Medical Diagnosis and Treatment Methods in Internal Medical Sciences-II

Editor
Assoc. Prof. Dr. Savas Karyagar

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PREFACE

Dear scientists,

Health sciences research is an interdisciplinary by nature. The production of knowledge and the sharing of the produced information within the scientific community, and its contribution to the solution of human health problems are the necessities of the age of science we are in. The book "Medical Diagnosis and Treatment Methods in Internal Medical Sciences" is serving an academic forum for both academics and researchers working in such fields. Scientists, especially those working in clinical branches, are trying to provide health services to their patients during the Covid 19 pandemic days, while on the other hand, they are trying to do scientific research and share scientific data in their field with the scientific community. In these days, when face-to-face training or getting together and sharing information is not possible, education has come into prominence online or through written texts. In this book, the selected articles have been reviewed and approved for publication by referees. I would like to thank all of my colleagues and publishing house for their contributions.

Assoc. Prof. Dr. Savas Karyagar

CHAPTER 1

WHITE COAT HYPERTENSION IN TURKEY

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1. INTRODUCTION

White Coat Hypertension (WCH) was first defined by Thomas Pickering in 1988 as the detection of higher blood pressure measurements in the office notwithstanding the blood pressure measurements being normal at home (1). With numerous studies since its first definition, these patients are known to have a higher cardiovascular risk than the normotensive population. In the hypertension diagnosis and treatment guideline of European Society of Hypertension (ESH) and European Society of Cardiology (ESC) updated in 2018; WCH is defined as the readings of three office blood pressures by the doctor being ≥140/90 mmHg and 24-hour ambulatory blood pressure measurements being ≤130/80 mmHg all day or ≤135/85 mmHg during the day or home blood pressure monitoring being in the normal range (≤130-135/85 mmHg). WCH, should be differentiated from the condition called White Coat Effect which is the increase of blood pressure measurement of normotensive or all hypertensive patients receiving treatment or not, in the presence of healtcare workers(2).

2. DISCUSSION

Pickering et al. found the frequency of WCH as 21% in the prevalence study of WCH that was conducted on 292 patients in 1988. Most of these patients were young women and people who were underweight (3). Also in the study of Finn- Home, 15.1% of the 1540 patients with the age ranging 44 to 75 years who could not have been treated was found to have WCH (4). In the study of PAMELA which confirms the importance of epidemiological studies in the field of several types of hypertension conducted in Italy; 2051 patients between the age of 25-74 were monitored for 16 years (1992-2008). Prevalence of WCH in this study was found at the rate of 15-45% and it was reported that WCH was seen in women and non-smokers more frequently (5). In a study that Erdogmus et al. conducted on 1053 patients in Turkey, prevalence of WCH was found to be 17% and while it was seen more frequently in women, there was no correlation with smoking (6). In another study also conducted in Turkey, prevalence of WCH was found to be 43% (7). Data related to prevalence and prognosis of WCH in the geriatric population is rather limited. In a prevalence study that Franklin et al. conducted, prevalence of WCH in 1168 elderly patients with untreated isolated systolic hypertension is 28,6% (8). Helvacı et al. observed in a study they conducted in Turkey that WCH prevalence was decreasing with aging (7). The rate of WCH prevalence is observed to vary widely around 15% to 45% in epidemiological studies conducted all over the world.

Dyslipidemia, impaired glucose tolerance (IGT), type 2 diabetes mellitus (DM), obesity and metabolic syndrome in WCH patients are observed more frequently. However, WCH prevalence observed in 856 patients with type 2 DM in China was found to be at the rate of 7.4% similar to the society in general. Again in this study, female sex, smoking and consumption of alcohol were observed as independent risk factors for WCH in type 2 diabetic patients (9). In a study Erdogmus et al. conducted in Turkey, it was observed that the prevalence of DM in WCH patients was 16.5% and there was no discrepancy of diabetic prevalence among WCH, sustained hypertensive (SHT) and masked hypertensive (MHT) patients (6). In light of this information, it is seen that WCH prevalence and risk factors in patients with type 2 DM do not differ from the normal population.

In the study that Björklund et al. presented 20-year follow-up of 602 patients over 50 years old, although the comorbidity and body components were similar at first, the increase in insülin resistance, blood glucose and insülin levels were higher in WCH patients compared to normotensive patients

(10). In the study of PAMELA, development of diabetes mellitus was observed 2,9 times more in the ones within WCH group among the patients followed for 10 years compared to normotensive patients (11). In the study of Erdogmus et al. no discrepancy was observed in body mass index (BMI) values among WCH, SHT and MHT patients (6). Again in another study conducted in Turkey, BMI and hip circumference in MHT group, waist circumference in SHT group were found to be high among WCH, SHT, MHT and normotensive patients (12). In a study that Afsar et al. studied fasting blood glucose (FPG) values among WCH, SHT, MHT and normotensive patients in Turkey, FPG was found to be higher in WCH, SHT and MHT patients compared to normotensive patients (13). In another study that Helvacı et al. conducted on WCH, SHT and normotensive patients in Turkey, it was observed that dyslipidemia was more prevalent in WCH patients. IGT and DM were encountered more in WCH patients but less in SHT patients compared to normotensive patients (14). As a result of these studies, existence of dyslipidemia, metabolic syndrome, IFG, IGT, and diabetes mellitus is seen more frequently in WCH patients than in normotensive patients. Due to this reason, it must not be forgotten that these comorbidities could develop in the follow-up of WCH patients.

Fundus examination, microalbuminuria, left ventricular mass index and Carotid Intima Media Thickness (CIMT) measurements to determine the end-organ damages in hypertensive patients are analyzed through these parameters. In the studies both PAMELA and Karter et al. conducted, left ventricular mass index was found to increase in WCH patients compared to normotensive patients; however, this increase was not as high as hypertensive patients. When evaluated through microalbuminuria values, there were no difference between WCH and hypertensive patients in both studies (11,15). In the study of HARVEST, early-stage hypertensive patients and normotensive people were followed for 5 years with the measurement of CIMT for evaluating the progression of atherosclerosis. Compared to normotensive patients, CIMT values in WCH patients were observed to be higher in the beginning of the study and after the end of 5 years while also the thickness increased faster. However, no discrepancy was observed when CIMT measurements of WCH and hypertensive patients were compared in the beginning and at the end of 5 years (16). In a study conducted among WCH, SHT, MHT and normotensive patients in Turkey, while left ventricular hypertrophy was most commonly encountered in SHT patients, it was seen in 12.5% of WCH patients and was observed to be especially higher than it is in normotensive patients (13).

Although the risks of stroke and cardiovascular disease in WCH patients are slightly increased compared to normotensive patients, they are not as high as in hypertensive and MHT patients (17,18). In the study of OHASAMA that was conducted in Japan, no statistical significance was found for stroke risk in the 10-year follow-up of WCH patients although there was a rise when compared to normotensive patients (17). In the study Pierdomenico et al. conducted to determine cardiac and cerebrovascular risk, 1732 patients were monitored on a span of 6 years. While cardiac and cerebrovascular risks in hypertensive patients were more than WCH patients and there was no difference between WCH and normotensive patients. WCH patients were found to need anti-hypertensive treatment more than normotensive patients in the follow-up process (18).

WCH patients should be monitored strictly due to the probability of developing increased cardiovascular risk, hypertension and end-organ damage. Lifestyle changes must be recommended before the anti-hypertensive treatment. Patients should be encouraged to do exercise (walking, running, swimming etc.), reduce salt consumption and a diet suitable for their comorbidities should be arranged to reach the ideal BMI. In the hypertension diagnosis and treatment guideline of ESH and ESC updated in 2018; first, lifestyle changes should be implemented (Class 1, Class C); If there is an end-organ damage, the necessity of starting the treatment (Class 2b, Level of evidence C) in addition to lifestyle changes are emphasized (2). Even if ambulatory blood pressure measurements are normal in WCH patients with the end-organ damage, anti-hypertensive treatment must be started for early protective purposes (2).

WCH patients should be monitored within 3 to 6 months intervals for comorbid conditions such as dyslipidemia, metabolic syndrome and type 2 DM. As it counts as a pre-hypertensive condition, it should be monitored with ambulatory blood pressure and home measurements once every 3-6 months according to patient's traits. WCH patients should have routine biochemical laboratory tests, annual fundus examination, the urine measurements of microalbuminuria and, if possible, CIMT measurements once every 6 months like in the follow-up of hypertensive patients (2).

3. CONCLUSION

WCH, hereby, is an important disease increasing tendency to hypertension and co-occurring with diseases that have significance over atherosclerosis

such as dyslipidemia, metabolic syndrome and type 2 DM. Screening tests for development of end-organ damage and these diseases should be done at regular intervals. Patients should primarily be monitored with ambulatory blood pressure measurements. It should be known that while cardiovascular risk is higher than in normotensive individuals, it is not worse than hypertensive population. To all WCH patients, lifestyle changes should be recommended first like in hypertensive patients and salt consumption must be restricted; however, if end-organ damage is detected, starting a medical treatment must not be delayed.

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CHAPTER 2

JUVENILE BEHÇET'S DISEASE

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1. INTRODUCTION

Behçet's disease (BD) was first described by Hulusi Behçet in 1937 as a disease with recurrent oral and genital aphthae (1). BD is a systemic vasculitis that can affect all types of vessels. It affects the gastrointestinal system, central nervous system, musculoskeletal system and cardiac system. The etiopathogenesis of the disease has not been fully elucidated. It is thought that infectious and environmental factors trigger the disease in individuals with genetic predisposition (2). BD mostly occurs in young adulthood period. However, the symptoms of 15-20% of the patients begin in childhood period (3). In pediatric BD, the frequency, severity and course of the disease differ compared to adults. Additionally, in childhood, the disease is mostly seen in an incomplete form, and the typical symptoms of the disease may take years to appear (4). There is no diagnostic laboratory examination in the diagnosis of BD, and the diagnosis of BD is based on clinical symptoms. The most commonly used diagnostic criteria are the ones developed by the International Behçet's Study Group (ISG) for adult patients (Table 1) (5). In the last decade, the Pediatric BD Group (PEDBD) developed diagnostic classification criteria for children (Table 2) (6).

Table 1: The criteria of the International Behçet's Study Group (ISG) (5).

Finding	Definition
Recurrent oral aphthosis	At least 3 attacks per year + (in addition to the following 2 criteria)
Genital ulceration	Scarred
Eye involvement	Anterior uveitis or posterior uveitis, retinal vasculitis
Skin involvement	Necrotic folliculitis, acneiform lesions, erythema nodosum
Pathergy test positivity	

Table 2: The criteria of the Pediatric Behçet's Disease Group (PEDBD) (6).

Finding	Definition	Score
Recurrent oral aphthosis	At least 3 attacks per year	1
Genital ulceration	Scarred	1
Skin involvement	Necrotic folliculitis, acneiform lesions, erythema nodosum	1
Eye involvement	Anterior uveitis or posterior uveitis, retinal vasculitis	1
Neurological involvement	Except for isolated headache	1
Vascular findings	Venous thrombosis, arterial thrombosis, arterial aneurysm	1

A score of ≥4 is required for the diagnosis of BD.

2. EPIDEMIOLOGY

The disease is mainly seen in regions on the ancient Silk Road extending from the Far East to the Mediterranean (Iran, Israel, Turkey) (3). The prevalence of the disease has been reported as 10.3 / 100000 worldwide, and the prevalence of BD in the Turkish population has been reported as 600 / 100.000 (7, 8). The median age of onset of BD in childhood ranges between 4.9 and 12.3 years, and the median delay time until diagnosis has been reported as 3 years (9). There is no difference between genders in terms of frequency. However, the prognosis is worse in male patients than in females (4). Family history has been reported with a high rate of 12-55% (3).

3. ETIOLOGY AND PATHOGENESIS

The etiopathogenesis of BD is still not fully understood. Activation of the natural and acquired immune system on the basis of genetic predisposition is

thought to result from the emergence of different clinical findings (2). The frequency of familial cases, the geographical distribution of the disease, and its relationship with *HLA-B51* suggest that genetic factors play an important role in its pathogenesis (10). There are some studies showing that certain genes which are responsible for innate and adaptive immunity (ERAP1, IL23R, IL10, STAT4) play a role in pathogenesis (11). Some microbial microorganisms such as streptococcal antigens are thought to trigger or exacerbate the disease (12). In addition to the adaptive immune system, neutrophil hyperreactivity and inflammation mediated by innate immunity have an important role in the pathogenesis. The role of the innate immune system, absence of autoimmune features, and episodic disease suggest that Behçet's disease is an autoinflammatory disease.

4. CLINICAL FINDINGS

4.1. Mucocutaneous Lesions

The most common initial clinical finding of BD is recurrent oral aphthous ulcers (87-98%). It is observed in almost all patients during follow-up. Aphthous lesions can be large or small; can be observed as single or multiple lesions; may be on the inner lip, tongue, cheeks, oropharynx or palate and usually heal without scar. The second most common clinical finding of BD is recurrent genital aphthous ulcers (55-83%) (Figure 1). They are larger and deeper than oral ulcers and have irregular borders usually accompanied by inflammatory discharge. They typically occur on vulva in girls and on scrotum and penis in boys. Genital ulcers are very painful, can restrict patients' physical activity, and they usually heal with scarring. Other skin findings detected in BD are erythema nodosum, pseudo-folliculitis and acneiform lesions. The skin of the patients is sensitive to minor traumas such as puncture and shaving. The pathergy test is an important diagnostic tool for the diagnosis of BD and is a characteristic finding showing the inflammatory hypersensitivity occurring within 24-48 hours after the traumatization of the forearm skin with a small needle (Figure 2). Pathergy test positivity varies between 14.5% and 80% among different regions (2, 3, 4). The pathergy test was included in the diagnostic criteria of the ISG, but it is not included in the PEDBD criteria developed for children (5, 6).

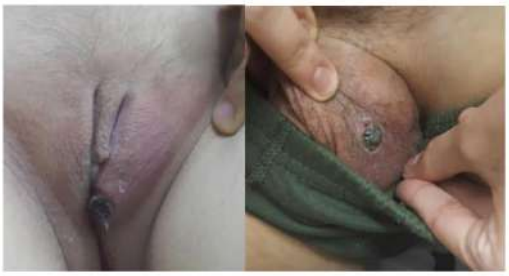

Figure 1: Genital ulcers.

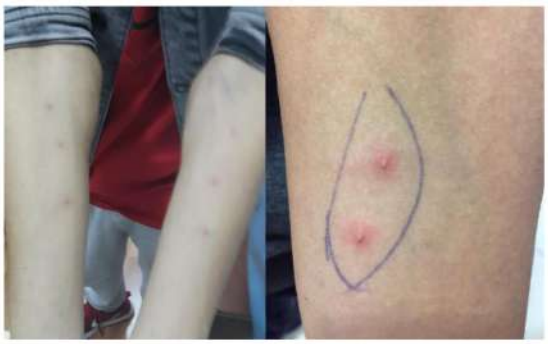

Figure 2: Pathergy positivity.

4.2 Joint Involvement

Findings related to joints are seen in approximately 20-40% of BD patients. Arthralgia is the most common musculoskeletal symptom. Arthritis is less common and is usually in the form of oligo-arthritis in the knee and ankle. In addition, sacroiliitis or enthesitis can be monitored. Joint findings are repetitive, last a few days or weeks, and typically heal without permanent damage (2, 3, 4).

4.3 Eye Involvement

The eye is one of the most frequently affected organs in BD and is the most important cause of morbidity. Therefore, every patient with suspected BD should undergo an annual eye examination. Recurrent eye findings are seen in 14.1-66.2% of the patients; It can affect one or both eyes. Blurred vision,

red eyes, pain and photophobia may occur. Although ocular involvement is less common in childhood compared to adults, it has a more severe course. The most characteristic ocular signs are hypopyon, pan-uveitis and retinal vasculitis. However, band keratopathy, retinitis, papillitis and macular edema are other eye findings that can be observed. Posterior synechiae, cataracts, glaucoma, retinal vein occlusion and vision loss may also occur. Eye involvement is more common in boys than girls and has a more severe course (2, 3, 4).

4.4 Neurological Involvement

Neurological involvement has been reported as a rate of 3.6-59.6% in childhood BD. Neurological involvement is divided into parenchymal and non-parenchymal involvement. Peripheral nerve disease is very rare in children. Non-parenchymal involvement in the brain is the most common in children, especially dural sinus thrombosis. It manifests itself with headache, papillary edema, motor and ocular nerve paralysis due to increased intracranial pressure, subacute hemorrhage, and cerebral vasculitis. In adults, the most common brain parenchyma is involved. More rarely, brainstem dysfunction, myelopathy, meningoencephalitis, and recurrent pyramidal findings can be seen. Neuro-BD may show an acute or progressive chronic course in patients (2, 3, 4).

4.5 Vascular Involvement

BD is a systemic vasculitis that can involve in all types and sizes of vessels, but venous involvement is more common than arterial involvement. Vascular involvement is less common in children than adults and has been reported with a frequency of 1.8-21%. Thrombosis occurs most frequently in the lower extremity venous structures. Thrombosis develops due to inflammation in the vascular wall, and typically emboli is not an expected finding in BD. Especially, it is seen more in boys than in girls. Recurrent aneurysms, stenosis and thrombosis can be seen. Deep vein thrombosis in the lower extremities, vena cava thrombosis, pulmonary artery aneurysm, abdominal aorta aneurysm, peripheral artery aneurysms, Budd-Chiari syndrome, iliac and femoral artery thrombosis, superior sagittal sinus thrombosis and cardiac thrombosis are the vascular manifestations that can occur in BD. Especially pulmonary artery involvement can be severe and it is the most common cause of mortality in BD (2, 3, 4).

4.6 Gastrointestinal System Involvement

The frequency of gastrointestinal involvement in pediatric BD is observed as a rate of 4.8-56.5%. It is more common in children than adults. Lesions can be seen anywhere in the entire digestive system, but most commonly in the ileum and colon. Abdominal pain, diarrhea, nausea, bleeding, and perforation are the most common clinical findings (2, 3, 4).

5. TREATMENT

The main purpose of treatment is to prevent organ damage and disease exacerbations by suppressing systemic inflammation. Multidisciplinary approach is important. The treatment is decided depending on the involvement and the severity of the disease. Colchicine is the most commonly used first-line therapy in the treatment of mucocutaneous lesions. Topical corticosteroids or oral corticosteroid treatments are used in the treatment of oral or genital ulcers. In the presence of severe neurological, vascular and ocular involvement, corticosteroids and immunosuppressive treatments (azathioprine, cyclosporine, cyclophosphamide) are used together. TNF-α inhibitors (infliximab, adalimumab, etanercept) are often preferred in patients with neurological, gastrointestinal, ocular or vascular involvement who do not respond to standard immunosuppressive therapy. Additionally, interferon alpha, anti-IL-1 (anakinra, canakinumab), anti-IL-6 (tocilizumab) treatments are used in selected cases. In recent years, there are studies reported that apremilast which is an oral phosphodiesterase inhibitor, decreases the frequency of oral ulcers (2, 3, 4).

6. PROGNOSIS

The disease is recurrent and the course of the disease is variable in each patient. New findings related to the disease may emerge over the years in childhood. Functional permanent deficiencies may occur in the presence of neurological and ocular involvement. Deaths may occur due to sepsis, vascular involvement, and neurological involvement.

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CHAPTER 3

FAMILIAL MEDITERRANEAN FEVER IN CHILDREN

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1. INTRODUCTION

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease with autosomal recessive inheritance (1-3). Autoinflammatory diseases, the prototype of which is the FMF are characterized by dysregulation of the innate immune system and uncontrolled inflammation (1). These diseases are also called periodic fever syndromes clinically, as many of them have recurring episodes of fever. The disease is caused by mutations in the Mediterranean fever (MEFV) gene. This gene is located on the short arm of chromosome 16. and encodes pyrin protein which involved in nucleation of the macromolecular pyrin inflammasome complex that catalyzes the release and cleavage of the proinflammatory cytokines IL-1$_\beta$ and IL-18. In addition, pyrin protein is involved in inflammatory cell death called pyroptosis (4). Clinically self-limiting recurrent episodes of fever and polyserositis, and an increase in acute phase reactants is typical during episodes. (5). Although it is seen worldwide, its prevalence is higher in ethnic groups of Eastern Mediterranean region including Arabs, Turks, Jews and Armenians compared to other countries (6). The most feared complication of the disease is amyloidosis and may result in long-term morbidity and mortality (7).

2. HISTORY

As far as is known, the disease was first described by Janeway and Rosenthal in 1908 as "unusual recurrent peritonitis" in a 16-year-old Jewish girl with recurrent abdominal pain, fever and leukocytosis. In 1945, Siegal defined the same clinical picture in 10 Ashkenazi Jews and called as "benign recurrent peritonitis". The familial inheritance of the disease and its relationship with amyloidosis was shown in 1951 by Mamau and Kattan. Finally, in 1958, for the first time the Familial Mediterranean Fever definition was used by Heller and Sohar (8-11). It was first found in 1972 by Emir Özkan and simultaneously Goldfinger that colchicine obtained from crocus flower can be used for the treatment of FMF (12). The MEFV gene, which enables us to understand the disease more clearly, was identified in 1997 (13, 14).

3. EPIDEMIOLOGY

It is thought to be the most common autoinflammatory disease with the presence of approximately 150000 patients worldwide. FMF is most common among North African Sephardic and Iraqi Jews, Turkish, Armenian, and middle east Arab populations. Its prevalence in these regions varies between 1 in 500-1000 (15). In addition, the carrier rates of the MEFV mutations (heterozygous) in ethnicities is reported to be high, reaching 1 in every 5 people (16, 17). The disease has also been shown in Greece, Poland, Australia, Belgium, Italy, Greece, Japan and Cubans (18). In the last century, it has started to be widely seen around the world, especially due to migration. While both FMF and amyloidosis are common in Sephardic Jews, FMF is rare in Askenazi Jews (1/73000) (19). The prevalence of the disease show regional characteristics in Turkey, and is higher the central region of Anatolia including Sivas, Tokat, Kastamonu rather than the Mediterranean coast region (20).

4. GENETICS

The MEFV gene, defined in 1997, was named with the initials of term "Mediterranean Fever". It encodes a 781 amino acid gene called Pyrin or Marenostrin, located on chromosome 16p13.3 (12, 14, 21). Currently 385

MEFV variants have been identified according to the INFEVERS database. This number is increasing in parallel with genomic sequencing (22). Most of these variants do not cause disease and have been identified as variants of unknown significance. Most mutations known to be pathogenic occur in exon 10. In a 2012 study, M694V, M680I, M694I, V726A, A744S, R761H, E167D, I692del, T267I were classified as common pathogenic variants and E148Q, K695R, P369S, F479L, and I591T as variants of unknown significance (23). The most common MEFV variant is M694V in FMF endemic regions and it is considered to be the most pathogenic variant. Other frequent pathogenic variants listed above and M694V variant constitute 75% of all FMF patients (24, 25). In patients with these heterozygous or homozygous or combined heterozygous pathogenic variants, the clinical manifestation of FMF is more typical and severe (26).

The most frequently detected mutation in Turks, Armenians and Jews in the Middle Mediterranean belt is M694V, followed by the M680I mutation in Turks and the V726A mutation in Arabs, Armenians and Jews. The most common mutation detected in Arabs is M694I (27-29). However, in countries such as Japan where FMF is not endemic, mutations of unknown significance such as E148Q and L110P can be seen frequently (30). Benign variants, possibly benign variants and variants of unknown significance are usually found in exon 2, and patients carrying these variants usually have more atypical clinical findings (31). In fact, despite many genetic studies, the correlation between phenotype and genotype has not been clearly elucidated.

Although FMF is inherited as autosomal recessive pattern, a approximately 30% of patients harbour single heterozygous mutation (32). This leads to the psödo-dominant inheritance with the accumulation of mutations in successive generations due to the high rate of consanguineous marriage, especially in FMF prevalent regions. In addition, a recent study showed that the frequency of FMF like symptoms was greater in patients with two high penetrance mutations than patients with a single low penetrance mutation, and there was a "dose effect" associated with the mutations. (32-34). Indeed, atypical clinical findings seen in heterozygous individuals can be explained by this theory. Another explanation may be the effect of other modifying genes such as the serum amyloid A (SAA) gene in heterozygous individuals. Atoyan et al. showed that SAA1 α allele is associated with amyloidosis in FMF patients (35). Furthermore, it should be kept in mind that environmental factors have an important effect on the phenotype of the disease.

5. PATHOGENESIS

The Pyrin protein weighs 86 kDa, consists of 5 different domains and contains 781 amino acids (36). Pyrin is mainly expressed from myeloid progenitor cells, such as neutrophils, monocytes, eosinophils, dendritic cells and synovial fibroblasts, and in case of disruption in cytoplasmic homeostasis it forms the pyrin inflammasome complex (37). The localization of pyrin in the cell is mainly related to in which cell it is expressed. Although the presence of the b-ZIP transcription factor domain suggested that pyrin is a nuclear protein, later studies showed that the full-length pyrin is mainly located in the cytosol and that the N-terminal half of pyrin colocalizes with both the actin cytoskeleton and microtubules (38).

The role of each pyrin domain and the proteins it binds to are different for each domain, and it contributes to inflammation through these proteins (39). Pyrin composed of the Pyrin domain (PYD) located at the N-terminal end and primarily responsible for the inflammatory process, b-ZIP transcription factor domain, the central boxed-box (B-box) domain, the coiled-coil domain, and the C-terminal PRY/SPRY (B30.2) domain (40). The PYD binds to the "apoptosis associated spect like protein with a caspase recruitment domain" (ASC), which is an inflammasome adaptor protein, causing caspase-1 mediated IL-1β production (41). B-box and α-helical coiled coil (CC) domain may play a role in the oligomerization of pyrin. These two domains have also been shown to interact with the proline-serine-threonine-phosphatase interacting protein, a protein that is important for the organization of the cytoskeleton (36). Most of the FMF-related mutations are associated with the B30.2 domain at the C-terminal end of the pyrin, thus this region is important for the underlying molecular mechanisms in FMF. In vitro studies have shown that this region directly interacts with caspase-1 (42). The structure of the pyrin is shown in figure 1.

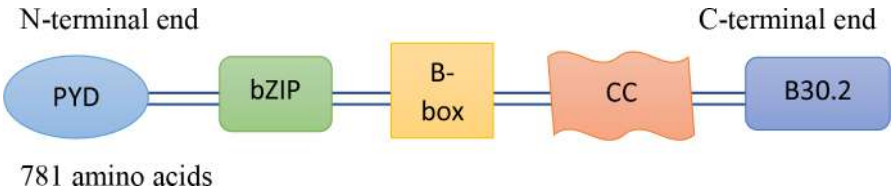

Figure 1: Pyrin protein

In FMF, inflammation occurs through several mechanisms. The first step includes the engagement of Pyrin domain at the N-terminal end of pyrin and the ASC protein driven by appropriate stimulation, afterwards the caspase recruitment domain (CARD) of ASC protein interacts with the CARD of procaspase-1, and the increasing procaspase-1 turns into the active caspase-1. The caspase-1 initiates inflammation by mediating the transformation of pro IL-18 and pro-IL-1β into mature forms (36). Until 2014, the factor causing pyrin activation was unknown. In 2014, Xu et al. showed that pyrin is sensitive to pathogen-induced modification of Rho guanosine triphosphatase (Rho GTPase) in the host cell (43). Park et al. demonstrated that inflammation occurs as a result pyrin mutation or in response to bacterial modification of Rho GTPase. Rho A linked serine-threonine kinases phosphorylate PKN1 and PKN2 pyrin. Subsequently, the chaperone 14-3-3 proteins bind to the phosphorylated pyrin. This interaction keeps the pyrin inactive state and thus active inflammasome cannot occur. The inactivation of Rho A (when modified) by the effect of various bacterial toxins leads to a decrease in PKN1 and PKN2 activation and thus a decrease in phosphorylated pyrin. Non-phosphorylated pyrin is cleaved from the 14-3-3 protein and forms the active pyrin inflammasome (44).

6. CLINICAL MANIFESTATIONS

Familial Mediterranean fever is a disease that occurs under the age of 20 in approximately 90% of cases. In a multicenter study involving pediatric and adult patients, ıt was observed that the average age for complaints to occur was 9.6 ± 8.6 years. and the mean age at diagnosis was 16.4 ± 11.6 years, respectively (45). Undoubtedly, diagnosis can be made at a much earlier age in regions FMF endemic regions. The Turkish FMF study group reported that the disease occurs equally in both genders (45). A mild male predominance has been observed in the literature (46), which may be due to underdiagnosed episodes triggered by menstruation in female.

Familial Mediterranean fever is a recurrent, spontaneously resolving disease characterized by inflammation of the serous membranes and fever, with episodes lasting 6 hours to 3 days. Sometimes simultaneous involvement of multiple serous membranes may be observed. During the episode, C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen known as acute phase reactants, increase. In addition, white blood cell, neutrophils and erythrocyte

sedimentation rate (ESR) are also higher. Patients do not have any complaints between episodes, and they return to their normal state of health (47). The episode patterns may vary among patients and within a single patient. It is possible to see different clinical pictures such as episodes of peritonitis and fever as well as pleuritis and fever in the same patient. This is thought to be due to the influence of various environmental factors and microbiota (26).

Although the main factor that triggers the episode is not known clearly, factors such as stress, fatigue, menstruation, and previous infections seems to be responsible.

Body temperature is mostly between 38-40˚C and decreases spontaneously within 6-72 hours. The level of fever may vary between patients and episodes. In the same patient, measured values may increase in some episodes and may decrease in others. Since fever may be the only clinical finding, especially in preschool children, differential diagnosis can be difficult (15). Peritonitis (93.7%), fever (92.5%), arthritis (47.4%), pleuritis (31.2%), amyloidosis (12.9%) and non-amyloid glomerular disease (0.8%) was observed in a study investigating 2838 Turkish FMF patients (45).

Abdominal pain occurs due to inflammation of the peritoneal lining. Although the severity of abdominal pain can vary from mild tenderness to acute abdominal symptoms, crushing abdominal pain is observed, particularly in children. In many cases, constipation complaints during the episode are frequent due to peritoneal inflammation slowing down peristalsis. Diarrhea can be seen in 10-20% of the patients. Some patients may develop peritoneal adhesions due to recurrent episodes of peritonitis. During the episode, abdominal examination findings are frequently confused with acute appendicitis. This explains the high number of patients undergoing appendectomy (20%) (45, 48).

Joint involvement can be seen as arthritis or arthralgia. Arthritis is less common than arthralgia. Arthritis is often monoarticular and non-destructive. Patients experiences recurrent attacks of arthritis involving the large joints of the lower extremity (knee, ankle). It usually resolves within 1-2 weeks without leaving erosion (47). Some patients may experience chronic arthritis.

Chest pain occurs due to pleural inflammation and usually presenting symptoms including painful breathing. The pain is mostly unilateral. In some patients, pleural effusion is found on chest radiography and respiratory sounds can be decreased on the affected side. In some cases, the cause of chest pain

is pericarditis. It has been reported that the rate of pericarditis in patients with FMF is 0.5% (12, 49).

The most common and pathognomonic skin manifestation is erysipelas-like erythema. These lesions are characterized by uniformly limited, red patch-like a tender, red, swollen, and painful eruptions that usually appears on the dorsum of the feet and malleolus (50). The biopsy reveals mixed cellular infiltrate (51). It occurs due to prolonged standing.

Muscle pain is common in FMF patients and usually occurs at a rate of 20% (52). The pain usually occurs after exertion in the evening and can last for hours or days, it is relieved with rest and resolved the use of with nonsteroidal anti-inflammatory (NSAID) medication (52). Patients may also experience prolonged myalgia syndrome, which is not associated with an episode. This condition is thought to be a vasculitis affecting the fascia of the muscle, and corticosteroids have been recommended for its treatment (53). Clinical conditions such as FMF-associated sacroiliitis have also been described in recent years (54).

It has been found that clinical findings are milder and fever, erysipelas and especially chronic arthritis are not evident in FMF that occurs at a later age. (47).

lthough rare, clinical entities such as scrotal involvement or a rash similar to Henoch Schönlein purpura (HSP) have been reported in familial Mediterranean fever. Difference of purpura in FMF from that seen in HSP is lack of IgA storage (55).

The prevalence of Behcet disease, Polyarteritis nodosa, HSP, inflammatory bowel diseases and glomerulonephritis has increased in FMF compared to the normal population (56, 57).

7. LABORATORY PARAMETERS

Acute phase reactants including CPR, SAA, and complement increases during episodes. In addition, an increase in ESR and white blood cell count is observed. In some cases, systemic amyloidosis can be suspected in case of a sustained high acute phase response. Amyloidosis is the most serious and feared complication of FMF and is characterized by LAA deposition in many organs (5).

The risk of amyloidosis increases with family history, male gender, a/a genotype of SAA1 and poor response to colchicine and homozygous M694V

mutation (58, 59). Since amyloidosis most often affects the kidneys, it is important to perform urinalysis at regular intervals in these patients. The best indicator of impaired renal function is the urine microalbuminuria assay. If proteinuria is present, amyloidosis should be confirmed by rectal or renal biopsy.

8. DIAGNOSIS

The diagnosis of FMF is basically characterized by the typical clinical findings (recurrent episodes of fever lasting 6 hours to 3 days, serositis), the spontaneous recovery of the clinical and laboratory picture following an increase in acute phase reactants in the blood test. Family history, ethnicity, and presence of the MEFV mutations also support the clinician for the diagnosis of FMF.

Tel Hashomer and Livneh criteria were first introduced for adult patients for FMF diagnosis. (60, 61). However, it has been noticed that in FMF endemic regions such as Turkey and in pediatric patients Hashomer and Livneh criteria were inadequate, and then Yalcinkaya and Özen criteria (62) has been developed in 2008. These criteria have been shown to be more specific than the Tel Hashomer and Livneh criteria and have been used for a long time. However, since none of these criteria include genetic and ethnic evaluation, criteria including genetic examination in the diagnosis were developed by Eurofever/PRINTO in 2019 (63). Yalçınkaya and Özen criteria are shown in Table 1 and Eurofever/PRINTO criteria are shown in Table 2.

Table 1: Yalçınkaya and Özen Criteria (62)

Criteria	Definition
Fever	Fever ≥3 times, lasting 6-72 hours, axillary 38^0C
Abdominal pain	≥3 times, lasting 6-72 hours, abdominal pain
Chest pain	≥3 times, lasting 6-72 hours, chest pain
Arthritis	≥3 times, arthritis lasting 6-72 hours, oligoarthritis
Family history of FMF	

Definitive diagnosis: Meeting 2 of 5 criteria

Table 2: Eurofever/PRINTO Criteria (63)

Clinical + Genetic Criteria	**Clinical Criteria Only**
Presence of confirmatory MEFV genotype and at least one among the following*	Presence of
1- Duration of episodes 1-3 days	1- Eastern Mediterranean ethnicity
2- Arthritis	2- Duration of episodes 1-3 days
3- Chest pain	3- Arthritis
4- Abdominal pain	4- Chest pain
OR	5- Abdominal pain
Presence of not confirmatory MEFV genotype and at least two among the following ‡	**Absence of**
1- Duration of episodes 1-3 days	1- Aphthous stomatitis
2- Arthritis	2- Urticarial rash
3- Chest pain	3- Maculopapular rash
4- Abdominal pain	4- Painful lymph nodes
*Pathogenic or likely pathogenic variants (heterozygous in AD diseases, homozygous or in trans (or biallelic) compound heterozygous in AR diseases) ‡In trans compound heterozygous for one pathogenic MEFV variants and one VUS, or biallelic VUS, or heterozygous for one pathogenic MEFV variant	**≥6 criteria**

Pathogenic, likely pathogenic and insignificiant mutations are available in the INFEVERS database.

9. DIFFERENTIAL DIAGNOSIS

In the differential diagnosis, the patient should be investigated in terms of infectious causes present with fever and immune deficiencies with recurrent fever. In some malignancy cases, recurrent fever may be seen. In addition, other monogenic autoinflammatory diseases (Mevalonate kinase deficiency, periodic fever- aphthous stomatitis- pharyngitis- lymphadenopathy syndrome, Majeed syndrome, IL-1 receptor antagonist deficiency, joint contracture-muscle atrophy-panniculitis-induced lipodystrophy syndrome, TNF-receptor-associated periodic syndrome, cryopyrin, Blau syndrome) and their clinical

features should be well known and considered in differential diagnosis of FMF. Systemic juvenile idiopathic arthritis, inflammatory bowel disease and Behçet's syndrome should also be kept in mind in differential diagnoses. It should be noted that FMF is often confused with periodic fever-aphthous stomatitis-pharyngitis-lymphadenopathy syndrome and the differential diagnosis of these two is difficult, and in some cases two diseases can coexist in the same patient (15).

10. TREATMENT

Colchicine obtained from crocus flower has been used as the main treatment in FMF since 1972. With the introduction of colchicine treatment, the attacks are controlled, the clinical picture is improved and amyloid accumulation is prevented. Although the underlying mechanism is not well understood, colchicine is thought to prevent vesicle transport, cytokine secretion, phagocytosis, neutrophil adhesion, chemotaxis, and cell division by blocking microtubule polymerization in neutrophils (64).

In addition, it has been recently found that colchicine prevents the formation of NLRP3 inflammasome by inhibiting caspase-1 activation, and thus the production and release of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-alpha (64). The response to colchicine treatment is very good in approximately 90% of FMF patients. Gastrointestinal system side effects of the colchicine are most frequent, with nausea, vomiting and especially diarrhea detected in 5-10% of patients. These side effects can be eliminated by dose reduction. In a study, it has been demonstrated that jejunal maltase, sucrase and lactase levels were decreased due to prolonged colchicine use (65). This study may explain colchicine-induced diarrhea. The appropriate dose for colchicine in children is 0.02-0.05mg/kg (1.2mg/m^2/day) day. The maximum dose is 2 mg, which is the dosage used in patients who develop amyloidosis. Increasing the dose during the episode is not the correct approach, because colchicine is a toxic agent that can be fatal if not used in the appropriate dosage and acute high doses are taken. During the episode, routine colchicine dose should be continued and NSAIDs should be used to reduce pain if necessary. Colchicine can be given as a single dose or daily divided doses if the patient tolerates it. Patients should be checked every 6 months for response to colchicine, toxicity and drug tolerance. If liver enzymes have increased twice as much as the reference value, the dose of colchicine should be reduced. It is

not recommended to discontinue colchicine during conception, pregnancy and breastfeeding. Colchicine does not need to be discontinued before conception in men. Rarely, in patients with severe oligospermia, dose reduction or short-term colchicine discontinuation may be applied. In some patients with chronic arthritis due to FMF, NSAIDs, intraarticular steroid administration, disease-modifying antirheumatic drugs or biological agents may be required in addition to colchicine treatment. In prolonged febrile myalgia syndrome, steroid can be given as the first treatment in addition to colchicine, but NSAID and IL-1 inhibiting drugs can also be used. (66).

In 10% of the patients who are resistant to colchicine treatment, episode or subclinical inflammation continue despite colchicine. Colchicine resistance is defined by ≥1 attacks per month in patients receiving appropriate treatment dose for ≥6 months. Considering the pathogenesis of the disease, especially IL-1 inhibitors, TNF-alpha (if chronic joint findings are prominent) and IL-6 inhibitors can be used in selected patients. Colchicine treatment should be continued at an appropriate dose, as it protects the patient from amyloidosis, even if these biological agents are initiated. In colchicine-resistant FMF, the first -line treatment is biological agents that inhibit IL-1 activity. There are 3 types of anti-IL-1 agents in clinical use. Anakinra (recombinant human IL-1 receptor antagonist) is used as a subcutaneous injection at a daily dose of 1-2mg/kg/day. Canakinumab is a human monoclonal antibody developed against IL-1 beta. It is given as a subcutaneous injection at a dose of 2 mg / kg every 4-8 weeks, and 150 mg directly if it is over 40 kg. Another agent is rilonacept, which is a fusion protein developed against IL-1 receptor and is not used in FMF (67, 68).

11. OUTCOME AND PROGNOSIS

The prognosis of the disease improved markedly as the hidden aspects and pathogenesis of the disease became known to clinicians and the use of biological drugs. The rate of amyloidosis is currently very low, and this usually occurs when the family does not understand the importance of the disease, does not adapt to treatment and follow-up, consults a physician with recurrent attacks, or applies to a physician in the late period after the development of amyloidosis. Although FMF is the best known monogenic autoinflammatory syndrome, it continues to surprise clinicians with its newly emerging features. However, the disease has ceased to be a scary health problem, especially with the use of colchicine and the development of biological drugs.

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CHAPTER 4

EVALUATION OF KINESIOPHOBIA IN PATIENTS WITH METABOLIC SYNDROME

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1. INTRODUCTION

Metabolic syndrome (MS) is a public health problem charactarized by central obesity, increased blood pressure and triglyceride levels, decreased high-density lipoprotein (HDL) cholesterol levels and insulin resistance. MS prevalance has increased rapidly into the biggest health problems in the world. Most studies indicate that cardiovascular disease and type 2 diabetes mellitus are major outcomes of MS. MS increases the probability of developing cardiovascular diseases more than 3 times and type 2 diabetes mellitus more than 5 times [1]. A few clinical definitions have been proposed for the diagnosis of metabolic syndrome (World Health Organization 1998, European Group for the Study of Insulin Resistance 1999, American Association of Clinical Endocrinologists 2003, National Cholesterol Education Program Adult

Treatment Panel III 2001, International Diabetes Federation 2005). The International Diabetes Federation (IDF), American Heart Association (AHA), and National Heart, Lung, and Blood Institute (NHLBI) define metabolic syndrome as central obesity (> 94 cm in men and >80 cm in women) based on waist circumference plus two or more additional metabolic risk factors (fasting plasma glucose > 100 mg/dL, blood pressure ≥ 130/85 mm-Hg or treated for hypertension, Triglyceride >150 mg/dL or treated for dyslipidemia, HDL cholesterol < 40 mg/dL in men or < 50 mg/dL in women or treated for dyslipidemia) [1-3].

Kinesiophobia is fear of movement due to the belief of increasing pain during the activity [4]. Kinesiophobia is associated with low physical activity level in patients with cronic pain [5]. Low physical activity leads to an increase in the risk of not only cronic pain, but also cardiovaskular disease. As a result, physical inactivity due to the kinesiophobia could cause obesity, dislipidemia and MS.

Our main hypothesis in this study was the presence of kinesiophobia in patients with MS. Secondarily, we thought that anxiety and depression levels were high in patients with MS.

Therefore, we aimed to evaluate whether patients with MS have kinesiophobia.

2. MATERIALS AND METHODS

80 participants (41 participants with MS and 39 healthy controls) were recruited from physical medicine and rehabilitation policlinic between the dates of 25 September2019-1 February 2020 . Flow chart of the study participants is demonstrated in Figure 1**.** Number of participants was determined assuming 12 points mean difference and 16.5 points SD of score at Tampa Kinesiophobia Scale with 80% power and 5% significance and 60 participants were decided to recruited [4]. The diagnosis of MS was determined according to International Diabetes Federation : central obesity (waist circumference > 94 cm in men and >80 cm in women) plus two or more additional metabolic risk factors (fasting plasma glucose > 100 mg/dL, blood pressure ≥ 130/85 mm-Hg or treated for hypertension, Triglyceride >150 mg/dL or treated for dyslipidemia, HDL cholesterol < 40 mg/dL in men or < 50 mg/dL in women or treated for dyslipidemia) [1-3]. According to International Diabetes Federation 2005 criteria's, participants who could not fully meet the diagnosis

of metabolic syndrome were included in the control group. Participants with rheumatic disease, knee and hip arthroplasty, operation of lumbar disc herniation, fibromyalgia, history of trauma, previous fracture and participants with pain in last week were excluded.

The demographic features, presence of diabetes mellitus and waist circumferance measurements were recorded. Venous blood samples were obtained at least a 12 hour overnight fast. All samples were collected between 07:30 and 09:30 AM. Triglyceride, HDL cholesterol and fasting plasma glucose level were recorded. All participants were evaluated with Hospital anxiety and depression scale, Tampa Kinesiophobia Scale and Short form-36 (SF-36) and all scores were recorded. All questionnaires were done by a blind researcher to participants' clinical and laboratory data.

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate the mood status. Higher scores of both anxiety and depression subscales indicate worse mood status. Aydemir et al. found that Turkish version of HADS is valid and reliable [6].

The Tampa Kinesiophobia Scale was used to measure fear of movement. The Tampa Kinesiophobia Scale includes 17 items associated with fear of movement and reinjury [5]. Total score of the scale ranges between 17 and 68 and higher scores associate with higher levels of kinesiophobia. Turkish version of Tampa Kinesiophobia Scale was shown as valid and reliable [7].

The Short Form-36 health survey (SF-36) is a measurement of quality of life. SF-36 consists of 36 items evaluating physical functioning, role limitation due to physical health, role limitation due to emotional problems, energy/fatigue, emotional well being, social functioning, pain and general health. Scores for eight subscales are calculated by summing up the item scores, which are coded in such a way that each subscale is scored from 0 to 100. '0' indicates the worst health status and '100' indicates the best health status [8]. Kocyigit et al. showed the reliability and validity of the Turkish version of the SF-36 [9].

The study was approved by the local ethics committee (decision number: 41, date: 18.09.2019). Study participants signed informed consent forms.

2.1. Statistics:

All data were analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) 15.0 program for Windows. The variables were investigated using visual and analytical methods for determining whether or not they are normally distributed. Continuous variables are expressed as mean ±

SD and categorical variables as numbers and percentages. Man Whitney U test was used to compare age, weight, triglyceride, HDL cholesterol, fasting glucose levels, systolic and diastolic blood pressure measurements, anxiety, depression, Tampa and short form-36 scores between groups. Independent samples student t testi was used to compare height, BMI, waist circumference measurement. $\chi 2$ test was used to compare to nominal values. Pearson correlation coefficient was used to evaluate the linear relationship between predictive variables. A value of $p < 0.05$ was considered statistically significant.

3. RESULTS

Forty-one participants with MS and thirty-nine healthy controls were included. Age, height and gender distribution were similar between two groups ($p>0.05$) (Table-1). Weight, Body-Mass Index (BMI), waist circumference were significantly higher in participants with MS than healthy controls ($p=0.026$, $p=0.004$, $p= 0.006$; respectively) (Table-1). The presence of diabetes mellitus was more common in participants with MS than healthy controls ($p<0.001$) (Table-1). Triglyceride, HDL cholesterol and fasting plasma glucose level, systolic and dyastolic blood pressure measurements were significantly higher in participants with MS than healthy controls ($p<0.05$) (Table-2). Depression and social functioning scores were significantly higher in participants with MS than healthy controls ($p=0.039$, $p=0.026$; respectively) (Table-2). Tampa score was significantly higher in participants with MS than healthy controls ($p=0.004$) (Table-2).

Waist circumference was significant positively correlated with Tampa score in participants with MS ($r=0.403$ $p=0.009$) (Table-3). Plasma fasting blood glucose level was significant positively correlated with depression score in participants with MS ($r=0.314$ $p=0.046$) (Table-3). There was significantly negative correlation between role limitations due to physical health, pain and Tampa Kinesiophobia Scale in participants with MS ($r=-0.334$ $p=0.033$, $r=-0.315$ $p=0.045$, respectively). There was no correlation between Tampa Kinesiophobia Scale and SF-36 subscales other than role limitations due to physical health and pain in two gruops.

4. DISCUSSION

In our study, results showed that participants with MS have higher levels of kinesiophobia and depression compared to healthy controls. To the best our

knowledge this is the first study to examine the association between metabolic syndrome and kinesiophobia.

Kinesiophobia is defined as fear of injury and movement avoidance behavior. This behavior is an important cause of decreasing physical activity [10]. Subjects suffering from chronic musculoskeletal pain reduce their physical activities due to fear of pain [5]. Because they feel safe by limiting physical activity [11, 12]. There is no study evaluating the relationship between MS and kinesiophobia. In this study we found that there was an association between MS and kinesiophobia. Obesity is an important risk factor of osteoarthritis, musculoskeletal pain and physical dysfunction [13]. Recently, several studies have investigated associations between MS and musculoskeletal diseases such as knee osteoarthritis [14], osteoporosis [15], and intervertebral disc degeneration [16]. Also the assosiation between low back pain and abdominal obesity [17], hypertension [18], impared blood glucose [19], and lipid disturbance [20] were invastigated in several studies. Kinesiophobia is associated with low physical activity level in patients with cronic pain [5]. So subjects with MS could have kinesiophobia and the relationship between MS and kinesiophobia could be explained by musculoskeletal pain. Possibly, sedentary lifestly developed due to kinesiophobia could cause MS. It is difficult to determine whether the kinesiophobia causes MS or musculoskeletal pain due to MS causes kinesiophobia. Therefore, fear and avoidance behaviors might limit physical activity and inadequate physical activity might cause MS.

In our study, we found that participants with MS have higher levels of depression compared to healthy controls. High depression level may also affect the level of kinesiophobia [21]. MS was found assosiated with lower quality of life and higher depression status and high physical activity level was found assosiated with higher quality of life and lower depression status in patients with MS [22]. But we did not found significant difference SF-36 scores (except social functioning) between participants with MS and healthy controls in our study. In some studies, there was a relationship between MS and anxiety [23,24]. But in our study there was no significant difference between participants with MS and healthy controls.

Physical activity and lifestyle changes are very important for prevent MS. Multimodal rehabilitation programs including education and physical training were effective on health-related quality of life and kinesiophobia level in patients with chronic pain [25,26]. Programss including education, physical activity and lifestyle changes may prevent to develop MS and kinesiophobia.

4.1. Limitations of the Study

There are some limitations in this study. The cross-sectional design of our study did not determine whether the kinesiophobia causes metabolic sendrome or musculoskeletal pain due to metabolic sendrome causes kinesiophobia. Prospective studies would provide more reliable results to test this hypothesis. Second limitation is that we did not know physical activity levels of participants. Lack of sample size is another limitation of our study.

5. CONCLUSION

Persons with metabolic syndrome may have kinesiophobia that might be associated with musculoskeletal pain. As physical activity is essential for bone and general body health, persons should be educated and counseled about sedantary lifestyle, MS and the importance of physical activity to overcome kinesiophobia.

Conflict of Interest: Authors have no conflict of interest.

Compliance with Ethical Standards: The study protocol was approved by the committee on Human and Research Ethics, Hitit University Erol Olçok Education and Research Hospital.

Informed Consent: All participants gave written informed consent to a protocol adhering to the 1964 Declaration of Helsinki.

Authors' Contributions: All authors had contributions to the conception, design, acquisition, analysis, interpretation of the results, and write of paper. All authors read and approved the final manuscript.

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CHAPTER 5

TREATMENT OPTIONS IN PATIENTS WITH DEDIFFERENTIATED THYROID CANCER

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1. INTRODUCTION

Distant metastasis develops in approximately 5-25% of differentiated thyroid cancer (DTC) cases (1,2). As long as metastases show radioactive iodine (RAI) uptake, that is, RAI-responsive, the prognosis is good and the 5-year survival is around 50%. 60-70% of metastatic patients become refractory/dedifferentiated (DeDTC) to RAI during follow-up. In (DeDTC) patients, the 10-year survival is 25-42% and the average life expectancy is 3-5 years (3).

Iodine taken in diet is absorbed in the form of iodide with the help of sodium-iodide simporter carrier protein (NIS) in the gastric mucosa. Inorganic iodine is taken into the cell by NIS, which is located on the basolateral membrane of the follicle cells close to the capillaries and enables the passage of two Na ions and one I ions into the cell against the electrochemical gradient. The activity of this pump is increased by thyroid stimulating hormone (TSH) and this pump is the rate limiting step in the synthesis of thyroid hormones.

1.1. Dedifferentiation process

The expression ability of thyroid-specific genes such as NIS, TSH-R and thyroglobulin (Tg) is lost. As a result of loss of NIS expression, RAI uptake capability deteriorates and RAI use becomes ineffective in treatment. With the loss of TSH-R,TSH suppression becomes ineffective. Generally, the clinical scenario is I-131 imaging negativity and serum Tg elevation. It is also defined as TENIS (thyroglobulin elevation/negative iodine scintigraphy) syndrome. In some cases, thyroglobulin synthesis property is also impaired. (DeDTC) is clinical diagnosis, not histopathological (4,5).

1.2. Definitions used in the literature and clinical practice in the definition of DeDTC

- No I-131 involvement in any of the recurrent-metastatic lesions on I-131 scintigraphy (scan after RAI treatment or with I-131 diagnostic scan)
- There are some recurrent-metastatic lesions showing I-131 involvement on I-131 scintigraphy (scanning after RAI treatment or with I-131 diagnostic scan), but there are also lesions that do not show I-131 involvement.
- Recurrence-metastatic lesions in RAI treatment progressed despite I-131 involvement (Radiological and/or biochemical? RECIST 1.1 / Duration? 6-12 months)
- Reaching the maximum cumulative dose in RAI treatment (1000-1100 mCi?)

Although it has been claimed that treatment with a RAI dose of more than 600 mCi has no clinical benefit, if the DTC patient is stable under RAI treatment and the lesions show RAI involvement, this patient should not be considered as DeDTC (6).

Scintigraphy with I-131 may not be the gold standard for defining DeDTC. Before I-131 scintigraphy, patient preparation should be made appropriately with a low iodine diet and there should be no contamination with iodine. Before imaging-treatment, the appropriate TSH level must be provided. The decision and evaluation process should be made carefully with I-131 imaging after diagnostic or post-treatment. Factors such as RAI dose, imaging time (early/late), technique (SPECT/CT, Planar), protocol and parameters are effective in the evaluation of I-131 scintigraphy.

F18 FDG PET/CT imaging is the most important imaging method in DeDTC diagnosis and treatment management. It is used for detecting metastatic lesions, predicting the effectiveness of RAI treatment, planning treatment and prognostic evaluation. As the dedifferentiation increases in the lesions, the use of glucose increases. There is an inverse relationship (Flip Flop Phenomen) between FDG uptake and RAI involvement. FDG positivity of metastatic-recurrent lesions and potentially low RAI uptake-RAI negativity are negative prognostic indicators. While the sensitivity is 87-97,3% in general, the specificity is 73,9-92% in the detection of metastatic lesions in DeDTC cases with F18 FDG PET-CT imaging (7) According to the ATA guideline, F18 FDG PET-CT imaging is indicated in high risk patients, RAI negative, Tg >10 ng/ml.

Tumor extent can be followed by serum Tg value in metastatic DeDTC patients. Doubling time of less than 1 year in serum Tg increase is an indicator of poor prognosis. However, in some aggressive DeDTC cases, poor Tg secretion may cause low serum Tg value. During the dedifferentiation process, thyroglobulin may not be produced at a sufficient level for follow-up. The Tg value in these patients is not reliable for monitoring tumor progression in DeDTC patients. Tg value is not reliable in antiTg positive cases.

Diagnostic studies and clinical evaluation are important. It is necessary to evaluate tumor biology and tumor burden and to evaluate clinical signs of local recurrence (esophagus / tracheal compression) and metastatic lesions (lung, bone, brain). It is important to evaluate symptomatic factors such as pain, weakness, weight loss, appetite, and quality of daily life. Because treatment with multikinase inhibitors (MSI) has potential side effects in asymptomatic patients.

They are mutations in the mitogen-activated protein kinase (MAPK) and Phosphoinositide 3-kinases (PI3K) pathways.

1.3. DeDTC molecular pattern

The main directing mutations in DTC are BRAFV600E and RAS mutations. The BRAFV600E mutation is associated with tumor aggression, risk of recurrence, and loss of RAI involvement. RAI causes involvement loss in RET/PTC and RET/PTC3 DeDTC.

PPARγ1 mutation, VEGF mutation, EGFR mutations, BRAF V600E and TERT mutations are associated with the presence of distant metastases in DTCT patients.

BRAF V600E mutation negatively affects genes in iodine metabolism (NIS, TSHR, Tg, TPO) with abnormal activation of the MAPK pathway. Histone deacetylation (HDAC) decreases NIS activity via the NIS promoter. Thyroid-gene transcription factor (PAX8) down-regulates transforming growth factor (TGFß) secretion through upregulation, leading to NIS suppression. MAPK(RAS/RAF/MEK) and PI3K/AKT/mTOR pathways are the main signaling pathways of thyroid cancer development.

Extracellular signals activate RTK and RAS. This activates the RAF, which is the BRAF in DTC. Activated BRAF phosphorylates and activates MEK. MEK phosphorylates and activates ERK. Phosphorylated ERK is translocated into the nucleus. Within the nucleus, ERK regulates the transcription of genes that affect cell differentiation, proliferation, survival, and thyroid-specific gene transcription. PI3K/AKT activates mTOR, a key regulator of cell proliferation, inhibition of apoptosis, and thyroid specific gene transcription (8,9,10).

2. TREATMENTS

2.1. Local treatments

- Surgical excision of local recurrence and metastases (The most effective treatment method, but operability?)
- Radiotherapy: In general, DTC cases are not very sensitive to RT. However, in the presence of local recurrence, recurrent lymph node metastases, bone metastasis, brain metastasis, it can be performed to stop lesion growth and for symptomatic control.
- Stereotactic radiosurgery: For brain and lung metastases
- Ablative laser treatment (especially in patients who have had RT before) or stent applications for trachea invasions
- Radiofrequency or Cryoablation (for local recurrence and metastases)
- Intra-lesion ethanol injection
- TARE / TACE

2.2. Systemic treatments

Although MKIs show effects in different ways towards their molecular targets in vitro, no efficacy difference was observed in those with BRAS or

RAS mutations in in vivo studies. Treatment with MCI should be initiated in DeDTC patients only in the presence of progression and in patients with high tumor burden, considering the side effect profiles and with the decision of the multidisciplinary council.

In the European Thyroid Association and NCCN guidelines, treatment with MKI such as lenvatinib or sorafenib is recommended in patients with progressive and / or symptomatic DeDTC (11). As a progression criterion, more than 20% growth in the lesions within 12-14 months can be used in the evaluation made according to RECIST.

Treatments with MKI are more effective in small tumors. There is no clear relationship between treatment efficacy and location, but efficacy is generally less in liver-brain metastases. There was no relationship between clinical symptoms and treatment efficacy. There is no clarity on the decision to start treatment with the presence or absence of symptoms. However, treatment efficiency is generally higher in ECOG 0-1 patients. The incidence of side effects is higher in elderly patients (median 71 years) compared to the younger patient group (median 56 years). For this reason, the benefit-risk analysis of the treatment should be done well.

Sorafenib and lenvatinib have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for DeDTC treatment. Phase III studies with MKI are the DECISION (Sorafenib) study and the SELECT (Lenvatinib) study (12,13).

Sorafenib (RAF, VEGFR 1-3, PDGFR, FMS-like tyrosine kinase 3 (Flt-3), c-Kit and RET inhibitor) is recommended at a dose of 400 mg (2 × 200 mg tablets) x 2 /day.

Lenvatinib (VEGFR1-3, FGFR1-4, PDGFR-α, RET and c-KIT inhibitor) is recommended at a dose of 24 mg (2 × 10 mg and 1 × 4 mg tablet) /day, and if there is severe renal failure or liver failure 14 mg should be used in mg /day.

DECISION study was a Phase 3 study of 417 patients, comparing sorafenib 400 mg x2 /day (207) versus the placebo group (210). There was no difference in OS between the sorafenib group and the placebo group, and the PFS in the sorafenib group was significantly higher (10.8 vs 5.8 months). Partial regression response was achieved in 12% of patients in the sorfenib group. 150 patients in the placebo group were switched to sorafenib treatment because of progression. Side effect rates in the sorafenib group were found as hand foot syndrome (76,3%), diarrhea (68,6%), alopecia (67,1%), rash-desquamation (50,2%) (12).

In the SELECT study, a phase 3 study of 397 patients, lenvatinib 24 mg / day (261) was compared with the placebo group (137). Median OS was not reached in the lenvatinib group and placebo group, and PFS was found to be significantly higher (18,3 vs 3,6 months) in the envatinib group. In the Lenvatinib group, complete response was achieved in 4 patients and partial response (64,8%) in 165 patients. 150 patients in the placebo group were switched to sorafenib treatment because of progression. Side effects detected in the lenvatinib group were HT (67,8%), diarrhea (59,4%), fatigue (59,0%), anorexia (50,2%), weight loss (46,4%). Treatment was discontinued in 37 patients in the Lenvatinib group due to side effects. 20 patients died and 6 of them were reported to be due to side effects related to lenvatinib (13).

In the DECISION and SELECT studies, there is no study target regarding redifferentiation after treatment with MKI and RAI treatment data after MKI treatments.

MKI drugs have a cytostatic effect and are not cytotoxic. Treatment should be discontinued when there is evidence of no clinical benefit. Dose reduction may be an option when partial regression or stability, slow progression of the lesions (progression of a single lesion while others are stable) is detected.

2.3. Side effects seen in treatment with MKI agents

Hypertension, palmar-plantar erythrodysaesthesia (Hand and Foot syndrome), rash, alopecia, diarrhea, injustice, fatigue, anorexia, mucositis, dysphagia, gastritis, weight loss, TSH elevation, proteinuria, heart failure, infarction hemorrhage, arterial or venous thrombotic events, cytopenias, arthralgia, myalgia, intestinal perforation, tracheal-esophageal fistulas, posterior leukoencephalopathy syndrome.

In terms of monitoring side effects, close follow-up is required especially for the first six months when treatment is started. It should be checked every 15 days for the first 2 months. Side effects are more common in the patient group aged >65 years and in the first 3-12 weeks. Radiological evaluation (CT/MRI and FDG PET) and serum Tg/AntiTg control should be performed 2-3 months after the initiation of treatment. After a monthly control up to 6 months, a 3-month control should be done up to the 1st year, if the patient is stable, it should be followed up with 4-6 months controls.

Because of side effects, more than 50% of the patients need to reduce the dose or temporarily pause the treatment, and about 15-20% of the patients need to terminate the treatment. When side effects are seen, treatment should

be interrupted according to its degree and treatment should be continued with a low dose if side effects pass or decrease.

2.4. Other Treatment agents

- Tyrosine Kinase Inhibitors: Sunitinib, Vandetanib, Axitinib, Pazopanib, Dovitinib
- BRAF Inhibitors: Vemurafenib, Dabrafenib
- MEK Inhibitors: Selumetinib
- MTOR Inhibitors: Everolimus

3. REDIFFERENTIATION TREATMENTS

- Retinoic acid
- Histon Deacetylase (HDAC) inhibitors
- PPARγ (peroxisome proliferator-activated receptors) agonists
- MAPK road inhibitors

3.1. Retinoic acid

In thyroid cancer in invitro and some clinical studies, re-differentiation can be achieved in cells by increasing thyroid-specific proteins (by stimulation of Type 1 5-deiodinase activity), in addition to thyroglobulin, NIS mRNA expression and cellular RAI uptake are increased, and RAI uptake is increased by 20-50%. has been shown to be stimulated. Response to RAI treatment after retinoic acid therapy may not always correlate with increased RAI uptake. In some studies, there was an increase in RAI uptake. in only 6-20% of patients after treatment with RA, and in some studies, the clinical effect of RAI treatment given after RA treatment was not observed. In the study of Simon et al., RAI uptake was detected in 4 out of 10 patients after a 6-week treatment of 13-cis-retinoic acid (Roaccutan) 1.5 mg / kg / day. In the meta-analysis study of Pak et al. In which 14 studies and a total of 314 patients were included, treatment response was reported in 27,6% (21,7-34%) according to the findings of I-123 and I-131 whole body scintigraphy. Treatment response was reported in 61.3% (56,6-83%) patients according to Tg values and 17% (0-45%) according to RECIST criteria (14).

3.2. Histon deacetylase (HDAC) inhibitors

Histone deacetylase inhibitors can change the transcription of DNA to mRNA by modifying the relaxation level of the histone-DNA complex. HDAC inhibitors regulate histone acetylation and intracellular molecular targets involved in cell growth and differentiation. Although the mechanism has not been explained, these inhibitors can induce blocked cell cycle and differentiation. In a study in the literature, patients with romidepsin 13 mg /m2 iv 1., 8., 15. days, and RAI uptake after rheumidepsin was detected in only 2 of 20 patients. However, partial or complete treatment response was not obtained in any patient. In the study of Nilubol et al., Valproic acid was administered orally at 50-100 mg /ml for 10 weeks, and none of the 13 patients had RAI uptake after valproic acid. A decrease in serum Tg was detected in 3 patients, but no partial or complete response was obtained according to RECIST criteria (15).

3.3. PPARγ (peroxisome proliferator-activated receptors) agonists

PPARγ agonists (antidiabetics such as rosiglitazone, pioglitazone, ciglitazone and troglitazone) have been shown to have an antiproliferative effect and induce apoptosis, suppress tumor growth and prevent distant metastasis. In a literature study, in which Rosiglitazone was administered orally for 6 months (4 mg /day for 2 weeks, then 8 mg /day), RAI treatment was applied in 4 patients who were found to have increased I-124 uptake by lesion dosimetry in 5 of 9 patients. Regression in lesion size was detected in 3 patients by volumetric analysis (16). However, the use of rosiglitazone in Europe is prohibited due to the side effects detected in diabetic patients.

3.4. MAPK road inhibitors

It has been shown that NIS expression and iodine uptake are partially increased with MAPK pathway inhibitors targeting BRAF or MEK. Selumetinib (MAPK pathway inhibitor), Dabrafenib (BRAF inhibitor) are drugs belonging to this group. In the study of Ho et al., Selumetinib was given to patients at a dose of 75 mg x 2 /day for 4 weeks, and increased uptake was detected in 12 of 20 patients on I-124 scintigraphy. 8 patients were given RAI treatment, 5 patients had partial treatment response and stable disease was achieved in 3 patients. Serum Tg levels decreased in all 8 patients (17). In the study of Irovani et al., Trametinib was used in patients with NRAS mutation and darafenib + trametinib or Vemurafenib + cobimetinib for 4 weeks in patients with BRAF V600E

mutation. Among 6 patients, RAI involvement occurred in 1 patient with NRAS mutation and 3 patients with NRAS + BRAFV600E mutation. Partial treatment response was achieved in 2 patients with NRAS + BRAFV600E mutation in the patient with NRAS mutation (18).

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CHAPTER 6

EVALUATION of UMBILICAL VENOUS CATHETER PLACEMENT and COMPLICATIONS USING ULTRASONOGRAPHY

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1. INTRODUCTION

The umbilical venous catheter (UVC) is frequently used as a vascular access route in neonatal intensive care units, especially in premature and low birth weight neonates[1]. UVC is performed in approximately 15% of newborn intensive care patients and almost half of the low birth weight newborns[2]. Usually, a double lumen (drug and fluid conduit) 3-5 F catheter is used[3]. The catheter sent from the umbilical vein in the umbilical cord first reaches the umbilicoportal confluence (Rex segment) in the left portal vein center, which is the beginning of the ductus venosus. The catheter continues through the ductus venosus and reaches the middle or left hepatic vein close to hepatic venous confluence. Subsequently, the catheter is placed in the suprahepatic segment of the vena cava inferior. (Fig 1)[1]. The catheter tip should be in the suprahepatic IVC or at the atriocaval border.

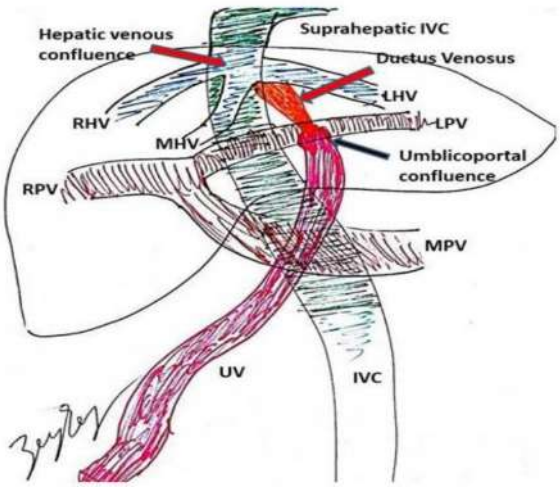

Figure 1: The relationship between the umbilical vein and the portal vein in the newborn is schematized. The umbilical vein joins the left portal vein at the umblicoportal junction (Rex segment). At the same level, the ductus venosus starts from the left portal vein as a narrow opening, gradually increasing in diameter, reaching the middle or left hepatic vein at a level close to the hepatic venous confluence. *IVC, inferior vena cava; LHV, left hepatic vein; LPV, left portal vein; MPV, main portal vein; RHV, right hepatic vein; RPV, right portal vein; UV, umbilical vein.*

Several complications may occur due to umbilical vein (UV) catheterization such as a liver parenchymal injury during the procedure, vascular thrombosis, infection, right ventricular thrombosis due to misplacement, rhythm disturbances, cardiac tamponade. Besides these complications, parenchymal/subcapsular collection, hemorrhage, inflammation, and necrosis may develop in case of leakage of hypertonic fluid from abnormally located UVC into the liver parenchyma[1,4–6]. Therefore, it is essential to be ensured that the catheter tip is correctly placed.

Catheter length is adjusted by measuring the distance between the infant's left shoulder and the umbilicus. Even small deviations in catheter length, especially in low birth weight infants, may cause UVC tip misplacement[7]. In clinical practice, after the insertion of the catheter, the endpoint of the catheter is evaluated in the anterior-posterior position by direct Roentgen graphy. On direct radiography, the catheter tip should be between the T8-T10 vertebrae[8] (Fig 2).

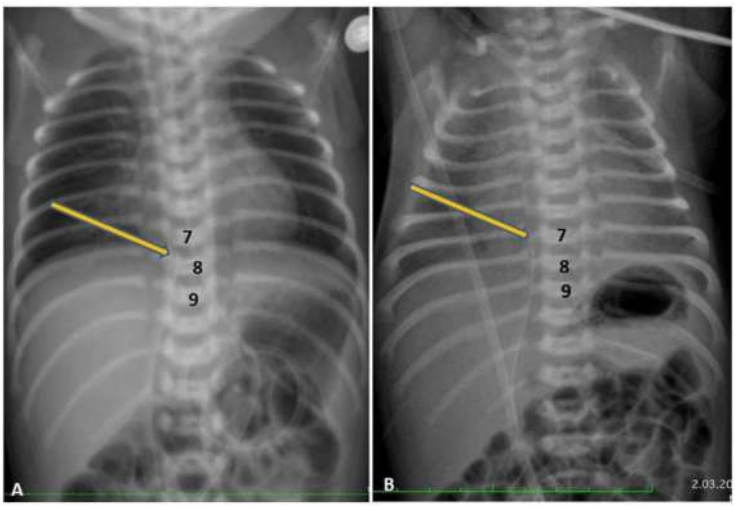

Figure 2: A) Normal radiographic appearance of the umbilical venous catheter (UVC). The tip of the umbilical venous catheter (arrow) ends at the thoracic 8 vertebra level. B) On the abdominal radiograph showing the abnormal position of the UVC, the tip of the catheter (arrow) is at the level of the T7 vertebra (possibly in the atrium).

If the catheter tip is lower than T10, it is regarded as intrahepatic and if it is above T8, it suggests that it is located intracardiac. This can be difficult to assess at times since the suprahepatic IVC level may vary according to inspi-ration and expiration. The catheter tip detected at the T8 or T10 vertebra level on a single radiograph may also be abnormally located. In this case, the posi-tion of the catheter tip concerning the right diaphragm should be checked. In cases where the diaphragm cannot be observed clearly, lateral radiography should be taken. The fact that the catheter tip is on the right diaphragm sug-gests that it is located intracardiac. Also, a catheter tip at the T10 level may be within the intrahepatic vascular structure[3]. Complications such as hepatic damage and thrombosis that may occur during or after the procedure cannot be evaluated with direct radiography. Also, exposure to radiation on X-ray is another disadvantage.

Recently, ultrasonography (US) has been frequently used in the evaluation of UVC catheters[9]. Showing the UVC outcome level by US is more accurate than predicting location by direct radiography[10,11]. Under US guidance, the catheter is placed accurately and securely. In addition, liver parenchymal damage, collections, laceration, and intravascular thrombosis due to UV cath-eterization can be evaluated by US. When abnormally located UVC is detected,

if complications have developed (such as hematoma, collection), it is more appropriate to remove the catheter rather than fix it[9]. Doppler US examination helps in evaluating the degree and extent of intravascular thrombosis. US is an inexpensive, time-saving, non-radiation, repeatable examination that can be performed at the bedside with portable devices. The disadvantage of the process is that it is difficult to access the examination in intensive care conditions since this procedure is performed by a radiologist[7]. However, this disadvantage can be overcome by ultrasound training to intensive care specialists for UVC catheter evaluation. Another disadvantage is that it is an examination dependent on the experience and skill of the performer.

2. EVALUATION OF UVC-RELATED COMPLICATIONS USING ULTRASONOGRAPHY

High-frequency linear probes should be preferred for the evaluation of liver parenchyma and vascular structures in newborns. The quality of the examination is highly dependent on the quality of the device and the experience and personal skill of the radiologist. Complications due to UVC are air in the portal veins, thrombosis due to abnormal location, cardiac pathologies (thrombosis, dysrhythmia, tamponade), vascular perforation and parenchymal penetration, inflammation due to irritation and leakage of hypertonic and alkaline fluids sent via UVC, necrosis and collections and infections.

The incidence of hepatic parenchymal lesions is about 7–10%[7]. Lesions are usually seen along the catheter course[9,12]. The reason for the lesions might be the perforation of the catheter tip to the vascular wall, hypertonic and high pH inflammation caused by total parenteral nutrition may be due to endothelial damage and parenchymal leakage[6,7,13]. The lesions may be focal single nodules, branching multiple small nodules, large heterogeneous mass lesions, or in more severe cases, laceration and it may be in the form of a perihepatic hematoma[7,14]. Parenchymal lesion due to leakage and perforation is observed as the only echogenic nodular formation adjacent to the catheter in the early period (Fig 3). Depending on the development of necrosis over time, its center is seen as hypoechoic[12]. Small echogenic lesions that appear as branching may represent areas of infarction secondary to hemorrhagic foci or portal vein thrombosis[7,15]. Later peripheral calcification may develop. Perihepatic collection and large hematomas resolve within months[9]. Acid may develop if the collection breaks the liver capsule integrity [4].

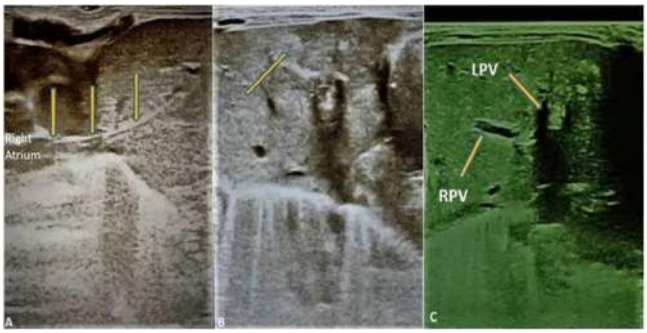

Figure 3: On ultrasound examination, an umbilical venous catheter (arrows) is seen abnormally terminated in the right atrium (A), and a single echogenic nodular lesion (arrows) is seen in the left lobe of the liver (B). In the ultrasound examination of another patient, the left portal vein is seen filled with echogenic thrombus material (arrow) (C). *RPV: right portal vein, LPV: left portal vein.*

One of the most common complications of UVC application is air in the portal vein[7]. The distribution of air is seen in the anterior and peripheral parts of the liver as echogenic foci giving reverberation artifact because the umbilical cord enters the liver from the left lobe anterosuperior. These air values that develop due to catheterization have no clinical significance and disappear completely within one week in the follow-up US examinations[7]. On the other side, portal air, which can also be seen in children with necrotizing enterocolitis (NEC), is a serious clinical condition. Differential diagnosis is made by real-time demonstration of mobile, small air bubbles in the portal veins that show phasis on vascular pulsation and edema in the bowel loops. In addition, typical X-ray findings (asymmetrical bowel dilatation, edema in the intestinal walls and intramural air) should be investigated in NEC.

Portal vein thrombosis (PVT) is one of the most common complications of UVC. However, a wide range of 1.3–43% has been reported about its frequency[16]. The increasing use of US in neonatal intensive care units has increased the rate of PVT detection[10]. In addition, the frequency of PVT increases due to the prolongation of UVC use, total parenteral nutrition fluids and drugs[17]. PVT is usually seen on the left portal vein. However, in severe cases, thrombosis may extend to other portal branches[10]. The most likely reason for the left PVT to appear frequently is the involvement of the umbilical vein in the left portal vein (in the umbilicoportal confluence or Rex segment) and the narrow ductus venosus junction because the origin of the ductus venosus is normally narrow. Therefore, it may be difficult to insert the catheter

through the umbilicoportal space into the ductus venosus and the catheter tip may turn towards the left portal vein[17–20]. In the retrospective evaluation of 70 patients who had UVC in the last year in our clinic, according to the US data we performed after the procedure and at the 1st and 4th weeks, PVT was detected in 60% (42/70) of the infants who underwent UVC. All of them had left PVT except one infant who had both right and left PVT. In the 4th week examination of the patient with right and left PVT, right PVT recanalized, but left PVT persisted. On the other hand, only 31.7% (13/41) of left PVTs were recanalized. In other words, approximately 70% of left PVTs were not recanalized in the first month of follow-up (unpublished data). Since we do not have US data after one month, the rate of chronic thrombosis development in infants is not known. However, it has been reported in the literature that 90% of PVT is completely resorbed[19]. This clinical experience shows that US follow-up in children with PVT due to UVC should be long termed in regards to chronic thrombosis and portal hypertension (PHT). Taking necessary precautions with an early diagnosis can prevent the development of PHT in the future. Indeed, UVC application has been shown as a cause of PHT in children[21]. Non-recanalized PVT may continue as chronic stage thrombosis. In this case, the left portal vein is observed as an echogenic band and the left lobe size decreases.

With Doppler US, loss of blood flow is observed in the thrombosed segment. It has been reported that thrombosis is completely resorbed usually within the first week[19]. However, as mentioned above, most of the thrombosis does not recanalize within the first month. More comprehensive studies are needed on this subject.

Another criterion that can be useful in the follow-up evaluation of PVTs is hepatic artery (HA) flow findings. Secondary to UVC, changes in HA currents have not been mentioned until now in PVT evalua-tion. However, our clinical experience shows that changes in HA currents in PVT provide important indirect information about the course of thrombosis. Approximately 70-75% of the blood coming to the liver is transported by portal vein (PV) and 25-30% by HA. The amount of blood coming to the postprandial liver with PV increases by about 50%. To balance the total hepatic blood volume, the HA blood flow is reduced by splanchnic vasoconstriction (hepatic arterial buffer response)[22]. Secondary to vasoconstriction, hepatic artery resistive index (HARI) increases.

According to our clinical experience, a similar mechanism occurs in PVT cases. Portal vein thrombosis secondary to UVC mostly occurs in the left PV[10]. To compensate for the left lobe blood volume, vasodilation in the left HA, an

increase in blood flow volume and a decrease in HARI are observed. In color mode, left HA coloration, which can be barely displayed in normal infants, becomes so apparent in PVT cases that if careful attention is not taken, it can be assumed as normal left PV. However, it can be distinguished from the portal vein by observing the arterial flow pattern in spectral examination. While HARI values are more than 0.70 in a normal infant, HARI values are measured below 0.60 in PVT. As the thrombosis begins to open, the HARI values progressively increase above 0.70 (Fig 4). HARI is especially useful for restless patients whom we cannot obtain sufficient images from PV in color mode. HARI's being over 0.70 may indicate that the left PVT is starting to open. However, to make this interpretation, it should be ensured that the infant is hungry for at least 4 hours.

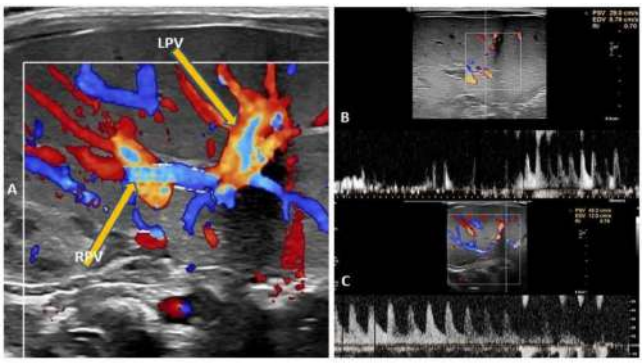

Figure 4: In the postprandial color Doppler US examination of the patient with partially recanalized left portal vein thrombosis, markedly increased blood flow signals in LPV (arrow) were detected (A). In the Doppler examination of the same patient, the left HARI was 0.70 at the postprandial 4th hour (fasting) (B), while the HARI was 0.76 in the postprandial examination (C). *RPV: right portal vein, LPV: left portal vein.*

If the baby was fed just before the examination, the HARI may be above 0.70 due to the HABR, although the left portal vein is occluded. This may lead to the misinterpretation that the left PVT is recanalized. In such a case, the presence of blood flow in the left PV should be investigated by making optimal doppler settings in color mode. In the case of satiety, it will be easier to evaluate in color mode, because the baby is less uneasy and the portal vein flow volume increases. In cases of doubt, the examination should be repeated after at least 4 hours of fasting and if the HARI is below 0.60, it should be considered that

the PVT continues. In other words, if Doppler US will be used to investigate the presence of PVT and recanalization, it would be appropriate to evaluate the PV blood flows in color mode after feeding (Fig 4A,C) and evaluate HARI in spectral mode after at least 4 hours of fasting (Fig 4B).

3. CONCLUSION

As a result, UVC can lead to several significant complications. The risk of complications is higher with catheterization, which is usually blinded by clinicians. Although X-ray is generally used to determine the endpoint of UVC, reliable interpretation may not always be made. Therefore, US-guided catheterization whenever possible will reduce the risk of this complication. Early diagnosis of developing complications and therefore early intervention will reduce morbidity. The US is the most appropriate radiological imaging method for early diagnosis and follow-up of complications. Doppler US examination provides important contributions in the early diagnosis and follow-up of portal vein thrombosis.

Keywords: Neonate, ultrasound, umbilical venous catheter

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