side effects.

2.5. Atherectomy

The main idea of PTA and stenting is to compress atheromatous plaques to the arterial wall and to provide luminal patency. Atherectomy devices provide luminal patency with obliterating atheromatous plaques. The major advantage of atherectomy is that reduces plaque and calcification burden. Moreover, a larger lumen diameter can be obtained with the atherectomy. In medical use, there is 4 type of atherectomy: directional, rotational, orbital, and laser atherectomy. In directional atherectomy, a cutting catheter is advanced across the occlusion. After that, a balloon is inflated with low pressure. The cutting surface of the device moves back and forth, thus the atherectomy has been performed. The directional atherectomy devices are effective in severely calcified plaques (25). The major disadvantage is arterial trauma or rupture (25). In a controlled trial, directional atherectomy and DCBs had similar results, in terms of revascularization in 1-year follow-up. The rotational atherectomy has a single diamond-like burr that rotates to drill occlusion (26). The rotational atherectomy devices have an aspiration tool for proving distal embolism. The major disadvantage of rotational atherectomy is the risk of particulate debris embolism (26).

The Rotational atherectomy with DCBs has near excellent long-term patency and very high safety (26). Orbital atherectomy includes a high-speed shaft and a crown to debulk calcified plaques and to obtain lumen patency. Orbital atherectomy allows the limited need for stenting and a favorable safety profile with long primary patency rates (27). In a trial reported, there is no difference between PTA and orbital atherectomy (28). Laser atherectomy consists of an excimer laser that obliterates atheromatous plaques using ultraviolet radiation. According to current technology, it can eliminate occlusion at a depth of 10 micrometers with each energy pulse without damaging the arterial tissue. In a randomized controlled trial, laser atherectomy has more primary patency rates than PTA (29). The advantages of laser atherectomy are using in-stent restenosis, obliterating thrombus, using in long segments, and very low vascular wall damage (30). The disadvantage of laser atherectomy is the prolonged procedure times.

3. Antithrombotic Medication

Antithrombotic medication after endovascular treatment of PAD is an essential issue for maintaining patency. Antithrombotic medication includes antiplatelet treatment and anticoagulant treatment. The recommendations of recent guidelines after lower extremity recanalization are depended on patient history. 2017 ESC/ESVS guidelines recommend long-term single antiplatelet treatment (SAPT) for all patients who have PAD (31). After recanalization, dual antiplatelet treatment (DAPT) should consider at least 1 month (31). ACC/AHA PAD guidelines recommend DAPT post-recanalization follow-up to avoid limb ischemic events (32). The society of the European Society of Vascular Medicine recommends DAPT in patients with lower extremity occlusion (33). Long-term SAPT is recommended in all patients (33). After recanalization, DAPT is considered to improve patency in patients who underwent infraingunial stenting for at least 1 month (33). Aspirin, clopidogrel, rivaroxaban are the common use antiplatelet drugs. While low-dose anticoagulation in addition to aspirin may be beneficial for patients with PAD. However, throughout the course and treatment

of their disease, more research is needed among real-world patients to confirm the benefits and risks (34).

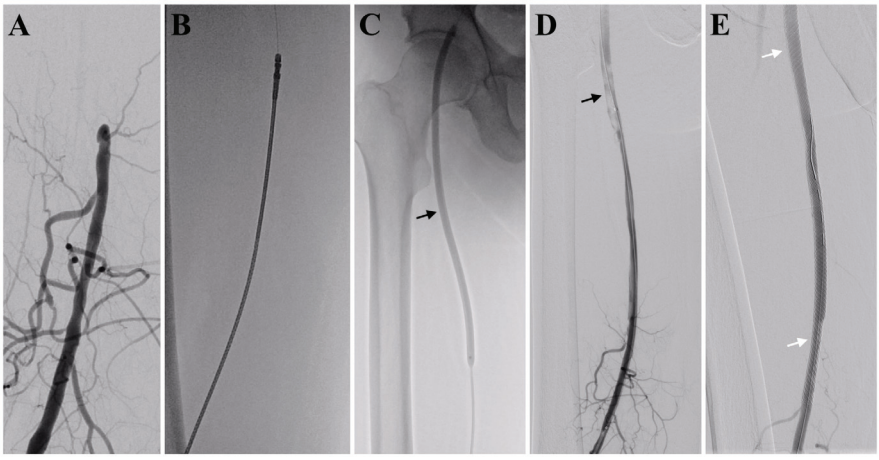

Figure: Intraoperative DSA images of a 65-year-old male patient. The figure shows femoropopliteal chronic total occlusion. A shows mid-femoral occlusion via ipsilateral retrograde (popliteal artery) approach. B shows a rotational atherectomy device to debulk ath-erosclerotic plaques. C shows percutaneous transluminal angioplas-ty (PTA) (black arrow). D shows intraluminal thrombosis (black arrow) and suboptimal recanalization. After that, stenting is per-formed to obtain optimal lumen patency. E shows sufficient paten-cy of the femoral artery (white arrows: stent).

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CHAPTER IX

PHYSIOTHERAPY AND REHABILITATION APPROACHES IN HALLUX VALGUS

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1. Introduction

Hallux valgus (HV) is one of the most common chronic foot deformities and it is the most common pathological condition in which the big toe is affected (1-3). HV deformity is a progressive deformity that changes the anatomy and biomechanical structure of the foot, characterized by the lateral orientation of the toe at the level of the 1st metatarsophalangeal (MTP) joint and the pronation and medial orientation of the 1st metatarsal bone (4, 5). If the deformity is not treated and it is allowed to progress, the patient's foot functions, daily life, and health-related quality of life will be adversely affected. HV deformity causes symptoms such as pain, problems with balance, difficulty walking, and problems with shoe selection (6).

To evaluate HV, angle measurements are performed on various radiological images, and special measurement tools inquiring about pain and functional status can be used. The severity of the deformity and the patient's complaints may not always be directly proportional. For this reason, the clinical evaluation of the patient is of great importance in terms of deciding on the treatment method and rehabilitation approach to be applied. There are surgical and conservative approaches to the

treatment of HV. In the literature, in the conservative treatment of HV, there are various approaches such as exercises (4, 7-9), orthosis (finger roller, night splint, insoles to prevent the pronation of the foot, etc.) (10-12), taping techniques (13, 14), and manual and manipulative therapy (11). Conservative treatment options are used to exclude or delay surgery, or to support the patient after surgery, prevent relapses, and increase comfort.

3. Definition of Hallux Valgus

Hallux Valgus (HV) is a progressive foot deformity manifested with the medial orientation of the first metatarsal bone, lateral deviation of the big toe at the level of the metatarsophalangeal (MTP) joint, and the pronation (eversion) of the first metatarsal bone in the longitudinal axis (5, 15, 16).

HV was first defined by Carl Huster in 1877 as a kind of deformity accompanied by static subluxation of the 1st MTP joint with a lateral deviation of the toe and a medial deviation of the 1st metatarsal bone. Afterward, the term *Hallux Abducto Valgus*, which includes the pronation deformity observed in advanced cases, has started to be used as a more accurate nomenclature (17, 18).

In the literature, this deformity has been described with the term bunion for many years. However, the term bunion fell short of describing HV as it has been used to describe any growth occurring in and around the MTP joint (17).

The American Academy of Orthopedic Surgeons defined abnormal 1st metatarsophalangeal joint angle/hallux valgus angle (HVA) greater than 15° and 1-2 intermetatarsal angles (IMA) greater than 9°. Radiological angle measurements such as HVA, IMA, distal metatarsal articular angle (DMAA), proximal phalangeal articular angle (PPAA), and interphalangeal angle are used to determine the severity of HV deformity (Figure 1). As the angular values increase, the severity of the HV deformity increases, and the symptoms may increase accordingly (3, 19-21).

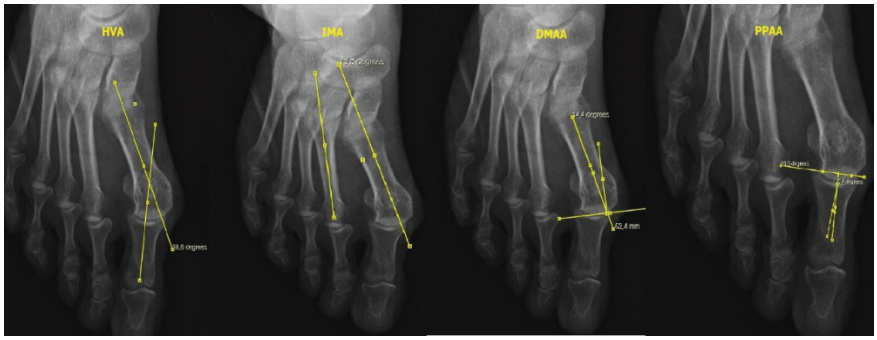

Figure 1: Hallux Valgus Related Angles (HVA: Hallux valgus angle, IMA: Intermetatarsal angle, DMAA: distal metatarsal articular angle, PPAA: proximal phalangeal articular angle)

There are also various clinical methods used to classify HV deformity and determine its severity. Garrow et al. developed the Manchester Scale, which classifies HV severity in 4 levels as absent, mild, moderate, and severe (22). The Manchester Scale is used as a non-invasive clinical tool that includes 4 photographs of the foot and has radiographic validity (23-25).

In a more detailed examination of the deformity, not only the radiographic angles, but also the osteoarthritic changes in the 1st MTP joint, the shape of the distal articular surface of the 1st metatarsal bone, the size of the medial prominence, the protrusion distance of the 1st metatarsal bone, and the degree of displacement of the sesamoid bones should also be evaluated (26).

Although the prevalence of HV varies between 21% and 74% as reported in epidemiological studies, it is higher in women and in individuals of older ages (1, 27). In a study conducted in Turkey investigating the prevalence of forefoot deformities, the prevalence of HV was reported as 54.3% (2). Depending on the deformity, problems such as foot pain, problems with gait and weight transfer, functional inadequacy, decrease in balance and quality of life, increase in risk of falling, and inability to wear the desired shoes are seen (15, 28-30).

4. Hallux Valgus and Foot Anatomy

The foot includes a total of 26 bones- 7 tarsal bones (calcaneus, talus, navicula, cuboideum, and 3 cuneiforms), 5 metatarsal bones, and 14 phalanges, and 31 joints between these bones, including the ankle joint (31).

The metatarsal bones are 5 long bones in forefoot, and they unite with the tarsal bones proximally to form the tarsometatarsal joint (Lisfranc joint). The proximal phalanges are located distal to the metatarsal bones, and the metatarsal bones and proximal phalanges combine to form the MTP joints. The first metatarsal bone articulates proximally with the medial cuneiform. It articulates with the 1st proximal phalanx distally and forms the 1st MTP joint. This joint is at the center of HV deformity (17, 32).

Bone structures are supported by ligaments, the plantar fascia, and intrinsic and extrinsic foot muscles. Intrinsic and extrinsic foot muscles function together to maintain balance, propel the foot forward in walking, and stiffen the foot in response to external forces (4). In HV, the moment and muscle balance in the joint deteriorates with the change of the bone alignment in the 1st MTP joint and the position of the intrinsic-extrinsic foot muscles (4, 33-35). While the static stabilization of the first MTP joint is provided by the harmony of the joint capsule, ligaments and joint surfaces, its dynamic stabilization is provided by the muscles surrounding it by all sides. It is thought that the strength losses of the musculus abductor hallucis, musculus adductor hallucis, and m. flexor hallucis brevis, which are the intrinsic muscles of the foot, and the tibialis posterior and m. fibularis longus, which are the extrinsic muscles of the foot, are associated with HV (4).

5. Etiology of Hallux Valgus

Although HV is one of the most common chronic foot deformities, there are still uncertainties in its etiology. Although it is thought that deformity may develop due to many different predisposing factors, its main cause is not fully understood (1, 6).

Factors that play a role in the development of HV are divided into two as extrinsic and intrinsic risk factors.

Extrinsic Factors

Shoes: The use of shoes in the etiology of HV has been accused for many years. In 1909, Porter (36) reported that the risk of recurrence of the deformity is higher in patients who underwent corrective surgery and did not want to wear appropriate shoes. In a study conducted in 225 participants in Hong-Hong in 1958, when shoe-wearing and non-shoe-wearing populations were compared in terms of HV prevalence, the result was found to be 33% and 1.9%, respectively (37). The fact that the incidence of HV is lower (38) in populations that do not wear shoes and that it is frequently (39) seen in individuals who wear high-heeled shoes with narrow toe boxes supports the place of shoes in the etiology (37). However, HV is seen in societies that do not use shoes (37) and in individuals who choose the right shoes; therefore, there is an opinion that the disorder is caused by an underlying mechanical reason exacerbated by the wrong choice of shoes, and that the symptoms increase due to the use of incorrect shoes (39). Menz et al. reported that wearing constrictive shoes in the age of 20s and 30s is critical for the development of HV in older ages (40). It is thought that shoes are an important factor rather in the progression of the deformity than its onset (6, 17, 41).

Excessive Weight Bearing: Since HV is a slowly developing deformity, it is argued that it may be a process related to cumulative trauma and overload (39). The fact that HV angulation is higher in ballet dancers than in the general population supports this idea (42). However, there is insufficient evidence to suggest that HV is associated with other factors that overload the MTP insertion, such as obesity or pregnancy (6, 17, 39).

Intrinsic Factors

Genetic factors: Approximately 80%-90% of individuals with HV deformity have a positive family history (3, 43). Although the

inheritance is thought to be autosomal dominant and the transmission is due to maternally inherited genes (3, 39), there are cases that indicate paternal origin of bilateral HV deformity (44). Deformity is observed approximately 2 times more in the white race than in the black race (6, 39). Hsu et al. investigated the genetic background in HV and reported that the genetic variants defined by emphasizing the complexity of the pathophysiological background of the deformity and the strong sex-related interaction contribute to the pathways affecting skeletal development and inflammation (45).

Gender: Although the ratio between sexes is not clear, HV is more common in women than in men (1, 6, 17). It is thought that the high prevalence in women may be related to shoe fashion and the anatomical structure of the metatarsal head being more suitable for deformity development, ligament laxity, and first-order hypermobility, which are more common in women (39).

Ligamentous laxity: Ligamentous laxity is thought to facilitate the development of HV by making the instability in the first-order tarsometatarsal and metatarsophalangeal joints evident (17). In addition, the incidence of HV is higher in diseases that cause ligament laxity (such as rheumatoid arthritis, Marfan syndrome, Ehler-Danlos syndrome) and its treatment is more difficult in such cases (39). An immunohistochemical study investigating the pathomechanics of HV showed abnormal collagen I and collagen III organization in the structure of the medial collateral ligament (46).

Age: Although there exist studies reporting that deformity often begins between the ages of 30 and 50, there are also studies reporting a higher incidence in the immature skeleton in the juvenile and adolescence period (6). Nix et al. reported the prevalence of HV as 7.8% in the juvenile population, 23% in adults, and 35.7% in older age, and its incidence increases with age (1).

Pes planus: Pes planus is widely blamed in the etiology of HV. It is thought that the collapse of the medial longitudinal arch during weight bearing will turn the whole foot into pronation, which will increase the load on the anterior region of the foot and the medial side of the toe, and will orient the toe laterally (17). In addition, the activity of m. abd. hal, which is

among the muscles that actively support the medial longitudinal arch and has an inhibitory effect on HV deformity, decreases in pes planus (47).

Other factors: First-ray hypermobility (4, 48-50), Metatarsus primus varus (39), toe abductor and adductor muscle imbalance (51), tense Achilles tendon and functional hallux limitus (17,39), first tarsometatarsal joint hypermobility (52), mismatch of MTP articular surfaces (53), and morphological features of the metatarsal bone (long first metatarsal bone, increased eversion of first metatarsal bone, rounded articular surface, etc.) are among the other factors (5, 6, 24).

6. Clinical Symptoms and Findings

Although HV is not always symptomatic, the most common symptoms in patients are pain over the medial prominence of the toe, 1st MTP joint pain, pain under the 2nd metatarsal bone head, inability to wear the desired shoe, bursa or skin irritation, and ulceration/infections (3, 52). Pain and limitation in physical functions negatively affect gait and quality of life (6, 15).

Clinical Evaluation

In the anamnesis and history section of the clinical evaluation, the patient's complaints, onset time of the deformity, duration and frequency of symptoms, severity and localization of pain, shoe preference, family history, occupation, and functional inadequacies should be questioned (6).

As HV and other deformities become more prominent with weight-bearing, assessments should be made in both standing and sitting positions (6). The most common findings in physical evaluation are the medial deviation of the 1st metatarsal bone, pronation and lateral orientation of the big toe, and the splayfoot of the forefoot (3). In addition, using some special scales related to the foot, both general pain and pain during different activities and functional level can be assessed. Some of these scales are:

In the evaluation made with the American Orthopedic Foot and Ankle Society (AOFAS) Hallux Metatarsophalangeal-Interphalangeal (MTPIP)

Scale, pain around the MTP joint, the resulting functional effects, and the smoothness of the MTP joint environment are evaluated (54).

The Foot Function Index (FFI) includes 23 items under 3 main headings: Pain, Disability, and Activity Restriction. The 9-item Pain subheading measures the level of foot pain in a variety of conditions. With the sub-heading of Inadequacy, which includes 9 items, the degree of difficulty in performing various functional activities depending on foot problems is determined. The Activity Limitation subheading, which consists of 5 items, evaluates activity limitations caused by foot problems. All items are scored with the Visual Analogue Scale (VAS) and symptoms within the previous week are considered while scoring (55).

The Manchester-Oxford Foot Questionnaire (MOXFQ) is a HV deformity-specific questionnaire. The questionnaire has three parts: walking/standing (5 items), foot pain (7 items), and social interaction (4 items). The questionnaire contains a total of 16 items with 5 different answer options. The answers of the items are scored between 0 and 4, and 4 represents the most severe condition (56).

The effects of pain and functional and social limitations on quality of life of individuals can be assessed by means of various quality of life questionnaires such as the Short Form 36 (15, 57).

In addition to clinical evaluations, radiological evaluation also plays an important role in determining and monitoring the severity of HV.

7. Rehabilitation Approaches

The selection of the methods to be applied should be made by considering the patient's complaints, symptoms, physical and radiological evaluation results, age, occupation, and general health. Conservative methods should be considered first in the treatment of hallux valgus (6).

Conservative Treatment

Conservative treatment methods play an important role in the treatment of HV due to their advantages such as shorter time to return to activity-daily life and low cost compared to surgical methods (13). Conservative

treatment in HV should begin with informing the patient about the disease. The basic pathological anatomy of the disease, the causes of pain, and ways of reducing pain should be explained. The followings are conservative treatment options used in the treatment of HV: Advice on shoe selection, foot orthoses, shoe modification, strengthening and stretching exercises, taping techniques, manual therapy, lifestyle changes (such as whole-body exercises and increased physical activity), dry needling, physical modalities and electrotherapy, massage, silicone metatarsal pads, and night splint (6, 13, 58).

In conservative treatment, first of all, it should be ensured that the patient chooses appropriate shoes. Proper shoe selection is known to reduce symptoms. To reduce pain and other symptoms, inter-toe rollers, foot orthoses, or bunion shield pad can be used together with appropriate shoes. However, these supports make it more difficult to wear shoes as they narrow the area of the big toe in the shoe (59). In this respect, banding techniques stand out as a good alternative method to use with shoes during the day, as they do not occupy an external space (60). In the literature, the necessity and benefits of exercise in the treatment program are emphasized (6, 13, 28, 58, 61). Bayar et al. showed statistically significant beneficial effects of a treatment program consisting of taping and exercise on HVA and rest and walking pain in patients with HV (7). A very important part of the rehabilitation program in HV is exercise (6, 7, 28).

7.0.1. Proper Shoe Selection and Shoe modification

Modern shoes are designed to adapt to changing outdoor environments and to meet the aesthetic needs of people. It has been reported that in some populations, especially women may prefer to wear shoes that are smaller and narrower than their feet. Improperly sized, tight-fitting shoes have been widely recognized as one of the main causes of HV development (62). In addition, it is thought that the use of minimalist shoes, which is a current approach, will normalize the forefoot morphology and neutralize the loading concentration for mild and moderate hallux valgus. From a different point of view, it is thought that the use of shoes that are small

for the feet of children in the developmental age may be a predisposing factor for the development of HV. According to the results of the studies, it is recommended to use suitable shoes in order to reduce the risk of HV, especially in adolescence, during the period when the foot grows rapidly (63). In addition, there are also studies showing that using wrong shoes, when combined with other risk factors, is a condition that increases symptoms rather than being a real risk factor for the development of the disease in patients with a predisposition to HV (41).

Shoe modifications can be made to reduce the symptoms and severity of HV by placing a soft insole inside the shoes of the person, using the bunion shield pad that covers and supports the 1st MTP joint, or placing a silicone metatarsal pad under the metatarsophalangeal joints in the anterior part of the foot.

7.0.2. Orthotic Use

There are various orthotic uses in HV treatment such as dynamic orthoses, static orthoses/night splint, toe separator, and bunion shield pad. Orthosis use allows the toe to be held in a mechanically corrected/correct position. Studies have shown that the use of orthoses in patients with HV may be insufficient to correct the radiological angles of HV, but even if there is no improvement in the angles, it improves the symptoms and increases the quality of life.

The efficacy of night-worn static orthoses in the treatment and prevention of hallux valgus progression has been shown. Therefore, the night splint, which is used to keep the toe in abduction to ensure correct joint alignment and correct position, is frequently used in the treatment of HV (64). It has been reported that night splint use reduces HV angle and HV-related pain (65). Even if there is no significant improvement in HV angle and deformity, long-term use of night splint provides a significant improvement in quality of life. However, according to studies conducted in recent years, dynamic splints are thought to be more effective than static splints in the treatment of HV. It is recommended to use dynamic orthoses that allow free movement of the joint without restricting the 1st MTP joint movement, but apply a corrective force during walking.

Long-term use is recommended to obtain beneficial results in orthotic use (66, 67).

7.0.3. Rigid Taping Application

While taping applications have been used only in athletes, currently they are widely used for purposes such as supporting damaged tissues, preventing injury, contributing to the healing process, positioning the joint correctly in many pathological conditions such as muscle imbalance, in situations where neural control is affected, for stabilization problems or joint problems. Taping applications appear as a good conservative treatment option, especially when combined with exercise, to position the 1st MTP joint correctly. Taping applications frequently used in HV treatment are rigid taping and kinesiology taping applications.

The area to be taped is brought to the correct position and fixed in this position. With taping, it is aimed to balance the loads on the nerves, joints, and muscles, and to correct the loading mechanics that are disrupted by HV. It is also stated in studies that taping application increases circulation and reduces edema, adhesion, and muscle spasm (68). Of the rigid taping techniques, some of the most frequently applied taping techniques are athletic, McConnell, and Mulligan taping techniques.

7.0.4. Kinesiology Taping Application

The Kinesio Taping® technique and Kinesio Tex® tape used as a supplement in the treatment of HV were developed in 1973 by Japanese chiropractic and acupuncture specialist Dr. Kenzo Kase (60). The purpose of the method is to support the joint and muscle structures as in standard tape applications, and also to eliminate the restriction in joint movements and functional activities, which are the undesirable effects of standard tape applications (60). While Kase et al. talk about the positive effects of tape applications by drawing attention to the followings: to increase the positional perception in the applied area by sending a signal to the central nervous system as a result of the stimulation of mechanoreceptors

through the skin; to arrange the alignment of the fascia tissue; to create stimulation or suppression to increase movement through applications made in different tensions and directions; and, to reduce pain. Data on the effectiveness and mechanisms of action of kinesiology tape are still insufficient (13, 60).

Kinesiology tape is often used with Y, X, I, Fan, and Web cut shapes. The cutting type of the tape is chosen according to the technique to be applied, the length of the muscle, the desired effect, and the area to be treated (69)(Figure 2).

Figure 2: Kinesiotape, Different Shapes of Kinesiotape and Kinesiotape Applied Hallux Valgus Deformity

Among the kinesiology taping techniques, the main methods applied include muscle techniques, fascia correction, area correction, functional

correction, and mechanical correction techniques. Neural technique, ligament technique, and lymphatic correction technique are also among the techniques applied (60, 69).

Kinesiology taping is recommended in the treatment of HV for the following purposes: to improve muscle strength and function, to control pain, to increase joint range of motion, to improve HV-related angles, and to provide mechanical correction (6, 13, 60, 70-72).

In a study examining the effect of short-term kinesiology taping on pain and joint alignment in the conservative treatment of HV, taping was applied 4 times on the 1st, 3rd, 7th, and 10th days. It was reported that, as a result of the taping program, HVA and pain intensity reduced and functional status improved (13). In a study conducted to compare the effectiveness of conventional taping and kinesiology taping in the treatment of HV, conventional taping was applied in one group of patients, kinesiology taping was applied in the other group, and the same home exercises were recommended for both groups. As a result of the 8-week treatment program, it was shown that HVA, IMA, and pain reduced in both groups, but there was a significantly greater reduction in the kinesiology taping group (71). In a case study investigating the effect of balance taping using kinesiology taping on HV, kinesiology taping was applied every day for 3 months and it was observed that HVA and IMA decreased and pain-free walking distance increased at the end of the treatment (73).

7.0.5. Electrotherapy and physical modalities

The goals of using electrotherapy and physical modalities in the treatment of HV are relief of pain and inflammation and reducing the severity of the deformity by strengthening the abductor hallucis muscle. Recommended modalities are laser therapy, ultrasound, low-frequency magnetic field therapy, shock therapy (ESWT), and High Voltage Pulsed Galvanic Stimulation (HVPGS) (64, 74). However, the number of studies with high level of evidence on this subject is very few, and mostly case reports are available.

7.0.6. Exercises

In the treatment of HV, active/passive joint movements and strengthening/stretching exercises within the general exercise discipline as well as exercises specific to HV treatment can be applied (7-9, 70). The necessity of exercises is emphasized in the literature. Characteristically, in patients with HV, there is an imbalance in the activities of m. abd. hal. and m. add. hal. (51). The activation of m. abd. hal. during the first MTP joint abduction was reported to be significantly reduced compared to activation of m. add. hal. that occurs during the first MTP joint adduction. While many studies have emphasized the importance of exercises to strengthen m. abd. hal., it has been reported in current studies that specific exercises should be applied in the treatment of HV. It is argued that increasing the strength of m. abd. hal. in the early period will be beneficial in terms of correcting the HV deformity and preventing its progression (9, 51). "Toe-spread-out" (TSO) exercises (Figure 3), defined by Keller, are an exercise method aimed to regulate muscle imbalance and increase flexibility (6).

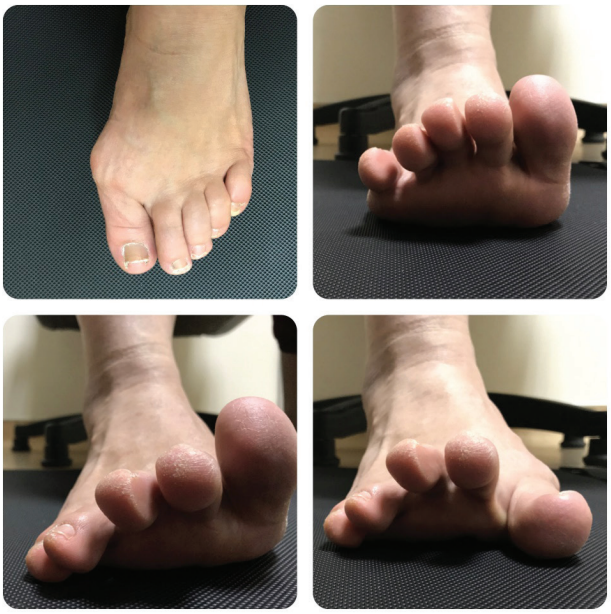

Figure 3: "Toe-Spread-Out" (TSO) Exercises

Kim et al. assessed the effects of two different foot exercises (1-toe spread out-toe sequential exercises (TSO); 2-short foot exercises (SF)) on m. abd. hal. and m. add. hal., and TSO was shown to significantly increase the activity of m. abd. hal. It was reported that TSO exercise is effective in preventing HV deformity and correcting early HV deformity (8). In another study investigating the effects of TSO exercises on HVA and cross-sectional area of m. abd. hal., it was shown that TSO exercises applied in addition to the use of orthoses for 8 weeks significantly reduced HVA and increased the cross-sectional area of m. abd. hal. compared to the orthosis-only group (9).

Although its effect on the etiology of HV deformity has not been fully shown, pes planus and foot pronation are commonly blamed. Therefore, exercises to increase the height of the medial longitudinal arch and the intrinsic muscle strength of the foot and to prevent pronation of the foot can be added to the treatment program (4, 6, 17, 75, 76).

8. Conclusion

Although HV is a common foot deformity, there are still uncertainties in its etiology. Since there can be many reasons affecting the severity and symptoms of the disease, the choice of treatment should be planned according to the needs of the patient. If conservative treatment is insufficient and symptoms, especially pain, cannot be managed, surgical treatment can be considered, but it should be noted that patients may still benefit from conservative treatment, and even if there is no improvement in deformity and HV-related aspects, serious relief may be provided in symptoms. Various combinations of conservative treatment approaches may be more beneficial for improving HV symptoms with longer follow-up durations.

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CHAPTER X

PSYCHOLOGICAL PREHABILITATION FOR MAJOR SURGICAL OPERATION IN CONSULTATION-LIAISON PSYCHIATRY

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1. Introduction

The risks stratification and prediction of major surgery procedures are difficult to evaluate before operation (1). The preoperative evaluation of comorbidities is recognised as an important issue for surgical therapy. The impact of surgery leads to significant homeostatic disturbance. Surgical interventions are applications to save the life of patients, but also these procedures are both psychological and physiologically trauma for patients (2). It is important to evaluate the general health status of the patient before the operation, to determine the possible risks and to provide holistic postoperative patient care (3). For preoperative risk assessment, medical, functional, psychological and social multidomain problems should be identified.

The surgical stress response is characterised by catabolism and increased oxygen demand (4). Major surgery is associated with a significant decline in functional capacity. The extent and duration of the stress response is proportionate to the magnitude of surgery and the associated risk of developing postoperative complications. These efforts have primarily focused on physical comorbidities but psychological comorbidities are also have an impact on surgical outcomes (5). Surgery is an experience

that threatens the patient psychologically as well as physiologically. Patients react with various emotional reactions may experience anxiety due to surgical intervention. Anxiety is defined as abnormal doubtfulness, uneasiness and restlessness accompanied by somatic symptoms (6, 7, 8). The preoperative period, which causes anxiety and fear, is also a crisis period. Surgical interventions cause both patients and their relatives to experience different emotional reactions. Patients experience anxiety as a reaction when they see a threat to their roles, body integrity and image in society and family. The patients are afraid and anxious because they does not know what will happen next after surgery.

In all surgical procedures, patients react with various emotional reactions. Patients experience anxiety as a reaction when they see a threat to their roles, body integrity and image in society and family (9). Psychological stress experienced by patients directly affects physiological functions. Regardless of the type of surgery to be applied to the surgical patient, it affects the patient physically, psychologically, socially and economically. Surgical interventions can cause serious psychological and psychosocial problems in patients because of the patients feel the lost of own control in their most intimate organs before surgery. Patients try to cope with the stress caused by surgery with positive or negative coping methods. Surgical interventions cause individuals to experience fear, excitement, tension and anxiety. Fears and anxieties experienced due to surgery may not be proportional to the severity of the surgery and no matter whether the surgical intervention that the patient will undergo is large or small. All patients who will undergo an intervention experience certain levels of anxiety and fear, and this patient's age, gender, type of planned surgical intervention, previous surgical experience and personality, etc. affected by factors. Patients experience a certain level of anxiety in the preoperative period, most frequently during the decision of surgery and due to the waiting period before the surgery.

Surgical interventions are a source of stress for the patient, as they involve applications that require entering the human body. Each individual may react differently to the same surgeries due to their unique characteristics. For this reason, physical, legal and psychological preparation of each patient for whom surgical intervention should be

planned very well. The aim of preoperative care should be to optimize the physical and psychological state of the patient before surgery.

Prehabilitation is defined as physical and/or psychological preparation designed to improve recovery time following surgical procedure (10). The goal is to ultimately increase functional capacity by ramping up mental and physical condition prior to a procedure for withstanding any postoperative decline.

In this review, preoperative evaluation of anxiety and prehabilitation of psychological factors that affect the results of major surgical treatments are discussed in current perspectives.

2.Evaluation of Anxiety in Patients Undergoing Major Surgical Operation

There is a growing recognition of the importance of psychological morbidity (11). The level of anxiety experienced by the patients before the surgical intervention affects the general condition of the patient during and after the surgery. The anxiety levels experienced by the patients in the preoperative period have a close relationship with the diagnosis, the organ and system involved by the disease, the difficulty and risk level of the surgery. Previous surgical intervention experiences of the patient may also affect the anxiety level positively or negatively (12). In addition, the patient's trust or distrust of the surgical team also affects the level of anxiety experienced. It is emphasized that preoperative anxiety prepares the patient for surgery spiritually and increases the cooperation with the healthcare team by informing the patient. Although preoperative anxiety varies from patient to patient, it is generally at a level that does not disrupt surgical treatment. When these feelings experienced by the patient can not controlled. The cultural characteristics and values of the social structure of the patient should be evaluated.

While it is known that anxiety experienced before surgery increases the incidence of postoperative complications, it is stated that postoperative complications also trigger psychological problems (13). Therefore, patients suffer from psychological problems and postoperative and they remain in a vicious circle between complications. Studies have shown

that patients with severe anxiety without treatment may experience severe complications as a result of surgical intervention, and the cost of surgical care, mortality and morbidity rates may increase.

Psychosomatic symptoms are associated with increased risk of disease, and also have a potentially poor prognosis after therapy. Preoperative anxiety symptoms are strongly associated with worse physiological surgical results in both the short and long term. Uncontrollable anxiety delays the patient's recovery and increases the risk of complications (12). On the other hand, it is stated that those with high preoperative anxiety experience more pain after surgery and therefore use more pain medication. The patients with anxiety have been seen to be at a higher risk of readmission and revision for surgery.

3.Psychological Prehabilitation

Prehabilitation is a new term in patient care that means a proactive approach to treat at risk patients before undergoing elective surgery. Prehabilitation is moving towards a multimodal approach, encompassing medical optimization, preoperative physical exercise, nutritional support, and stress/anxiety reduction (14).

Prehabilitation has garnered significant attention in recent years as evidence grows describing benefits to clinical and quality of life outcomes. Recent research examining hospital length of stay and readmission rates provides promising findings with respect to the value of prehabilitation in economic and sustainable healthcare models. It is important to support the patient psychologically, reduce anxiety and fears, provide pain management, and increase the comfort level and satisfaction of the patient (15).

It is important for patients undergoing major surgical procedures to establish realistic expectations on how their psychological comorbidities may result in worse function and pain control after surgery. Regardless of having psychological or psychosocial comorbidities, patients who are well informed about their procedure are more likely to be satisfied and have less regret. It is essential that for a successful result he including standardized presurgical psychological evaluation as an integral part of

complex surgical procedure (16, 17). The studies attempt to quantitate the surgical patients' anxiety, depression, body image and subjective quality of life by way of standardized self-assessment questionnaires. The real reason should be revealed by questioning why patients experience fear and anxiety in the preoperative period. The state of the patient's psychological health before the operation affects the satisfaction of the patient after the operation.

Cognitive methods (dreaming, positive thinking, distraction, etc.and music therapies are effective methods to reduce the anxiety experienced by patients before surgery. Patient participation should be ensured in the selection of these methods (15). Information about the care and treatments applied to the patient reduces the patient's anxiety. In addition, respecting the cultural and religious beliefs of the patient and ensuring his participation in his treatment helps control the anxiety experienced. For this reason, the surgical nurse should know about the spiritual and cultural habits and beliefs of patients (15).

4.Discussion

Psychological factors affect physiological and psychological outcomes postoperatively in a range of surgical contexts including orthopedic surgery (15, 18) and general surgery (16), cardiac surgery (19, 20) and vascular surgery (21). It was published that patients who are planned for surgical intervention experience anxiety as negatively affects the healing process physiologically and psychologically at a rate of 40-60% in the preoperative period (11, 13, 19, 20, 21).

In Güzelhan's study conducted with patients who had coronary artery bypass surgery, it was evaluated the relationship between gender and coexisting anxiety (19). Forty-five per cent of patients of patients undergoing coronary artery surgerywere classified as presenting clinically significant anxiety symptoms on Spielberger State-Trait Anxiety Inventory (STAI score of ≥ 40). It was found that the female patients' Spielberger State-Trait Anxiety Inventory scores were significantly higher than men in state and trait anxiety, both preoperatively and six months postoperatively. Postoperatively, there was not any significant

decrease in the level of trait anxiety when comparing the level of state anxiety in female patients. This study results indicate that the STAI was a valuable instrument for identifying and supporting patients with higher levels of anxiety, which could aid in determining patients that may have poor adjustment after CABG surgery. In another study, physical and mental domains of quality of life were measured using the 36-item Medical Outcomes Short-Form Health Survey self-administered questionnaire, and anxiety symptoms were assessed using the Spielberger State-Trait Anxiety Inventory (STAI) in patients undergoing open heart surgery (20). The two STAI sub-scores of the State Anxiety Inventory and the Trait Anxiety Inventory were found to be high (≥ 40) the patients experienced similar anxiety either preoperatively or 6 months postoperatively (G). While in another Güzelhan's study investigated the effect of anxiety with adverse outcome with health-related quality of life in surgical treated patients having chronic occlusive vascular disease (21). The two STAI sub-scores of Spielberger State-Trait Anxiety Inventory (STAI-S and STAI-T) were found high (≥ 40) before surgery and there were no significant decrease of the levels of anxiety postoperatively.

The transplantation studies were published to quantitate the recipients' anxiety, depression, body image and subjective quality of life by way of standardized self-assessment questionnaires. Before the transplantation, 50% of patients reported an increase in anxiety and 35% of patients recorded scores that indicated mild-to-moderate levels of depression (13). Thirty-seven per cent of patients showed a deterioration in the quality of their lives and 34% of patients had a negative body image. After the transplantation, significant improvements occurred in all parameters, which were maintained at follow-up. The recipients' satisfaction were their degree of rehabilitation at 12 months and their attitudes to various aspects of treatment after the transplantation (17).

It was stated that the anxiety levels of patients who are prepared for the surgical process with the diagnosis of cancer are very high, and therefore, patients should be supported by psychologists who are experts in their field and have experience (22). Postoperative cancer-specific quality of life was measured by the EORTCQLQ-Q30 (European Organisation for Research and Treatment of Cancer Quality-of-life

Questionnaire Core 30). It was stated that the body resistance of surgical patients with increased anxiety level decreases and their susceptibility to infection increases (22, 23).

5.Conclusion

All of the patients who will undergo surgical intervention, although at different levels, experience surgery-related anxiety. This anxiety before the operation may continue after the operation. However, the anxiety experienced before the operation causes the patient to experience non-compliance before the operation, to take more anesthetic during the operation, to experience more pain after the operation, to increase the complications, to prolong the hospital stay, to increase the cost, to decrease the patient satisfaction, to increase the rate of infection, to increase the mortality and morbidity. On the other hand, it is known that patients who are psychologically well prepared for the surgery have less anxiety, less anesthetic use during the surgery, less need for analgesics for postoperative pain control, can cope more effectively with the trauma caused by the surgery, the patient recovers more quickly and is discharged from the hospital in a shorter time.

For these reasons, anxiety control should be ensured in the preoperative period by appropriate psychological evaluation of the patients, necessary patient education and interventions. In this way, the postoperative recovery period of the patients will be shortened, and their satisfaction and quality of life will be increased. Patients will be discharged in a shorter time and cost-effective patient care will be provided. It is necessary to be supported by professionals in matters pertaining to patient consent and surgical ethics, and the stan should be well informed, and its well-being and health should be promoted.

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CHAPTER XI

EXPERIMENTAL THERMAL, MECHANIC AND CHEMICAL NOCICEPTION MODELS IN RODENTS

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1. Introduction

Experimental animal studies are basicly defined as testing the complex processes on a simpler system (1). In experimental pain studies, the aim is either to explain the characteristics and nature of pain, or to explain the possibility of any substance on the perception of pain (2). It is very difficult to evaluate pain threshold and analgesia in animals. Apart from the fact that the concept of pain is subjective, its association with animal behavior has still not been adequately defined. The response is often a simple reflex.

2. Experimental Model Selection Criteria

When choosing an experimental animal model for a scientific research, genetic, physiological and anatomical compatibility of the animal to the human should be considered. The number, age, breed, height and weight of the animals included in the study should be optimized as the suitability of the model directly affects the accuracy of research (3). Considering these factors, the appropriate animal model should be preferred in the experimental setup. Any changes in environmental conditions may create a stress factor on the animal and negatively affect the data. Therefore, environmental factors that may affect the animal biology, quality of life and behavior should be eliminated during experiment design.

Reflective pain tests are known to evaluate the evoked behavior responses subsequent noxious stimuli such as heat, cold, mechanic, and electric, which are raised from the activation of nociceptors and result in reflexive motor responses (4). Changes in thresholds or latencies at the wound site after stimulation is defined as primary hyperalgesia, and is responsible for the sensitization of nociceptive primary afferent neurons. Secondary hyperalgesia is involved in the sensitization of spinal cord neurons or central nervous system (5).

3. Experimental Conditions

The important thing in pain models is to evaluate the behaviors correctly and to determine when the animal perceives pain. Rats and mice are the most used subjects in pain studies. It is extremely important that the animal is brought to the experimental environment a certain time before the experiment and that the animal gets used to being handled. In addition, the inbredness of the experimental animal, its gender and age (usually it is recommended to be 6-8 weeks old) are important for the reliability of the experiment. The standardization of the conditions in which the experimental animals are kept is both an ethical necessity and a factor that directly affects the scientific quality of the studies. In accordance with international standards, the subjects should be isolated against external factors, in 12/12 hours of light/dark cycle adjusted automatically, and the temperature should be appropiately 20 ^{o}C with humidity constant around 60% (6).

4. Nociception and Analgesia Tests

4.1. Tests Using Thermal Stimulus

4.1.1. Tail Flick Test

The radiant heat is applied on a certain point on the tail of the animal by means of a lamp in tail flick test. There is a photosensor under the area where the tail is placed. The animal pulls its tail when it feels

pain, and it is turned off by the photosensor. The time elapsed from the start of the application until the tail is withdrawn is determined. This simple spinal reflex determines the pain threshold of the animal and the administration of analgesics significantly prolongs this time. This test is used in the measurent of spinal nociceptive reflex in which a mouse's normal reaction time ranges from 2 to 10 seconds on average. It is not recommended to apply radiant heat for more than 20 seconds as it will cause tissue damage. Therefore, a cut-off time must be determined (7).

The parameter measured is the time until the tail reflexively withdraws following exposure to the heat-evoked stimulus. It is expressed in seconds. Heat stimulation can be achieved by a beam of infrared heat, or by immersing tail in a bath at a controlled temperature (8).

4.1.2. Hot-Plate Test

This is one of the most used methods in the evaluation of the pain threshold of rodents. It basically consists of a surface (copper or aluminum) heated to 50-55 °C. The time from placing the mouse on the surface until the animal pulls its hind foot is determined. The antinociceptive response is the time until the first behavioral sign of nociception is observed. A mouse's normal reaction time ranges from 5 to 20 seconds on average. The test should not be applied for more than 30 seconds as it will cause tissue injury (9).

To eliminate the individual differences in paw withdrawal time, percentage should be converted to the maximum possible effect (% MPE) by:

$$\%MPE = \frac{(\text{Postdrug latency} - \text{Predrug latency})}{(\text{Maximum latency} - \text{Predrug latency})} x100$$

Pain responses obtained from the hot plate test are at the supraspinal level, allowing for repeated measurements as the parameter is usually paw licking latency(8). However, the biggest disadvantage of the method is that the reaction time shows a lot of individual variability (10).

4.1.3. Thermal Plantar Test

The thermal plantar test is one of the most used methods in the evaluation of the thermal hyperalgesia of rodents. This test can be defined as the paw withdrawal test after radiant heat application. Also it is known as the Hargreaves method. Animals are kept in glass boxes and a controlled heat beam system under the glass reached the paw of animal. Stimulus initiation starts the timer, while claw retraction stops the timer automatically. The thermal stimulus is transmitted in repeated measurements, to the mid-plantar area of the right/left hind paws, by means of movable radiant heat source under the glass plate in which the animal is located. When the rat feels pain and retracts its paw, the radiant heat source is automatically turned off and set the withdrawal time. If the animal does not retract its paw, the radiant heat source will automatically turn off at 25 s (cut-off latency) to avoid tissue damage (11).

The measurements in the thermal plantar test takes longer time than hot plate test. The reasons are the requirement of time for the animal to acclimate to the box before each test procedure. In addition, left and right hind paw are recorded independently and measured repeatedly to average the results. On the other hand, the advantage of this test is that it allows to see the differences in the response of both paws. Therefore, this model is more suitable for pain models created unilaterally by paw or knee injections or manipulations of the sciatic nerve. It can also be used for topical agents that provide a control measurement for contralateral paw (8).

4.1.4. Cold Stimulus Test

Cold is rarely used in acute pain experiments. However, the use of cold stimuli is common in chronic pain/neuropathies. It is generally performed by immersing the tail in cold water or leaving the animal on the cold platform. Applying a drop of acetone to the hind paws is also a method to evaluate cold allodynia. Evaporation of acetone produces a stimulus that is not usually perceived as nociceptive but it produces cold allodynia in models with neuropathic pain. (12).

5. Tests Using Mechanical Stimulus

5.1. The von Frey Filament Test

It is one of the most used methods in the evaluation of mechanical allodynia of rodents. Mechanical allodynia is detected with von Frey filaments (0.25-2.5 g). Rats are kept in individual glass boxes on a stainless steel mesh floor. A force of 2.5 g/s is applied to the plantar surface of the animal's hind paw through a flat metal filament with a diameter of 0.5 mm. When the animal feels pain and lifts its foot, the threshold is digitally recorded in grams. It automatically shuts down when mechanical stimulus reaches 50 g cut-off force to prevent tissue damage (2).

Values obtained from the von Frey filament test in rodents may appear in different numbers depending on the type of filaments used. For example, mechanical thresholds for paw retraction in mice can range from 0.3 g to 7-10 g (13).

6. Tests Using Chemical Stimuli

Tissue injury or inflammation caused by environmental pathogens causes various chemical substances to release locally from damaged tissues or surrounding tissues, and they reduce the threshold in nociceptors, resulting in an increase of pain sensitivity. These models examine the anti-inflammatory effects of many natural and synthetic substances in acute inflammation. Mostly, male Sprague-Dawley rats, Wistar rats and Swiss albino rats are preferred to perform the setup. Formalin, carrageen, histamine, serotonin, bradykinin, dextran, lipopolysaccharide, arachidonic acid, croton oil, oxazolone, acetic acid, serotonin, kaolin, platelet activating factor and mustard oil can be used as the chemical stimulants (14).

6.1. Formalin Test

This is the most common model used to evaluate the nociception and inflammation in rodents. The advantages of this test are the convenience of testing procedure with a single implementation and the evaluation of nociceptive responses with two separate interpretations. A biphasic

activity is observed in rat dorsal horn neurons, which are predominantly stimulated via unmyelinated nerve fibers. With continued nociceptor discharge from the nociceptors, a prerequisite for spinal sensitization and secondary hyperalgesia is achieved. In fact, in the formalin test, spontaneous pain behavior of the injected paw is evaluated (15). In this test, lifting or licking of the formalin-injected paw is scored. These values are recorded separately in two phases; early and late phase. The early/acute phase begins immediately following formalin administration and lasts 5-10 minutes, named the neurogenic phase. The late/tonic phase starts about 15 minutes after the injection and lasts for about an hour, denominates the inflammatory phase (9). It is known that the formalin receptor pathway is mediated through an ion channel, the transient receptor potential ankyrin 1 (8). In the early phase, nociceptors are directly stimulated with chemicals, while inflammation accompanies the late phase. About 10 minutes after injection, a period of minimal pain occurs to differentiate the phases, called the interphase. The time remaining between the two phases consists of the inhibition at the spinal and supraspinal levels (16).

The formalin test differs from most pain models since it determines how an animal responds to sustained pain produced by injured tissue. Because of the tissue damage, formalin test is considered a more valid model than testing 'phasic' responses by mechanical or thermal stimuli. The nociception in the formalin test is termed 'tonic' and an injection of formalin can induce a condition closer to clinical conditions with acute cutaneous stimulation (16).

6.1.1. Formalin-Induced Paw Edema

A concentration of 5-10 % formalin solution (volume approximately 20 µl in mice, 30 µl in rats) is administered into the subplantar region of the paws of animals. A plethysmometer is used to measure paw edema in models of acute inflammation. Paw volume is measured and recorded before formalin injection to the paw. Later, paw volume is re-measured at 1 hour to detect the edema volume. The difference in paw volumes is taken as inflammatory response (9).

6.2. Abdominal Writhing Test

In abdominal writhing test, mostly, phenylquinone or acetic acid (0.6-0.9 %) is used. Writhing occurs as a natural reflex of the injected animal. The basic behavior is the abdominal muscles contractions and extension of hind legs. Frequency of abdominal muscle contraction in each mouse is counted for 30 minutes. Abdominal contractions begin a few minutes after injection and reach a maximum in 5-10 minutes. The difference in the number of abdominal contractions between rodents treated and untreated with the compounds is expressed as the antinociceptive response (17).

6.3. Capsaicin-Induced Paw-Licking Test

Capsaicin (volume of 20 μL) is injected intraplantarly on the hind paw of mice. Similar like the formalin test, immediately following capsaicin injection, animals are observed for the behavior of licking or biting the capsaicin-injected paw. Their behavior for 5 minute is considered as nociceptive response (17).

7. Conclusion

Experimental pain studies are the important areas of reseaching on the nociception response. Over time, this process, which started by providing basic information, has developed various tests and models. Adequate correlation of relevance of the protocols is critical in order to derive useful implications for humans. Similarly, the existence of additional modalities that can alter the pain response is now expanding the scope of these studies. Therefore, it seems that the field is not only based on the current models, but in addition, it is in a continuous development in order to increase the quality of research, to detail the tests, to analyze the data correctly, to access new parameters and to present them for the benefit of human beings.

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CHAPTER XII

ANTIOXIDANT DEFENSE MECHANISM AGAINST FREE RADICALS

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1. Introduction

Reactive oxygen species (ROS) are constantly formed in the cells throughout life, but there is an antioxidant defense system that interacts with them and reduces their effects. If the balance required by these two mechanisms is disturbed in favor of ROS, superoxide radicals accumulate in the cell and oxidative stress occurs. Free radicals damage the proteins, lipids and nucleic acids in the cell, disrupt the intracellular signaling pathways and cause many effects at the molecular level in the organism. Oxidative stress induced by free radicals can lead to the formation of many diseases such as neurological, immune system, endocrine system, cardiovascular system disorders and cancer. The effect of oxidative damage caused by free radicals is also great in the formation of aging and degenerative diseases related to aging (1).

2. Free Radicals

Atoms or molecules with one or more unpaired electrons, which are obtained as a result of many physiological and pathological formations,

are defined as free radicals (2). Any compound can become a free radical by losing or gaining electrons. Free radicals can also be formed by homolytic bond breakdown. As a result of homolytic cleavage, the covalent bonds are separated symmetrically, and an electron remains in each of the two resulting fragments, and as a result, a free radical is formed. Free radicals can be positively or negatively charged or neutral. Radicals may be elements of a much larger structure or may be in the form of smaller and freely diffusing species. Free radicals are formed in cells due to internal and external factors.

Exposure to chemicals such as paraquat and alloxan, drug poisoning such as carbon tetrachloride and paracetamol, radiation from ionized and ultraviolet rays, herbal chemicals causing air pollution, environmental factors such as smoking, solvents, and addictions such as alcohol and drugs are among the external factors. Free radicals are also of great importance in terms of toxicology due to the presence of substances that are toxicologically (3).

Free radicals are atoms or molecules with an odd number of electrons in their outer orbita. They exist as both organic and inorganic molecules. If the electron is not paired, the molecule becomes more reactive and unstable. Reactive oxygen molecules are divided into two groups: those that can donate a single electron to another molecule (radicals) and those that can combine with other molecules more weakly than radicals (non-radicals), although they do not lack electrons. It is not molecular oxygen itself that is toxic to living things. Oxygen radicals formed by incomplete reduction of oxygen constitute toxicity (4).

The central nervous system is more susceptible to oxidative damage than other organs in the body. Possible reasons for this can be summarized as follows:

1. The brain uses 20% of the body's oxygen. Because oxygen products are toxic, neural tissues are more susceptible to oxidative damage than other organs.
2. Oxidative in the brain metabolic activity rate is high.
3. Brain to resist oxidative damage is limited. This is due to low levels of important antioxidant enzymes.

4.Neural membrane contain high concentrations of polyunsaturated fatty acids such as phospholipids, easily oxidized linoleic acid and arachidonic acid (5).

Under normal conditions, most of the molecular oxygen in biological systems is reduced to water as a result of a series of reactions to produce ATP by aerobic glycolysis, and some electron leakage occurs during these events. As a result of this leakage, reactive products such as superoxide anion, hydrogen peroxide and hydroxyl radical are released with the reduction of oxygen (6).

Adding energy to O_2 creates a singlet oxygen ($^1O_2$) molecule. The superoxide anion radical (O_2^-) is formed as a result of the addition of a single electron to O_2. The O_2^- radical is catalytically reduced to hydrogen peroxide (H_2O_2) by the enzyme superoxide dismutase. The superoxide anion radical (O_2^-) is formed as a result of the addition of a single electron to O_2, O_2^- radical, superoxide. It is catalytically reduced to hydrogen peroxide (H_2O_2) by the dismutase enzyme. Hydrogen peroxide has low toxicity but readily penetrates cellular membranes. It is particularly concerned with the formation of O_2^- and H_2O_2 highly reactive hydroxyl radicals in the presence of transition-metal ions (iron, copper). This reaction is known as the "Fenton Reaction" (5, 6).

Free radicals have different chemical structures such as OH, O_2^-, NO and lipid peroxidase radicals. The most important free radicals in biological systems are those formed from oxygen. O_2 is reduced to the O_2^- group by the action of some Fe-Na containing oxidation-reduction enzymes and flavoproteins. The superoxide group, which is very effective and causes cell damage, is converted to hydrogen peroxide and oxygen by the copper-containing enzyme SOD (3).

2.1. Formation Mechanisms of Free Radicals

Oxygen radicals are the most important radicals in biological systems. The oxygen molecule (O_2) has two unpaired electrons and is chemically diradical. Although the unpaired electrons in the O_2 molecule are in separate orbitals, their direction of motion is the same. The O_2 molecule

acts as an electron acceptor and oxidizes. However, due to the feature in its orbital structure, while oxygen is thermodynamically inclined to gain electrons, it does not want to donate electrons kinetically. If the oxygen diradical is going to oxidize a molecule or an atom, that is, if it gains two electrons, there must be electrons moving in the opposite direction of the movement of these electrons (7).

2.1.1. Mitochondria Electron Transfer Chain

The main source of formation of free oxygen radicals is the mitochondrial electron transport chain (8). Under normal conditions, O_2 is converted to water by the cytochrome oxidase system in mitochondria (9-11). Many compounds in electron transport chain (such as NAD, FAD, Coenzyme Q) react with O_2 and cause $O_2^{\cdot-}$, which is defined as monovalent oxygen leakage. During normal O_2 consumption, 2-5% ROS occurs as a result of leakage in the mitochondria (12-15).

2.1.2. Enzymes

O_2, the last molecule of the respiratory chain, takes 4 electrons and is reduced to water. However, O_2 is not always fully reduced. Under normal conditions, 1-2% $O_2^{\cdot-}$ radical and H_2O_2 occur. During oxidative phosphorylation, the mitochondrial cytochrome oxidase enzyme system controls the reduction of molecular oxygen to water by gaining 4 electrons. In other steps (Cytochrome b-ubiquinone) partially reduced reactive oxygen species cannot bind and the normal functions of the cell may be impaired due to their reactivity (15).

2.1.3. Phagocytic Cells

Cells responsible for phagocytic activity are also among the important sources of free radicals. Cytotoxic O_2 radicals are used to eliminate normally phagocytosed microorganisms. When macrophages and neutrophils become active, they consume large amounts of oxygen, almost all of which is converted to the $O_2^{\cdot-}$ radical. The reason for this

process, which is also called respiratory burst, is the activation of the reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme (15).

2.1.4. Peroxisomes

Peroxisomes are important cellular sources of H_2O_2. They cause the production of H_2O_2 without the $O_2^{\cdot -}$ step. Although most of the formed H_2O_2 is metabolized by peroxisomal catalase, H_2O_2 can diffuse into the cytoplasm at certain rates (16).

2.1.5. Oxidation of Small Molecules

Thiols, hydroquinones, catecholamines and Hb, which are soluble and can give oxidation-reduction reactions in neutral liquid environments, also have roles in the formation of free radicals. They cause the reduction of O_2, leading to the formation of $O_2^{\cdot -}$ (16).

2.1.6. External Factors

The substances released by the combustion of chemical and organic substances are important sources and carriers of radicals. Free radicals can be formed by environmental factors. Smoking, air pollution, various chemicals, drugs and hyperoxygenation can be counted among them (17).

The main importance of metal ions in free radical reactions is their effect on lipid peroxidation. Rather than initiating lipid peroxidation, they increase the harmful effects of free radicals by catalyzing the breakdown of synthesized lipid hydroperoxides and the chain reactions of lipid peroxidation (6).

Transition metals are in the structure of the mitochondrial cytochrome oxidase enzyme (SOD), which protects cells from lipid peroxidation. Free copper acts as a prooxidant agent on the cell membrane (18).

It has been suggested that alcohol consumption causes lipid peroxidation by inducing oxidative stress in liver and non-hepatic tissues, which is a complex and interactive process (19). The level of

catecholamines increases in stress and the oxidation of catecholamines is a source of free radicals (6, 20).

2.2. Classification of Free Radicals

Electrons exist in groups of two in orbitals. Unpaired single electron moieties in atomic and molecular structures are called free radicals. Free radicals, which have unpaired electron regions in this way, easily exchange electrons with other molecules, and such molecules are called oxidant molecules or ROS (21).

While atoms, groups of atoms or molecules containing unpaired electrons are called free radicals, transition metals such as Fe3+, Cu2+, Mn2+ and Mo5+ are not considered as free radicals although they have unpaired electrons. However, these elements play an important role in the formation of free radicals (6).

Considering the definition of free radical, oxygen in the molecular structure is considered a biradical. Although bi-radical oxygen reacts very slowly with non-radical substances, it reacts easily with other free radicals. For this reason, oxygen in the molecular structure tends to form a high degree of ROS due to its biradical character (6).

The most common type of oxidant in living things are those in lipid structure. The lipid radical is formed by the removal of hydrogen from the unsaturated allyl group. This radical reacts with oxygen, resulting in a lipid peroxide radical. Lipid radicals can also turn into products that cause cell poisoning. The most important product showing cytotoxic properties in this way is MDA (21).

If the oxygen molecule has an unpaired electron in its orbital, it is called an O_2 radical. The $^1O_2$ molecule has two unpaired electrons in its structure. $^1O_2$ directly reacts with polyunsaturated fatty acids in the cell membrane, leading to the formation of lipid peroxides (22).

Since O_2 is suitable to be a radical due to its structure, when free radical is mentioned, free oxygen radicals and, in a more general definition, ROS should come to mind. Table 1 shows the classification of free radicals.

Table 1 . Classification of free radicals

Reactive Oxygen Species (ROS)	**Reactive Nitrogen Species (RNS)**	**Reactive Sulfur Species (RSS)**
Superoxide radical Ozone Singlet oxygen Hydrogen preoxide Hydroxyl radical Hypochlorous acid Alkoxyl radical Peroxyl radical Hydroperoxyl radical	Nitric oxide Nitric dioxide Peroxynitric	Thiyl radical

2.2.1. Superoxide Radical (O_2^-)

It occurs as a result of the reduction of O_2^-, which has lower reactivity compared to other radicals and has an oxidizing function in the organism, with other radicals it causes to occur, by gaining an electron (23).

$$O_2 + e \rightarrow O^-$$

As a result of environmental factors and enzymatic and non-enzymatic reactions in the organism, the most O_2^- radical is released. Its main importance is that it is a source of H_2O_2 and a reducer of transition metal ions. They have a long half-life and are lipophilic. For this reason, they can spread by diffusion to distant regions from the regions where they occur. Its damaging effects are not high (25).

The OH radical that emerges as a result of the reaction called Haber-Weiss is the most important factor in the risk of superoxide radical and causing damage to the tissues.

$$O_2^- + H_2O_2 \rightarrow O_2 + OH + OH$$

When the ambient pH is low, the superoxide radical can take up a proton and convert to the more reactive perhydroxyl radical (HO_2^-). However, the perhydroxyl form that occurs when the ambient pH is within physiological limits is below 1% (24).

2.2.2. Hydrogen Peroxide (H_2O_2)

H_2O_2, which has the ability to easily pass through the membranes, is a long-lasting oxidant and its main production occurs by dismutation of superoxide. Taking two protons, 2 molecules of superoxide give rise to hydrogen peroxide and molecular oxygen.

$$2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$$

Non-free radical H_2O_2 is among the reactive oxygen species and plays an important role in free radical biochemistry. The reason why H_2O_2 is so important is that it reacts with superoxide and breaks down to form the hydroxyl radical, which has very reactive properties and causes significant damage by showing harmful effects (24).

2.2.3. Hydroxyl Radical (OH^-)

The hydroxyl radical is formed by reduction of hydrogen peroxide in the presence of transition metals. The half-life of the hydroxyl radical, which can also be formed as a result of exposure of water to high-energy ionizing radiation, is very short and can cause serious damage where it occurs.

$$H_2O_2 + Fe^{+2} \rightarrow OH^- + OH^- + Fe^{+3}$$

This reaction is a reaction catalyzed by iron ions and is also known as the Haber-Weiss (Fenton) reaction (24).

2.2.4. Singlet Oxygen ($^1O_2$)

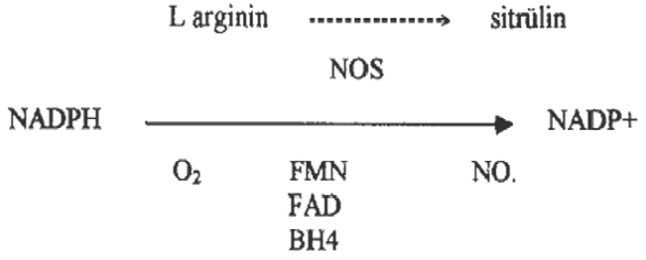
Singlet oxygen occurs when one of the unpaired electrons of the oxygen changes direction from the orbital in which it is located as

a result of energy, to another orbital or to the opposite direction of rotation (26).

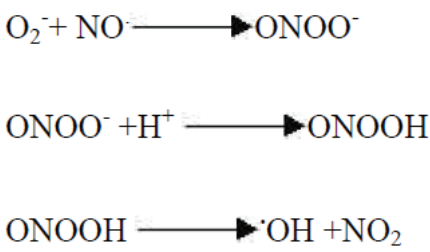
It has two forms, delta and sigma. In this energetically stimulated form of oxygen, its reactivity is quite high due to the elimination of the spin restriction. It can give the energy it receives to the environment in the form of wave energy and return to oxygen. When it interacts with other molecules, it transfers the energy it contains or enters into covalent reactions. In particular, carbon double bonds are bonds in which singlet oxygen has reacted (27).

2.2.5. Nitric Oxide ($NO^{\cdot}$)

Nitric oxide, a colorless gaseous inorganic free radical, has an odd number of electrons. It emerges with the activity of nitric oxide synthase (NOS) enzyme in living things. Nitric oxide is produced by the NOS enzyme during the conversion of L- arginine to L- citrulline.



Nitric oxide, which has a neurotransmitter effect in the brain and is among the most important molecules in this context, has an important effect on the fulfillment of functions such as learning, memory formation, vision, smelling and pain perception. Neuron damage may occur in living beings due to excessive nitric oxide synthesis. It is thought that the main responsible for nitric oxide-induced toxicity is peroxynitrite ($ONOO^-$), which is formed as a result of the reaction of O_2^- with nitric oxide. The diffusion of $ONOO^-$, which occurs as a result of this extremely rapid reaction, is limited. $ONOO^-$ is rapidly decomposed into OH^- and nitrogen dioxide (NO2) at physiological pH. As a result, it causes serious damage to cells and may even lead to cell death (28, 29).



There are conflicting opinions regarding the role of nitric oxide in neuron damage due to its vasodilator effect increasing cerebral blood flow and its neuronal damage-causing free radical property. It is suggested that whether nitric oxide acts as neuronal protective or damaging will be determined by the redox state of the radical. In some studies on the subject, it has been shown that the NO-ONOO- pathway leads to apoptotic cell death (30).

Although radicals are highly reactive products from the content of unshared electrons, the reactivity of nitric oxide, which has unshared electrons, is quite low compared to other radicals. Because the unshared electron is not localized on N and O atoms, it is delocalized on two atoms (30).

2.2.6. Hypochlorous Acid (HOCl)

It is produced by neutrophils by enzymatic pathways and is a strong oxidant. It plays a very important role in the elimination of bacteria by phagocytic cells. Neutrophils convert hydrogen peroxide into hypochlorous acid, which is a strong antibacterial agent, by combining the hydrogen peroxide with chloride ion by dismutation of singlet oxygen with the enzyme myeloperoxidase they contain (13).

2.3. Antioxidant Defense Mechanism

Organisms have enzymatic (intracellular) and non-enzymatic (extracellular) defense mechanisms against the harmful effects of ROS. Intracellular antioxidant defense basically has antioxidant enzymes

called SOD, CAT and GPx. The antioxidant defense system generally prevents the oxidation of oxidized substances such as proteins, lipids, carbohydrates and DNA in the cell (31).

2.3.1. Superoxide Dismutase (SOD)

Superoxide dismutase cleans the superoxide anion by converting it to H_2O_2. SOD forms a defense mechanism that catalyzes the H_2O_2 dismutation of the $O_2^{\cdot -}$ radical.

$$2O_2^{\cdot -} + 2H^+ \xrightarrow{SOD} 2H_2O_2 + O_2$$

There are different isoforms of superoxide dismutase. Cu and Zn (CuZn-SOD) in the cytosolic SOD structure, manganese (Mn-SOD) in the mitochondrial SOD structure. Superoxide dismutase prevents $O_2^{\cdot -}$ radicals from reacting with potential substrates, thus forming more toxic products such as $^{\cdot}OH$ radical (32). The concentration of the $O_2^{\cdot -}$ radical in the extracellular space is not under strict control. Plasma Cu-Zn SOD activity is very low (33).

2.3.2. Glutathione Peroxidase (GSH- Px)

Glutathione peroxidase is an antioxidant enzyme that catalyzes the reduction of H_2O_2. GSH -Px, which has a tetrameric structure, has 4 selenium atoms. The activity of GSH-Px depends on the NADPH produced in the hexose monophosphate pathway (24, 29).

Low levels of hydrogen peroxide are primarily cleared by GSH -Px. This enzyme is reduced H_2O_2 with high specificity in the environment where glutathione is converted to oxidized glutathione. In the reaction in which reduced glutathione turns into oxidized glutathione, H_2O_2 is also reduced to water by the GSH-Px enzyme. Later, oxidized glutathione is reduced by using NADPH with the reaction catalyzed by the glutathione reductase enzyme (24, 34).

2.3.3. Glutathione-S-Transferase (GST)

Glutathione S-transferases (GST) are a family of dimeric and largely cytosolic enzymes. Enzymes in this family have detoxifying properties as well as intracellular binding and transporter functions. GSTs are involved in the detoxification of mutagenic or carcinogenic substances. By demonstrating these properties, it has been determined that GSTs have a role in the detoxification of carcinogens, mutagens and toxic chemicals. In addition, it has been determined that they bind many non-metabolizable compounds and xenobiotics, and these structures act as binders and carriers in the cell. GSTs are divided into three groups as π-acidic, α-basic and μ-neutral (35).

2.3.4. Catalase (CAT)

Catalase (CAT) is a hemoprotein in glycoprotein structure, consists of 4 subunits. Its specific activity in the brain is less than in most other tissues. It is abundant in mitochondria and peroxisome particles, but is also found in the endoplasmic reticulum and cytoplasm. In cases where there is an excess of H_2O_2, it steps in and turns it into water. Catalase activity is against small molecules such as hydrogen peroxide, methyl and ethyl hydroperoxides and is not effective on hydroperoxides of large molecules. In addition to its peroxidase activity, CAT also uses hydrogen peroxide as an electron donating substrate (6).

The erythrocytes provide most of the catalase activity and contain high levels of CAT. CAT enzyme activity is higher in kidney and liver tissues compared to other tissues. CAT has activity in tissues mainly in the peroxisome, mitochondria, cytoplasm and endoplasmic reticulum. In cases where the amount of H_2O_2 in the environment is low, antioxidant enzymes (GSH-Px) such as GSH-Px, which use H_2O_2 as a substrate, step in and remove hydrogen peroxide from the environment. The intracellular action sites of CAT and GSH-Px enzymes, which have the same effect, differ. While CAT is more active in peroxisomes, the GSH-Px enzyme shows activity in the cytosol and mitochondria (34).

Non-enzyme antioxidants are evaluated in 3 groups:

α-tocopherol, ß-carotene are found in the lipid phase, ascorbic acid, cysteine, urate, ceruloplasmin, transferrin, lactoferrin, myoglobin, hemoglobin, ferritin, albumin, bilirubin and glutathione are found in the liquid phase, melatonin is found in both liquid and lipid phase (24, 34).

As a conclusion, the oxidant and antioxidant system in the human body must be in balance, and when this balance is disturbed, the homeostasis of the body may be impaired, causing various diseases.

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CHAPTER XIII

CORRELATION OF LABORATORY PARAMETERS AND RT-PCR RESULTS OF COVID-19 PATIENTS

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Introduction

Thirty years after their first recognition as animal pathogens in the 1930s, coronaviruses were also identified as human respiratory pathogens (1). The Coronavirus family has four subgroups known as alpha, beta, gamma and sigma. The beta coronavirus group includes also human pathogens including SARS (Severe Acute Respiratory Syndrome), MERS (Middle East Respiratory Syndrome-Coronavirus) and SARS-CoV-2 (2, 3).

In 2003, SARS-CoV was identified as a new respiratory pathogen responsible for the global epidemic. The epidemic, which first appeared in China in 2002, lasted 9 months and caused approximately 9000 people

to be infected and 774 people to die. The data show that SARSCoV evolved from viruses found in horseshoe bats and civet cats and other wild market animals were intermediate hosts. SARS CoV typically causes symptoms including fever, myalgia, headache, weakness, chills, cough and dyspnea in 3-5 days; in addition diarrhea may also appear in some patients. Laboratory findings include lymphopenia, thrombocytopenia, and increased serum lactate dehydrogenase (LDH) and creatinkinase levels (4-7).

In 2012, MERS-CoV was identified as a new CoV responsible for the epidemic of respiratory diseases in the Kingdom of Saudi Arabia. It has been reported that MERS CoV most likely evolved from bats and its intermediate host was camels. As of May 2016, approximately 2000 cases and 700 deaths have been reported. Although asymptomatic infections and a mild disease spectrum are observed in MERS-CoV, severe symptoms similar to SARS-CoV may also emerge. Fever, myalgia and chills, dry cough and dyspnea are observed after a few days after exposure. Approximately 25% of patients also experience vomiting, diarrhea or abdominal pain. Similar to SARS, thrombocytopenia, lymphopenia and high LDH levels are observed in MERS-CoV laboratory findings (4-7).

In December 2019, the SARS-CoV-2 infection epidemic, which spread rapidly all over the world, was named Coronavirus Disease (COVID-19) by the World Health Organization (WHO). COVID-19, a respiratory disease similar to that caused by other coronaviruses, was first detected in Wuhan, China, in December 2019 and, was declared as a pandemic by WHO on 11 March 2020 due to its spread and mortality rate (1, 6).

Coronavirus virion particle that is round shaped and 120-160 nm in diameter, contains club-shaped bulges made of S protein on the surface. The S protein provides the attachment of the virus and its fusion to the membrane during infection. In addition to S protein, the virion also contains membrane protein M, envelope protein E and nucleocapsid protein N [2, 4]. The viral genome of SARS-CoV-2 is a 29891 base RNA genome. It has 79.5% similar sequence with SARS-CoV and 91.3% similar sequence with RaTG12 virus isolated from bats. Cell entry occurs when the S protein of the virus binds to Angiotensin Converting

Enzyme-2 (ACE-2), an enzyme on the lung type 2 pneumocyte cell surface (8, 9).

The main clinical symptoms of COVID-19, like other coronaviruses, are fever, dry cough, fatigue, muscle pain and shortness of breath. After an average incubation period of 4-6 days, the patients generally experience fatigue, fever, dry cough, myalgia and dyspnea. In addition, nasal congestion or runny nose, headache and sore throat can be observed, although they are not common. It has also been reported that some patients experienced vomiting and diarrhea as in other coronaviruses diseases (7, 10).

In the light of this information, the laboratory tests in relation to the determination of the severity of disease, the treatment to be applied and clinical follow-up are of great importance. These laboratory tests include various biochemical parameters including complete blood count (erythrocyte, lymphocyte, monocyte, granulocyte and immunophenotypic features of these cells) albumin AST, ALT, total bilirubin, kidney function tests, electrolytes, glucose, LDH, CRP, cytokine, ferritin and cardiac tests (4, 11).

In COVID-19 patients, along with the signs of hypoalbuminemia, lymphopenia and thrombocytopenia in particular; increased levels of AST, ALT, total bilirubin, D-dimer, CRP, PTZ and procalcitonin, troponins, creatinine are very important in terms of follow-up of the disease. However, the role of laboratory parameters in the diagnosis of COVID-19 cases has not been fully elucidated. Therefore, in this study, it was aimed to investigate the correlation between the laboratory parameters and threshold cycle values (Ct-Cycle Threshold) in patients who were COVID-19 positive diagnosed by real-time reverse transcription polymerase chain reaction (RT-PCR) analysis.

Materials & Methods

A total of 259 patients with positive Covid-19 PCR test between April and August 2021 and early stage and outpatient treatment at Mersin University Hospital were included in the study. Panel tests as arranged by the Medical Biochemistry Laboratory were conducted, and the results

were retrospectively evaluated. Approval for this study was obtained from the Ministry of Health and the ethics committee.

In the COVID-19 PCR analysis, COVID-19 RT-qPCR Detection Kit with a brand name of Bio-Speedy (Bioeksen the R & D Technologies Co. Ltd. Istanbul / Turkey) was used. Rapid detection with the kit was achieved with the use of single-step reverse transcription (RT) by targeting the RdRp (RNA-dependent RNA polymerase) gene fragment with the help of Rotor-Gene (QIAGEN) brand real-time PCR (qPCR) (RT-qPCR) device.

Biochemical parameters

Complete blood count was measured by electrical impedance and flow cytometry method (XN-1000, Sysmex). Troponin-I was determined by chemiluminescence immunoassay method (DXI 800, Beckman Coulter, Inc.) and urea, AST, ALT, LD, CK, CK-MB enzymatic, albumin, creatinine colorimetric, D-dimer and CRP turbidimetric and electrolytes were studied by ISE methods (AU680, Beckman Coulter Inc.).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median [25.Persentil-75.Percentil] according to the normality assumption. Categorical variables were summarized as counts and percentages. Independent sample t test was used to compare two independent groups in terms of CT-values. The spearman correlation coefficient was calculated for detecting the relationship between two numerical variables and scatter plots were drawn for significant correlations. A p value<0.05 was considered statistically significance level.

All analyses were performed with SPSS software (version 11.5).

Results

Out of total 259 patients with the age range of 18-92 years (mean ± SD: 39.76 ± 15.07) included in the study, there was 144 (55.6%) male and

115 (44.4%) female. The average values of the biochemical parameters of the patients are given in Table 1.

When the results of biochemical parameters of patients were examined, it was found that HGB, WBC, MCV, MONO, NEUT, EO, LYMPH%, NEUT%, PLT, PDW, RDW CV, RDW SD, urea, potassium, AST, ALT, CK, GFH and Na values corresponded to values of 70% or above in the reference interval, while HCT, RBC, LYMPH, MONO%, MPV, NRBC%, CRP, CKMB, creatine and LD values corresponded to values of 50% or above in the reference interval. Among those parameters, whether the values of LYMPH, NEUT, EO, MONO%, PLT, PDW, CRP, AST and GFH were in the reference range found to be statistically significant when compared with the Ct values. It was also determined that MCH, troponin and albumin levels of COVID patients were outside of the reference range. However, the statistical analysis conducted to find whether these parameters were in the reference range by comparing to their corresponding Ct values, a significant difference was only found in MCH levels (Table 2).

The allocation of reference range group ratios is not optimal for the parameters of MCH, NEUT, PLT and PDW. However, since the present study includes a cross-sectional design and it only aims to interpret the results of COVID-19 cases on current blood parameters.

The statistical results revealed that Ct was positively or negatively correlated to most of blood parameters either positively or negatively. [HGB (r=0,205, p<0,001), HCT (r=0,161, p=0,009), MCH (r=0,205, p<0,001), MCHC (r=0,219,p<0,001), LYMPH (, r=0,290, p<0,001), EO (r=0,296, p<0,001), BASO (r=0,260, p<0,001), NEUT% (r=0,184 , p=0,003), EO% (r=0,171, p=0,006), PLT (r=0,234, p<0,001), PDW (r=0,131, p=0,035), PCT (r=0,290, p<0,001), IG (r=0,263, p<0,001), CRP (r= - 0,249, p<0,001), Kreatinin (r= - 0,137, p=0,027), AST (r=-0,215, p<0,001), GFH (r=0,205, p=0,006)]. Although correlation coefficients were found to be statistically significant, it was not possible to discuss about the results. Because there was a weak clinical correlation and statistically significant correlations were dependent to the large sample size.

Therefore, the correlations between CT and WBC (r=0,437, p<0,001), NEUT (r=0,408, p<0,001), D-dimer (r= 0,468, p<0,001)

and MONO% (r=-0,372, p<0,001) were discussed due to their higher correlation coefficients. These results are summarized in Figure 1.

Discussion

According to current evidence, the main route of COVID-19 transmission from person to person is through respiratory droplets and contact. Although the transmission period is not clearly known, the range for the incubation period is 0-24 days, but this period is generally 5-7 days in the majority of cases. Most COVID-19 patients are asymptomatic on lung imaging and experience mild fever with minimal symptoms. In addition, although most of the patients with moderate symptoms experience respiratory symptoms, 20% of the patients exhibit signs of severe lung damage. Patients with severe illness show symptoms and signs such as dyspnea, dry cough, fever and bilateral infiltration on lung imaging. In addition, ARDS, liver damage, acute myocardial damage, acute renal failure, septic shock, and multiple organ damage can also be observed as complications of the disease (12, 13).

Depending on the severity of the disease, the clinical course of COVID-19 can be classified into three stages: "early infection", "pulmonary phase" and "hyperinflammation phase". Each stage is characterized by specific biochemical changes. The initial stage in which the virus is highly expressed in lung pneumocytes by infecting ciliary bronchial epithelial cells through the interaction with ACE-2 is associated with an early inflammatory response based on innate immunity, primarily monocytes and macrophages. The pulmonary phase is characterized by viral pneumonia associated with inflammation localized in the lung. Among biochemical properties, an increase is observed in lymphopenia and transaminases, as well as in systemic inflammation biomarkers such as CRP (12, 13). The third stage of COVID-19 is the most severe stage characterized by systemic inflammation or cytokine storm leading to ARDS and multi-organ failure. Several inflammatory biomarkers increase significantly during the third stage. Moreover, most patients may also experience heart and kidney damage that can be detected by circulating biomarkers. In addition, the current evidence suggests that

there are various changes in the central nervous system of COVID-19 patients (14).

The definite diagnosis of COVID-19 is made using molecular tests. These tests are based on the investigating the presence of virus's genetic material by RT-PCR in the throat and/or nasal swab taken from the person (15). It has been found that the viral load is higher in the early stages of the disease and can be detected in greater amounts in nasopharyngeal samples. RT-PCR Ct values represent the number of amplification cycles required for the target gene to exceed the threshold level. Therefore, Ct values are inversely proportional to the viral load, and low Ct values have been shown to be associated with more severe disease (16, 17).

Five studies have been conducted for the determination of the correlation of Ct value with biochemical and hematological markers (18-22). Low Ct values was found to be associated with low levels of lymphocyte count and percentage, T cell count and serum albumin levels; in addition, it was also associated with an increase in the levels of LDH, CKMB and troponin I. Two studies have shown that lower Ct values were associated with higher neutrophil counts and/or percentages, while one study has pointed out that there was a negative correlation (18-22). While Yuan et al reported that CRP levels were negatively correlated with the Ct value, another study indicated that there was no significant relationship (20). In addition, there are studies in the literature reporting that Ct values were also associated with basophil and eosinophil counts, and myoglobin, N-terminal pro-brain natriuretic peptide and calcium levels (21).

In the present study, it was determined that the parameters outside of the reference interval were MCH, troponin and albumin. In addition, there was a positive correlation between Ct values and HGB, HCT, MCH, MCHC, WBC, LYMPH, NEUT and percentage, EO, BASO, EO%, PLT, PDW, PCT, IG, D-dimer, troponin levels; while a negative correlation was found between Ct values and MONO%, CRP, Creatinine, AST, and GFR levels. Considering the magnitude of correlation coefficients, a stronger correlation was found between CT and WBC, NEUT, D-dimer and MONO%.

While lymphopenia is often described in COVID-19 patients, the white blood cell count is generally within normal limits and is slightly decreased in mild cases but increased in severe or critically ill patients. Serum levels of ALT, AST, troponin and / or creatinine may be elevated in patients with CRP levels and extra pulmonary systemic complications. Information obtained from literature reviews shows that this variability in the levels of biochemical parameters is related to viral load. However, there is an inverse relationship between increasing viral load and Ct values. In this study, especially the positive correlation between Ct value and lymphocyte levels and the negative correlation between Ct and CRP level support this relationship. Different symptoms that occur as a result of different organ damage creates difficulties in determining the course of the disease. Although reporting the COVID-19 PCR results as positive or negative is sufficient for the diagnosis, considering the changes in biochemical parameters resulted from the disease would be valuable in terms of the correct treatment and follow-up of the disease.

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Table 1. The averages of Biochemical Parameters

Parametres (n=259)	Mean	Median	Std. Deviation	Percentiles		Reference Range
				25	75	
HGB (g/dL)	13,89	14,00	1,85	12,60	15,20	11,7-15,5
HCT (%)	41,61	42,00	4,76	38,00	45,00	39-50
RBC (10^6/µl)	5,28	4,97	5,07	4,61	5,29	3,8-5,1
MCV (fL)	83,77	85,00	6,49	82,00	87,00	81-100
MCH (pg)	28,06	28,00	2,58	27,00	30,00	26-35
MCHC (gHb/dL)	33,02	34,00	3,79	33,00	34,00	32-36
WBC (10^3/µL)	6,90	6,40	2,58	5,05	8,37	4,5-11
LYMPH (10^3/µL)	2,03	1,85	,84	1,420	2,55	1,5-4
MONO (10^3/µL)	,68	,66	,284	,48	,84	0,2-0,95
NEUT (10^3/µL)	4,04	3,52	2,10	2,52	5,04	1,5-6,7
EO (10^3/µL)	,092	,05	,12	,02	,12	0,02-0,5
BASO (10^3/µL)	,03	,03	,02	,02	,05	0-0,15
LYMPH (%)	31,14	31,00	10,41	24,00	38,00	20,5-51,5
MONO (%)	10,43	9,00	4,01	7,00	13,00	1,7-9,3
NEUT (%)	56,66	57,00	11,17	50,00	64,00	42,2-75,2
EO (%)	1,27	,80	1,44	,30	1,60	0-0
BASO (%)	,51	,40	,40	,30	,60	0-0
PLT (10^3/µL)	238,21	233,00	64,42	193,00	273,00	150-400
PDW (fL)	12,07	12,00	2,65	11,00	13,00	9-17
RDW CV (%)	13,01	12,70	1,43	12,20	13,30	11,6-14,8
RDW SD (fL)	39,23	39,20	4,17	37,40	41,10	<46
MPV (fL)	10,23	10,20	1,47	9,60	10,90	7,4-10,4
NRBC (%)	,091	,00	,148	,00	,20	0-0
PCT (µg/L)	,24	,24	,07	,20	,28	0-0
P_LCR (%)	27,59	26,60	8,34	22,10	33,00	0-0
IG (10^3/µL)	,03	,02	,025	,01	,03	0-0,09
IG (%)	,35	,30	,267	,20	,40	0-0,6

D-dimer (µgFEU/mL)	,02	,00	,064	,00	,00	0-0,5
CRP (mg/L)	12,64	4,13	30,13	1,60	11,26	<5
CKMB (ng/mL)	1,36	1,00	1,75	,50	1,70	0,6-6,3
Troponin (ng/mL)	,004	,002	,007	,0010	,003	0,012-0,02
Ürea (mg/dL)	28,83	27,40	12,40	21,50	33,30	17-50
Creatine (mg/dL)	,84	,80	,26	,67	,98	0,5-0,9
Potassium (mEq/L)	4,16	4,14	,59	3,97	4,39	3,7-5,4
Chloride (mEq/L)	93,06	104,00	31,10	101,00	106,00	94-110
AST (U/L)	28,37	24,00	16,26	19,00	33,0	<32
ALT (U/L)	27,83	23,00	20,53	14,00	35,00	<55
LD (U/L)	184,95	187,00	93,34	153,75	219,25	135-214
CK (U/L)	143,23	87,00	259,9	46,00	129,50	<170
Albumin (g/dL)	,14	,00	,78	,00	,00	3,4-4,8
GFH (ml/dk/1.73 m2)	100,89	105,49	23,10	90,20	116,93	>90

Table.2 The Relationship Between the Biochemical Parameters' Being in Reference Range and Their CT values

Biochemical parametres	Being in the Reference Range	N %	Ct Mean	p
HGB	Normal	185 (71.42)	23.1879	0.429
	Abnormal	74 (28.57)	24.0628	
HCT	Normal	176 (68)	23.3125	0.715
	Abnormal	83 (32)	23.7039	
RBC	Normal	154 (59.46)	23.2868	0.715
	Abnormal	105 (40.54)	23.6595	

MCH	Normal	9 (3.47)	30.7944	0.005
	Abnormal	250 (96.53)	23.1731	
MCHC	Normal	233(89.90)	23.6679	0.168
	Abnormal	26(10.10)	21.3769	
WBC	Normal	194 (74.90)	23.5808	0.622
	Abnormal	65 (25.1)	23.0114	
MCV	Normal	215 (83.01)	23.7806	0.129
	Abnormal	44 (16.99)	21.7634	
LYMPH	**Normal**	**178 (68.73)**	**24.2781**	**0.008**
	Abnormal	**81 (31.27)**	**21.5915**	
MONO	Normal	222 (85.71)	23.3850	0.796
	Abnormal	37 (14.29)	23.7554	
NEUT	**Normal**	**227 (87.65)**	**22.9172**	**0.005**
	Abnormal	**32 (12.35)**	**27.1316**	
EO	Normal	204 (78.76)	24.0868	0.012
	Abnormal	55 (21.24)	21.0313	
LYMPH %	Normal	211 (81.47)	23.3705	0.778
	Abnormal	48 (18.53)	23.7342	
MONO %	**Normal**	**137 (52.9)**	**26.4820**	**<0.001**
	Abnormal	**122 (47.1)**	**20.0195**	
NEUT %	Normal	223 (86.1)	23.5795	0.481
	Abnormal	36 (13.9)	22.5608	
PLT	Normal	239 (92.3)	23.7038	0.008
	Abnormal	20 (7.7)	20.2600	
PDW	Normal	239 (92.3)	23.7038	0.008
	Abnormal	20 (7.7)	20.2600	
RDW CV	Normal	230 (88.8)	23.6431	0.247
	Abnormal	29 (11.2)	21.8103	
RDW SD	Normal	251 (96.9)	23.2585	0.206
	Abnormal	8 (3.1)	29.0675	
MPV	Normal	148 (57.14)	23.0672	0.392
	Abnormal	111 (42.86)	23.9322	
NRBC %	Normal	142 (54.83)	22.7485	0.128
	Abnormal	117 (45.17)	24.2747	

IG	Normal	253(97.6)	23.3658	0.349
	Abnormal	6(2.4)	26.4800	
CRP	**Normal**	**139 (53.67)**	**25.4345**	**<0.001**
	Abnormal	**120 (46.33)**	**21.1252**	
CKMB	Normal	179 (69.11)	23.7952	0.250
	Abnormal	80 (30.89)	22.6385	
Troponin	Normal	5 (1.93)	25.0720	0.647
	Abnormal	254 (98.07)	23.4057	
Ürea	Normal	224 (86.49)	23.3617	0.700
	Abnormal	35 (13.51)	23.9254	
Creatine	Normal	172 (66.41)	22.9803	0.198
	Abnormal	87 (33.59)	24.3425	
AST	Normal	214 (82.63)	23.9295	0.008
	Abnormal	45 (17.37)	21.1000	
ALT	Normal	231 (89.19)	23.6782	0.072
	Abnormal	28 (10.81)	21.4554	
LD	Normal	161 (62.16)	23.7437	0.415
	Abnormal	98 (37.84)	22.9356	
CK	Normal	212 (81.85)	23.4522	0.952
	Abnormal	47 (18.15)	23.3734	
Albumin	Normal	7 (2.7)	20.2229	0.284
	Abnormal	252 (97.3)	23.5272	
GFH	**Normal**	**199 (76.83)**	**24.2268**	**0.004**
	Abnormal	**60 (23.17)**	**20.8215**	
Na	Normal	247 (95.37)	23.3426	0.387
	Abnormal	12 (4.63)	25.4008	

Abbreviations: HGB, hemoglobin; HCT, hematocrit; RBC, erythrocyte; MCV, mean erythrocyte volume; MCH, mean erythrocyte hemoglobin; MCHC, mean erythrocyte hemoglobin concentration; WBC, white blood cell; LYMPH, lymphocytes; Mono, monocyte; Neut, neutrophil; EO, eosinophil; Baso, Basophil; PLT, platelet; PDV, Platelet Distribution Width; RDW, Red Blood Cells Distribution Width; MPV, mean platelet volume; NRBC, Nucleated Red Blood Cells; PCT,

procalcitonin; P_LCR, large platelet cell ratio; IG, immature granulocyte; CRP, C-reactive protein; CKMB, creatine kinase isoenzyme; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LD, lactate dehydrogenase; GFH; Glomerular filtration rate.

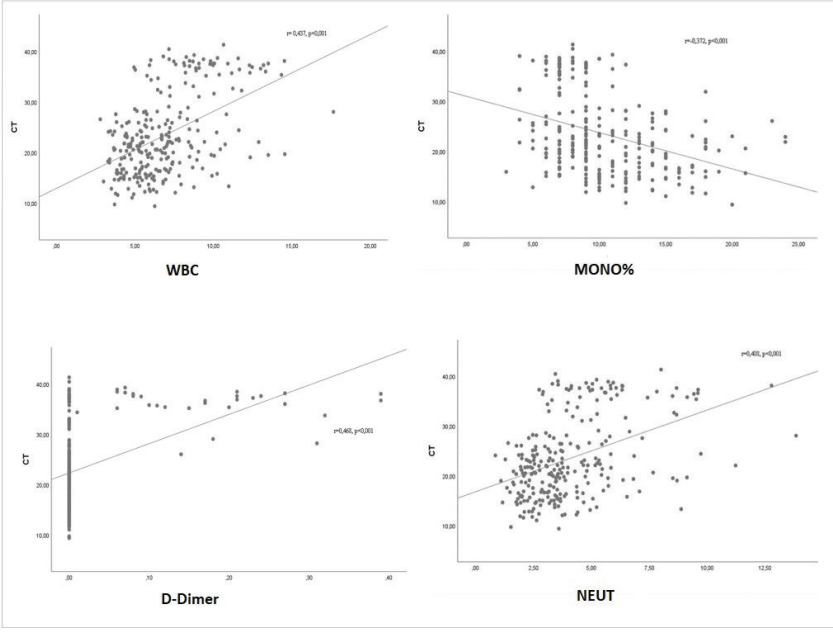

Figure 1. The correlation between CT and WBC, NEUT, D-dimer and MONO%

CHAPTER XIV

THE RELATIONSHIP OF NUTRITION WITH THE IMMUNE SYSTEM AND SOME DISEASES

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1. INTRODUCTION

Immune system elements take on the role of immunity in our body. They prevent and control the spread of infections, support our lifelong health and create a layer of protection for us. In this system, there are some organs in our body such as bone marrow, spleen, thymus, and some cell types such as leukocytes. However, cytokines also interact in the immune response. Cytokines are substances produced by immune or non-immune cells and activated by antigen stimulation. Nutrition is one of the environmental phenomena that affect the immune system. Epidemiological and clinical data show that nutritional deficiencies alter immunocompetence and increase the risk of infection. In cases where nutrition is inadequate and unbalanced, a deficit occurs in the immune system due to the lack of necessary components. As nutritional deficiencies and deficiencies cause many diseases, a visible improvement in diseases can be detected when nutrients are replaced. Antioxidants, which are a part of the immune system, also prevent or reduce damage

by destroying reactive oxygen species, that is, free radicals, formed as a result of metabolic activities with different mechanisms. Antioxidants also prevent oxidative stress that occurs as a result of the metabolism of macromolecules during nutrition. For this reason, it is of great importance to consume foods with high antioxidant content in order to prevent the damage caused by free radicals. In this study, some diseases caused when the immune system does not work properly, vitamins C, D and E, zinc, selenium and phenolic compounds, carotenoids, probiotics and prebiotics and their relations with the immune system, as well as the antioxidant activities of these compounds are mentioned.

2. IMMUNE SYSTEM

There is a surprising and interesting defense mechanism in our body called the immune system. The task of the immune system, which continues its duty throughout life, is to prevent microorganisms from entering the body, to destroy them if they enter, to prevent or delay their spread (1).

Immune system elements consist of a number of organs and several different cell types. The organs of the immune system are the bone marrow, thymus, spleen, Peyer's patches, and lymph nodes. The cells of this system are leukocytes or white blood cells. There are two categories of leukocytes: 1) phagocytes, including neutrophils, monocytes, and macrophages that form part of the innate immune system and provide non-specific immunity, and 2) lymphocytes that mediate adaptive or specific immunity. The two main types of phagocytes are mononuclear cells such as monocytes and macrophages and polymorphonucleargranulocytes such as neutrophils, basophils and eosinophils (2).

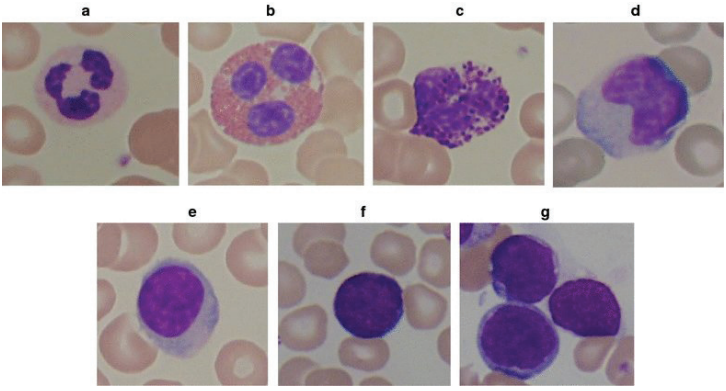

Figure 1: a.Neutrophilcell, b.eosinophilcell, c.basophilcell, d.monocytecell, e.lymphocytecell, f.singleblastcell, g.connectedblastcells (3)

Immune system elements are effective in controlling the spread of infection and destroying the invading organism. Specific immune responses form the basis of prophylactic vaccination against common infectious diseases such as measles, respiratory diseases caused by Haemophilus influenza and systemic disease caused by Salmonella. In the body, non-specific and anti-specific defenses act together (4).

Antigen-specific mechanisms include the B-cell system of antibody production and the T-cell system of cell-mediated immunity. T cells are differentiated in different subpopulations in time, Thelper FH or T cytotoxic suppressor cells, with different markers to identify them: CD4+ for TH and CD8+ for T cytotoxic or suppressor cells. There are three subtypes of TH cells, TH1, TH2, and THO, which are functionally their secretions (5).

B cells differentiate in the bone marrow and consist of two populations; The initial population makes up 15% of the population. It is identified by a characteristic marker, CD5+, and is located in the peritoneal cavity. The other population makes up 85% of B cells and is found in the blood and all organs of the immune system (6).

There is also a population of "null" cells, non-T non-B cells, which are killer (IC) and natural killer (NK) cells. These cells have important functions in host defense against tumors. When a foreign antigen enters

the body, massive cellular infiltration occurs, which, through cellular interaction of the immune system, releases inflammatory mediators (7, 8). The first step in the inflammatory response is characterized by the appearance of neutrophils that perform their phagocytic function at the site of the lesion. To attract macrophages participating in the second stage, it must release chemotactic substances. Macrophages have a phagocytic function similar to that of neutrophils, but after the antigen is degraded, some peptides of this antigen can be expressed on the macrophage membrane. Therefore, the macrophage can present the antigen to lymphocytes that participate in the specific immune response. This presentation is accomplished by combining the antigen with special molecules found on their surface: histocompatibility antigens (9). There are two types of human leukocyte antigen (HLA): HLA class I is expressed on all cells of the body and HLA class II is expressed on immune cells and some non-immune cells such as epithelial cells (10).

The induction of an immune response requires not only cellular interaction but also cytokines and adhesion molecules. Cytokines are substances produced by immune or non-immune cells and activated by antigen stimulation (11). Cytokines contain interleukins (IL). Currently, more than 11 ILs are known; this IL is produced by different TH lymphocytes, macrophages, endothelial cells, epithelial cells and fibroblast cells (12). Adhesion molecules between cells are the second signal to get an immune response. Molecules called integrins or selectins are intercellular adhesion molecule, leukocyte function-associated antigen (LAF1 and LAF2) and very late antigen (VLA1 and VLA2) (13).

2.1 Systemic Immune Response

When the antigen penetrates the body parenterally, a systemic immune response is produced. The non-specific immune response occurs through the inflammatory response with phagocytic active participation. The processed antigen is expressed on the membrane of the antigen presenting cell and is displayed to lymphocytes via the HLA class I or class II pathway. In this way, a cytotoxic cellular response occurs and cooperates

with B lymphocytes (BL) that become plasma cells that produce any of the Ig class (IgM, IgG, IgA, IgE and IgD) (14).

2.2 Secretory Immune Response

Luminal antigen is transported into Peyer's patch via M cells of the follicle-associated epithelium and presented to T cells by HLA class II dendritic cells or macrophages. Antigen is presented to B cells by T cells. Primed T and B cells enter the peripheral bloodstream and extravasate mainly in the intestinal laminapropria and other exocrine tissues. Intestinal B cells differentiate into plasma cells producing IgA and CD8+ T cells that migrate to the epithelium to mediate oral tolerance to food antigens (15).

It has recently been generally accepted that nutrition is an important determinant of immune responses. Epidemiological and clinical data show that nutritional deficiencies alter immunocompetence and increase the risk of infection. Poor sanitation and personal hygiene, knowledge of overcrowding, contaminated food and water, and malnutrition add to this sensitivity. Recent studies have confirmed that impaired immunity is a critical co-factor in malnutrition-associated infection (4).

3. ANTIOXIDANTS

Free radicals are atoms or compounds that contain unpaired electrons in their final orbitals. It can be caused by the natural metabolism of people, as well as the drugs, chemicals and radiation they take. The most important feature of free radicals is that they are highly reactive. In this way, they can react with other structures they encounter in living tissue. It can cause many diseases such as cancer, diabetes, cardiovascular diseases, liver damage by damaging the cell membrane, lipids, proteins, nucleic acids, and DNA in the cell structure (16, 17).

Antioxidants prevent or reduce damage by destroying reactive oxygen species, that is, free radicals, formed as a result of metabolic activities. It does this through four different mechanisms.

1. Scavenging effect: It performs its function by weakening free radicals, that is, by turning them into a weak molecule.

2. Suppression (Quencher) effect: This effect, which is mostly made by flavonoids, is to neutralize free radicals by giving hydrogen.

3. Repair effect: It works by removing the damage.

4.Chain-breaking effect: By binding oxidants by hemoglobin and vitamin E, it inhibits their functions (18,19).

Antioxidants can be synthesized by the body (endogenously) as well as taken from outside (exogenously) by consuming natural foods (eg, hemoglobin). Antioxidants also prevent oxidative stress, which occurs as a result of the metabolism of macromolecules, namely protein, carbohydrates and fats, during nutrition. For this reason, it is of great importance to consume foods with high antioxidant content in order to prevent the damage caused by free radicals (20).

4. EFFECTS OF NUTRIENTS ON THE ORGANISM

Without adequate nutrition, the immune system is clearly deprived of the necessary components to mount an effective immune response. Human malnutrition is often a complex syndrome of multiple nutrient deficiencies. However, observations in laboratory animals deprived of a dietary element, as well as findings in rare patients with a single nutrient deficiency, have confirmed the important role of several vitamins, minerals and trace elements in maintaining immunocompetence. These are vitamin A, beta-carotene, folic acid, vitamin B12, vitamin C, vitamin E, riboflavin, iron, zinc and selenium (21, 22). For example, antioxidant nutrients play a very important role in maintaining the antioxidant/oxidant balance in immune cells, protecting them from oxidative stress and maintaining their adequate functions (23). Adding deficient nutrition back to the diet can restore immune function and resistance to infection. However, excessive amounts of some nutrients also impair immune function (24).

As important components in diets, lipids are substances that have a profound effect on the modulation of the immune system. The fatty acid composition of lymphocytes and other immune cells is modified according to the fatty acid composition of the diet. Therefore, an

immunomodulatory role has been proposed for dietary lipids, which can be used in the treatment of certain diseases involving inflammatory processes, such as autoimmune diseases (25).

Nutritional deprivation, such as protein energy malnutrition (PEM), often results in increased frequency and severity of infection, thymusatrophy, and wastage of peripheral lymphoid tissue, resulting in immunodeficiency, mainly due to cell-mediated mechanisms (26). Malnutrition causes constant changes in the thymus gland. The organ undergoes severe atrophy due to thymocyte depletion due to apoptosis plus reduction in thymocyte proliferation (27). Recently, one hypothesis has suggested that thymocyte depletion due to malnutrition may be mediated by hormonal control (28).

5. THE EFFECT OF AGING ON NUTRITION

Older individuals tend to have a high prevalence of nutrient deficiencies. Based on human studies, immune changes associated with aging include delayed-type hypersensitivity (DTH) responses, decreased IL-2 production and proliferation of lymphocytes, decreased serum IgA, and decreased antibody titer after vaccination (22). The ratio of mature/immature T lymphocytes and naive/memory T cells is reduced and NK cells are more abundant (29). However, functions that are more associated with oxidative stress, such as adhesion, free radical and proinflammatory cytokine production, increase with age. These mechanisms are associated with a general decline in immune system activity. Nutritional supplements such as vitamin B6, zinc, vitamin C, vitamin E may be important for promoting health and preventing certain diseases (23).

6. EATING DISORDERS

Research on the impact of eating disorders such as anorexianervosa (AN) or bulimianervosa (BN) on the immune system has produced controversial findings. On the one hand, patients with AN tend to have leukopenia with relative lymphocytosis (30) and a decreased response to delayed-type hypersensitivity skin testing. On the other hand, however,

immune disorders are less severe than would be expected given the highly imperfect nutritional status of the patients, and also surprisingly appear to be free of infectious complications or even common viral infections (31).

There are several points worth noting to understand why these patients are less prone to infection than those with typical malnutrition. First, the fasting diet is deficient in multiple vitamins and proteins, while in AN the primary dietary deficiencies are carbohydrates and fats. Furthermore, hypothetically, cytokines and some of the complex interactions that occur between the endocrine system and the central nervous system may provide some compensatory mechanisms to adapt to the limited nutrient supply and possibly cause under-perception of infection symptoms. A dysregulated cytokine production and altered acute phase response to infection, cortisol and leptin are considered potential factors involved in the adaptation processes that occur in these syndromes (32).

7. GASTROINTESTINAL DISEASES

The primary activity of the mucosal immune response is to protect the mucosa by blocking microbial, toxin and antigen entry through secretion and transport of IgA into the intestinal lumen, a process mediated by a particular type of memory T cell capable of providing B-cell assistance. Such cells can be found in the laminapropyl of the intestinal barrier and therefore interact and receive signals from the endogenous microbiota of the gut (33). Reduction of normal commensal bacteria in the context of infection or after antibiotic treatment may interfere with nutrient availability and impair beneficial stimulation of the gastrointestinal immune response. In this sense, probiotics have been proven to be helpful in preventing infectious diarrhea and shortening attacks.

In the light of this information, some ingredients that affect the immune system will be mentioned.

8. ANTIOXIDANT ACTIVITIES OF SOME NUTRIENTS AND THEIR RELATIONSHIP WITH THE IMMUNE SYSTEM

8.1 Vitamin D

1,25-dihydroxyvitamin D3(1,25(OH)2D3), the active form of vitamin D, is known to be an important player in bone formation and regulate calcium and phosphorus metabolism. In addition, 1,25(OH)2D3 is an immunomodulator that targets a variety of immune cells, including monocytes, macrophages, dendritic cells (DCs), as well as T-lymphocytes and B-lymphocytes, thereby modulating both innate and adaptive immune responses. 1,25(OH)2D3 plays a role in maintaining immunohomeostasis. Some epidemiological studies have linked insufficient vitamin D levels to a higher susceptibility to immune-mediated disorders, including chronic infections and autoimmune diseases (34).

8.2 Vitamin E

Vitamin E (α-tocopherol) is found in nearly all cell membranes, but the main storehouse of membrane-bound vitamin E is in the inner mitochondrial membrane, which is the site of the electron transport system. It is a type of fat-soluble antioxidant. It acts as an antioxidant as a chain breaker. Vegetable oils such as olive oil, hazelnut oil, oil seeds such as hazelnuts, almonds, walnuts, sunflower seeds, vegetables and greens such as spinach, cress, parsley, lettuce, celery, cabbage, broccoli, pumpkin, poultry, anchovies, salmon, tuna found in fish species (35).

One study examined the effect of vitamin E supplementation on the immune response of healthy older adults in a double-blind, placebo-controlled study. Subjects received placebo or vitamin E (800 mg dl-alpha-tocopheryl acetate) for 30 days. Alpha-tocopherol content of plasma and peripheral blood mononuclear cells (PBMCs), delayed type hypersensitivity skin test (DTH), mitogen-stimulated lymphocyte proliferation as well as interleukin (IL)-1, IL-2, prostaglandin (PG) E2 and serum Lipid peroxides were evaluated before and after treatment. Vitamin E

supplemented group 1) alpha-tocopherol content was significantly higher in plasma and PBMCs, 2) cumulative diameter and number of positive antigen responses in DTH response increased, 3) IL-2 production and mitogenic response to optimal concanavalin A doses were increased, and 4) PGE2 synthesis and plasma lipid peroxides were reduced by PBMCs. Short-term supplementation of vitamin E has been observed to increase immune response in healthy elderly subjects (36). Vitamin E is a powerful antioxidant and has the ability to modulate host immune functions.

In vitamin E deficiency, immunity tends to decrease and infectious diseases tend to increase. In contrast, vitamin E supplementation has several beneficial effects on the host immune system. Decreased cellular immunity with aging or during the development of AIDS is significantly improved by the intake of a high vitamin E diet. In addition, supplementation of vitamin E promotes early recovery of thymicatrophy following X-ray radiation (37).

8.3 Vitamin C

The immune system can be divided into epithelial barriers and the cellular and humoral components of innate (non-specific) and acquired (specific) immunity (38). More than half a century of research has shown that vitamin C is a key player in various aspects of the immune system, particularly immune cell function (39, 40).

Vitamin C is effective in protecting against oxidative damage in tissues with its antioxidant property. Their antioxidant effects are due to the fact that they donate their electrons very easily. In this way, it cleans the hydroxyl radicals in the environment. Green-red pepper, citrus fruits, rose hips, kiwi, strawberries, cranberries, blackberries, zucchini, red pepper flakes, fibrous green vegetables, potatoes and cruciferous vegetables are among the best sources of ascorbic acid (41).

Vitamin C is an essential nutrient that cannot be synthesized by humans due to the loss of an important enzyme in the biosynthetic pathway. Severe vitamin C deficiency results in the potentially fatal disease scurvy. Scurvy is characterized by weakening of collagen structures resulting in poor wound healing and impaired immunity. Individuals

with scurvy are highly susceptible to potentially fatal infections such as pneumonia. Initially, it was noted that scurvy frequently followed infectious outbreaks in populations, and cases of scurvy were reported after respiratory tract infection (42). This is especially evident for people who are already malnourished.

Due to the body's low storage capacity for the vitamin, which is a water-soluble and powerful antioxidant, a regular and adequate intake is necessary to prevent hypovitaminosis C. Epidemiological studies have shown that hypovitaminosis C (plasma vitamin C <23 μmol/L) is relatively common in the West. Vitamin C deficiency (<11 μmol/L) is the fourth leading nutrient deficiency in the United States (43). In countries where food availability and supply will be sufficient, there are conditions such as poor dietary habits, lifestyles, various diseases, and economic reasons for insufficient vitamin C intake. 'Health' in industrialized countries may be at risk due to dieting or lifestyle-related factors such as eating an unbalanced diet, and people experiencing periods of extreme physical or psychological stress (44,45).

Vitamin C is a cofactor for hydroxylase enzymes, which are central to the cardiovascular response to severe infection, such as catecholamine hormones such as norepinephrine and amidated peptide hormones such as vasopressin. Furthermore, research over the past 15 years has revealed new roles for vitamin C in the regulation of gene transcription and cell signaling pathways through regulation of transcription factor activity and epigenetic marks. For example, asparagyl and prolylhydroylases, which are required for downregulation of the pleiotropic transcription factor hypoxia inducible factor-la (HIF-la), use vitamin C as a cofactor. Recent research has shown that vitamin C plays an important role in the regulation of DNA and histonemethylation, acting as a cofactor for enzymes that hygoxylate epigenetic marks (46, 47).

8.3.1 Vitamin C and Leukocyte Fuction

Leukocytes, such as neutrophils and monocytes, actively accumulate vitamin C against the concentration gradient, resulting in values 50 to 100 times higher than plasma concentrations. These cells accumulate

maximum concentrations of vitamin C at dietary intakes of ~100 mg/day. Accumulation of millimolar concentrations of vitamin C to neutrophils, especially after activation of their oxidative burst, is thought to protect these cells from oxidative damage. Vitamin C is a potent water-soluble antioxidant that can scavenge a large number of reactive oxidants and also regenerate the important cellular and membrane antioxidants glutathione and vitamin E. Therefore, vitamin C can modulate immune function either through modulation of redox-sensitive cell signaling pathways or by directly protecting important cell structural components (48).

8.4 Carotenoids

Carotenoids are natural pigments so common in plants and animals, therefore they provide the natural yellow, orange or red colors of many foods, and are also widely used as non-toxic natural or nature-identical colorants. Carotenoids contain conjugated double bonds, which indicates the unsaturation of carotenoids. Unsaturation gives a structure that is not easily oxidized and unstable. Due to this double bond, it functions as both a free radical scavenger and reactive oxygen suppressant, and antioxidant properties increase as the number of double bonds increases (49, 50).

8.5 Phenolic compounds

They are water-soluble antioxidants. They have aromatic chain structure. They show their antioxidant activities through free radical capture, scavenging and chain disruption reactions, thanks to the hydrogen donor properties of the hydroxyl groups in their structure. It is found in high concentrations in fruits and vegetables, tea, coffee and cereals (51).

In a study by Gadani et al. in Saudi children, oxidative stress and antioxidant status were examined. In the study, 30 autistic children aged 3-15 years and 30 control groups were used. Lipid peroxidation, vitamin E and vitamin C levels were measured. Lipid peroxidation was found to be significantly higher in autistic children compared to the control group, indicating that the antioxidant level is low. Vitamin E was also significantly low. Vitamin C was low, but this was not a significant value.

This study concludes that autistic children should be supplemented with antioxidants (52).

In the study of Sesso et al., the role of flavonoids in the prevention of cardiovascular diseases was examined. 24.5 mg of quercetinflavonoid content per day was given. It is found in broccoli, apples and tea. There was an improvement of 13-22% in women who consumed them, but there was no significant result and they stated that more studies should be done (53).

In a study by Moslemi and Tablobakhsh, selenium and vitamin E were examined in infertile men with idiopathic asthenoteratozoospermia. It has been stated that selenium with antioxidant properties is necessary for testicular development and spermatogenesis. It also protects cellular membranes and organelles by acting through glutathione peroxidase. A study was conducted by giving 200 mg of selenium and 400 mg of vitamin E daily to infertile men. Sperm motility and morphology improved in 52% of patients, with an increase of 10.6% in pregnancy (54).

8.6 Zinc

It is well known that zinc is an important trace element that affects growth and the development and integrity of the immune system. It is clear that this trace element has a broad effect on important immune mediators such as enzymes, thymicpeptides and cytokines, which explains the greatest importance of zinc status in the regulation of lymphoid cell activation, proliferation and apoptosis. Future studies may lead to public health interventions with dietary doses of zinc supplements to increase resistance to infections (55).

8.7 Selenium

Selenium (Se), a micronutrient, is essential for growth, development and antioxidant defense (56). Proteins called selenoproteins, on which selenium forms the basis for their functioning, have important metabolic functions such as cell signals, antioxidant defense system, thyroid hormone metabolism and maintenance of immune response systems.

Selenium deficiency can impair the function of selenoproteins and thus affect the health status of the organism (57). To give an example from today, an epidemiological study was conducted in 17 cities in China and the amount of selenium in the hair samples and the recovery rates of COVID-19 were examined and a positive correlation was found (58).

8.8 Probiotics

Probiotics are microorganisms (bacteria, yeast) that exert a beneficial effect on host health. When some of these microorganisms are ingested, they can resist the physicochemical conditions prevailing in the digestive tract, and the strains most commonly used as probiotics belong to the Bifidobacterium and Lactobacillus genera. They play protective roles in the immune system by directly blocking intestinal chymatogenic microbes and increasing mucosal integrity through epithelial cell stimulation (59).

8.9 Prebiotics

Various molecules can be prebiotic, but the vast majority are dietary fibers such as oligosaccharides. Its main effects are related to the metabolism of the microbiota. Indeed, if the colon lacks any dietary fiber, anaerobic bacteria get their energy from protein fermentation. This metabolism leads to the production of toxic and potentially carcinogenic compounds (such as ammonia or phenolic compounds). In contrast, fermentation of carbohydrates (such as dietary fiber) generates SCFAs such as acetate, propionate or butyrate and are potential fuels for epithelial cells. For example, in an in vivo rat model, a fructan (inulin, FOS) enriched diet increased SCFA production (60). Prebiotics act first to provide selective stimulation of the activity of beneficial autochthonous bacterial strains. Some prebiotics may exert a direct antimicrobial effect, as they can adhere to the binding sites of bacteria on the enterocyte surface, thereby preventing the adhesion of pathogenic bacteria to intestinal epithelial cells (61, 62).

In conclusion, while it is clear that prebiotics have some effect on the microbiota (modification, stimulation, antipathogenic effect), little

is known about the specific effect of each type of oligosaccharide on the various genera and species that make up the microbiota.

9. CONCLUSION

As a result, our immune system is a system that can be strengthened with our support throughout life, or weakened by our negligence, as well as innate immunity. Many antigens that infect the host are destroyed or slowed down or weakened by the host's strong immune system, that is, the host's immunity is the most important tool in the fight against infections. This means that if we have a weakened immune system, adding the deficient nutrition back to the diet as needed can restore immune function and resistance to infections. In addition to this, people's desire for a healthy and long life, their desire to increase their living standards, and factors such as chronic heart diseases, gastrointestinal disorders, diseases such as cancer, increased death rates, smoking, alcohol, stress, etc., have led consumers to focus on the antioxidant content of foods. Now, researches have started to intensify researches on antioxidants specific to a certain food (eg, only the antioxidant properties of apples or pomegranates, etc.) apart from antioxidants in general. The role of antioxidants in the health and immune system of the organism is an undeniable factor. As seen in our research, many diseases can be affected by nutrition and improvements can be seen with nutrition therapy, and even if we consider aging, quality age can be achieved with nutrition therapy. Nutrients such as vitamin D, vitamin E, vitamin C, zinc, selenium, probiotics, prebiotics, and cellular mechanisms for immunity, antioxidant activities, are cult elements of our immune system. The presence of these elements in our diet will create a set for many diseases and accelerate the healing process of diseases. It is an obvious fact that this information will be supported by future studies as well as by many studies.

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