International Archives of Medical Research

Cilt/Volume: 16, Sayı/Issue: 1 – 2024
ISSN : 2146-6033

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Adress : Dicle Universty,Faculty of Medicine.Department of Microbiology / Diyarbakır
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web : https://dergipark.org.tr/tr/pub/iamr
Online ISSN : 2146-6033

International Archives of Medical Research 16:1 (2024) 1-10

ORIGINAL RESEARCH

Hemifasiyal Spazm ve Blefarospazm Hastalarında Botulinum Toksin Enjeksiyonu Tedavisi Sonrası Depresyon ve Anksiyete Durumunun Değerlendirilmesi

Received Date: 03.03.2024, Accepted Date: 26.04.2024 **DOI: 10.56484/iamr.1446484**

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Özet

Amaç: *Botulinum toksin tedavisi (BTT) alan hemifasiyal spazm (HS) ve blefarospazm(BS) hastalarında mevcut klinik duruma bağlı oluşan depresyon ve anksiyete durumunun, hastalık süresi ve yaşla ilişkisi ve tedavi sonrası parametlerdeki değişimin araştırılması amaçlandı.*

Gereç ve yöntem: *Araştırmaya 125 hemifasiyal spazm, 14 blefarospazm hastası ,70 sağlıklı gönüllü kişi kontrol grubu olarak alındı. Hasta ve kontrol grubuna beck depresyon , beck anksiyete ölçekleri uygulandı. BTT tedavisinden 4 hafta sonra hasta grubuna test tekrarlandı.*

Bulgular: *Kontrol grubuna göre tedavi öncesi vaka grubunun Beck anksiyete ve Beck depresyon ölçekleri puanı daha yüksekti. Hem HS hastalarında hem de BS hastalarında tedavi sonrası Beck anksiyete ve Beck depresyon skorları düşüş gösterdi. Gruplar arasında blefarospazm grubunda, tedavi sonrası Beck anksiyete puanları hemifasiyal spazm grubundan istatistiksel anlamlı olarak daha düşük bulundu. Vaka grubunda hastalık süresi arttıkça depresyon ölçek puanı da artmaktaydı. İleri yaş hastalarda anksiyete ve depresyon skorlarının daha düşük olduğu gözlendi. BTT tedavisi ile hastaların Beck depresyon ve Beck anksiyete puanlarında iyileşme gözlendi.*

Sonuç: *HS ve BS hastalığı yüz kaslarında fiziksel sorunlara yol açtığı için hastaların aynı zamanda fonksiyonel durumları ve duygu durumunu da olumsuz etkilemektedir. Bu hastalığa genellikle anksiyete ve/veya depresyon eşlik etmektedir. BT tedavisi HS ve BS hastalarında fonksiyonel kas sorunlarını düzelterek hastalığın tedavisinin yanında duygu durum üzerine de olumlu etkiler sağlamakta ve hastalığa bağlı anksiyete ve depresyon bulgularını da düzeltmektedir.*

Anahtar Kelimeler: *Hemifasiyal Spazm, Blefarospazm, Anksiyete ve Depresyon*

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Assessment of Depression and Anxiety After Botulinum Toxin Injection Treatment in Patients with Hemifacial Spasm and Blepharospasm

Abstract

Objective: *The aim of this study was to investigate the relationship between depression and anxiety due to the current clinical situation, disease duration and age, and the change in post-treatment parameters in patients with hemifacial spasm (HS) and blepharospasm (BS) receiving botulinum toxin therapy (BTT).*

Materials and methods: *125 hemifacial spasm patients, 14 blepharospasm patients and 70 healthy volunteers were included in the study as control group. Beck depression and Beck anxiety scales were applied to the patient and control groups. The test was repeated in the patient group 4 weeks after BTT treatment.*

Results: *The Beck anxiety and Beck depression scale scores of the case group were higher before treatment compared to the control group. Beck anxiety and Beck depression scores decreased after treatment in both HS and BS patients. Among the groups, the post-treatment Beck Anxiety score in the blepharospasm group was statistically significantly lower than in the hemifacial spasm group. The depression scale score increased with increasing disease duration in the case group. Anxiety and depression scores were lower in older patients. Beck depression and Beck anxiety scores of the patients improved with BTT treatment.*

Conclusion: *Since HS and BS cause physical problems in the facial muscles, it also negatively affects the functional status and emotional state of the patients. This disease is often accompanied by anxiety and/or depression. After CT treatment, functional muscle problems are corrected in HS and BS patients, providing positive effects on mood as well as the treatment of the disease and correcting the anxiety and depression findings related to the disease.*

Keywords: *Hemifacial Spasm, Blepharospasm, Anxiety and Depression*

Introduction

Hemifacial spasm (HS) is a movement disorder characterized by irregular, tonic-clonic seizures of the muscles innervated by the facial nerve on the same side[1]. The most common cause of this clinical disorder is compression of the facial nerve for any reason and possible vascular structural abnormalities in the brainstem[2]. Furthermore, HS can also develop following peripheral facial paralysis (PFP) secondary to trauma[3]. Blefarospazm (BS) is a type of focal dystonia originating in the basal ganglia manifested by involuntary contractions of the muscles around the eyes[3]. Although their pathophysiologies are different, both clinical conditions result in contraction of the orbicularis oculi muscle and involuntary closure of the eyelid. Since these two types of focal dystonia directly lead to involuntary contractions in the patient's facial muscles, they result in social anxiety disorder, withdrawal, and secondary anxiety and depressive mood in the patient[3]. Botulinum toxin injection

treatment (Botox) is routinely applied in 3-4 month periods as part of the medical treatment in such cases of focal distoni[4]. The fact that there is improvement in the facial muscles for up to 3-4 months following the Botulinum toxin injection treatment applied in such clinical conditions somewhat alleviates patients' anxieties at the conclusion of the treatment. In our study, we aimed to determine the anxiety and depressive mood that will arise in the patients under our follow up who are diagnosed with HS/BS, as well as the relationship of this condition with the disease duration and patients' ages as well as the changes in the post-treatment anxiety and depression scores.

Materials and Methods

The study was conducted in accordance with all procedures, ethical principles, and Helsinki pursuant to the decision of Van Yüzüncü Yıl University Hospital Clinical Research Ethics Committee (Date: 21.09.2022, Decision No.: 03).

After obtaining the approval from our hospital's ethics committee, a total of 139 cases were included from the adult individuals, diagnosed with focal dystonia (hemifacial spasm and blepharospasm patients), aged between 18-65, who have applied to our dystonia clinic for the botulinum toxin treatment (BTT) applied as part of each 3–4-month treatment period. The demographic data of the patients to be included in the study, such as age, gender, marital status, and occupational information, were recorded. In addition to these, patient information such as disease duration, presence of comorbidities, and duration of treatment were obtained and afterwards the patients filled out the Beck Anxiety Scale (BAS) and Beck Depression Scale (BDS) questionnaires prior to Botulinum toxin injection treatment, and these questionnaires were then filled out again after the treatment during the 1-month clinical follow-up visit, where their neurological examinations were also checked.

Patients with malignancy, history of use of medications that may cause dystonia, those with a prior diagnosis of depression or anxiety undergoing psychiatric follow-up and treatment, individuals under 18 and over 65 years of age were determined as exclusion criteria.

Botox preparation of botulinum toxin type A, which is one of the three different preparations (Dysport, Botox-Allergan, Nabota) approved by the FDA in our country and licensed and approved by the Turkish Ministry of Health, is available in vial form in the market. In our study, we used the Botox preparation of the toxin. The medication was diluted with 2.5 ml of 0.9% saline solution before use.

Beck anxiety inventory: Beck Anxiety Score (BAS) is a self-assessment scale consisting of 21 items used to measure the level and severity of anxiety symptoms. Each item is assigned with a score between 0 and 3, resulting in a total score ranging from 0 to 63. The total scores of the test are

interpreted as follows: 0-7 minimal anxiety, 8-15 mild anxiety, 16-25 moderate anxiety, and 26-63 severe anxiety. Validity and reliability study for the Turkish adaptation was conducted by Ulusoy et. Al[5].

Beck depression scale: Beck depression score (BDS) is used to determine the risk in terms of depression and measure the level and severity of depressive symptoms. Beck depression scale is developed by Beck et. al. in 1961[6]. It is a self-assessment scale consisting of 21 items administered to measure the level and severity of depression symptoms. This questionnaire form consisting of 21 questions is used to assess the Beck depression score. The patients were asked to select the option from these questions that best suited their own conditions. This test is scored using a four-point Likert scale. Each item assigned with a score between 0 and 3, and the sum of these scores results in a total score ranging from 0 to 63. According to the scores obtained using the scale developed by Beck et. al. (1996), depression levels are classified as follows: 0-13 points indicate no depression, 14-19 points indicate mild depression, 20-28 points indicate moderate depression, and 29-63 points indicate severe depression. The reliability and validity study of the scale in the Turkish culture was conducted by Hisli[7].

Data were analyzed using SPS 24.0. In the study, tests of normality were conducted by calculating kurtosis (a measure of the peakedness of a frequency distribution curve) and skewness (a measure of the lack of symmetry of a probability distribution of a real-valued random variable). As a result, parametric tests were used in the comparative tests and correlational test. Chi-squared test was used for the relationship between categorical variables and groups, independent samples t-test was used for comparing groups, and Pearson correlation test was used for the relationship.

Results

Of the patients included in the study, 69 (49.6%) were male and 70 (50.4%) were female. There were 26 (37.1%) male and 44 (62.9%) female participants in the control group. The youngest patient was 19 years old, and the oldest was 78 years old, and the mean age of all patients was 49.93 years. The mean age of the control group was 39.16 years. In terms of occupation, the highest percentage in the group with “HS” disease were homemakers (45.6%) and pensioners (17.6%). Similarly, in the group with “BS” disease, homemakers (42.9%) and pensioners (28.6%) were also the most prevalent. However, there was no significant difference between the two disease types in terms of occupation groups ($\chi^2(6) = 2.976$, $p = .812$).

Demographic data and the analysis of intergroup variables, disease duration, patients’ ages, duration of the treatment administered, and the pre- and post-botox treatment BAS and BDS scores, are detailed in Table 1 and Table 2.

Table 1. *Demographic data, Analysis of inter-group variables*

		Group				Chi-squared	p
		Btx		Control			
		n	%	n	%		
Sex	Male	69	49,6	26	37,1	2,933	,087
	Female	70	50,4	44	62,9		
Marital status	Single	14	10,1	20	28,6	10,378	,001*
	Married	125	89,9	50	71,4		
Occupation	Homemaker	63	45,3	38	54,3	19,483	,003*
	Pensioner	26	18,7	5	7,1		
	Self-Employed	5	3,6	7	10,0		
	Student	8	5,8	6	8,6		
	Public	13	9,4	12	17,1		
	Unemployed	11	7,9	0	0,0		
	Worker	13	9,4	2	2,9		
Comorbidity	No	75	54,0	54	77,1	10,593	,001*
	Yes	64	46,0	16	22,9		

Table 2. *The Descriptive Statistics and Normality Test for the Entire Cohort*

	Minimum	Maximum	Mean	ss	Skewness	Kurtosis
Disease duration (years) (n=139)	1,00	20,00	8,22	3,97	,540	,540
Age (N=189)	18,00	78,00	46,32	13,57	-,283	-,647
BAS-1 (n=189)	0,00	55,00	13,52	11,47	1,055	,685
BDS-1 (n=189)	0,00	55,00	10,97	10,94	1,341	2,007
Duration of treatment (years) (n=139)	1,00	10,00	4,14	2,24	,213	-,898
BAS-2 (n=139)	2,00	35,00	11,25	6,08	1,189	1,369
BDS-2 (n=139)	0,00	40,00	9,95	6,80	1,447	2,943

BAS-1: *Pre-treatment Beck anxiety score,* ***BDS-1:*** *Pre-treatment Beck depression score,* ***BAS-2****: Post-treatment Beck anxiety score,* ***BDS-2:*** *Post-treatment Beck depression score*

Mean of pre-treatment Beck anxiety score (BAS-1) and Beck depression scores (BDS-1) of the patients in the case group administered with Botox treatment was significantly higher than those of the control group. ($p<0,05$). (Table-3).

Table 3. *Analysis of Case and Control Group BAS-1 and BDS-1 scores*

	Group				t	p
	Case		Control			
	Mean	ss	Mean	ss		
BAS-1	18,55	10,85	3,51	2,90	15,293	,000*
BDS-1	15,59	10,67	1,80	2,13	14,668	,000*

While the post-treatment Beck anxiety ve Beck Depression scores manifested decrease in both cases groups (HS, BS), the mean of post-treatment Beck anxiety score (BAS-2) scores with HS as disease type was significantly lower than those of patients with BS as disease type ($p<0,05$) (Table-4). There was no significant different in terms of other variables.

Tablo 4. *Sub-Group Analysis of Anxiety and Depression Scores in the Case Group*

	Disease type				t	p
	HS		BS			
	Mean	ss	Mean	ss		
BAS-1	18,05	10,89	23,07	9,65	-1,653	,101
BDS-1	15,54	10,67	16,07	11,02	-0,177	,859
BAS-2	10,75	5,87	15,71	6,24	-2,980	,003*
BDS-2	9,85	6,72	10,79	7,63	-0,484	,629

There is a statistically significant difference between the initial measurement of BAS score and the post-treatment second measurement, and the BAS score has decreased in the second measurement. There is a statistically significant difference between the first measurement of BDS score and the post-treatment second measurement, and the BDS score has decreased in the second measurement (Table-5). Regression is observed in the anxiety and depression score points of post-treatment patients.

Table 5. *Pre-Treatment and Post-Treatment Scores in the Case Group*

	Pre-Treatment Score (initial measurement)		Post-Treatment Score (second measurement)		t	p
	Mean	ss	Mean	ss		
BAS	18,55	10,85	11,25	6,08	11,165	,000*
BDS	15,59	10,67	9,95	6,80	11,292	,000*

Age, duration of treatment, and BDS-1 scores also increase as the disease duration increases in the correlation test results among the variables of the case group receiving botulinum toxin treatment

(Table-6). As the age increases, the disease duration is prolonged, and the BAS-1 score decreases. As the duration of treatment is increased, the BDS-1 scores also increase.

Table 6. *Case Group Analysis of Variables*

		Disease duration (years)	Age	Duration of treatment (years)	BAS-1	BDS-1	BAS-2	BDS-2
Disease duration (years)	r	1	,495**	,783**	,164	,204*	,048	,046
	p		,000	,000	,053	,016	,573	,588
Age	r		1	,474**	-,186*	-,071	-,168*	-,137
	p			,000	,028	,404	,048	,109
Duration of treatment (years)	r			1	,157	,205*	,068	,081
	p				,064	,015	,426	,343
BAS-1	r				1	,761**	,722**	,585**
	p					,000	,000	,000
BDS-1	r					1	,677**	,855**
	p						,000	,000
BAS-2	r						1	,760**
	p							,000
BDS-2	r							1
	p							

Discussion:

Blepharospasm is a disease characterized by involuntary contractions of the orbicularis oculi muscle and is presented with continuous or intermittent eyelid closures. The condition is referred to as a type of focal dystonia originating from a disorder in the basal ganglia[8]. Hemifacial spasm, on the other hand, is characterized by tonic-clonic contractions involving half of the face, including the orbicularis oculi and other facial innervated muscles. Although the symptoms and subjective impairment of both diseases are clinically similar, hemifacial spasm is not associated with basal ganglion dysfunction but rather arises from irritation of the peripheral facial nerve[8]. Medical treatment of dystonia is challenging in clinical practice. Currently, Botulinum toxin type A treatment applications have been widely accepted for many types of hyperkinetic movement disorders, including HS and BS. Better results are obtained with Botulinum toxin type A treatment applications for both mentioned clinical conditions compared to medical treatments[4].

Our cohort mainly consisted of patients with HS spasms. HS is typically seen in middle-aged women and occurs in the 5th decade of life[9]. 50.4% of our patients were female, with a mean age of 46.32 years. The most common cause of HS is the relationship between the facial nerve at the root entry zone in the brainstem and pathological vascular structures in this area[10]. In our

patients, while the inquiry in terms of possible comorbidity or ischemic vascular disorder revealed a comorbidity in 46% of cases with hypertension identified in 40 patients as part of the medical history interview, Type 2 Diabetes Mellitus was identified in 24 patients. The magnetic resonance imaging of the brain of the patients revealed no ischemic-vascular or tumoral formation were identified in the brainstem and facial nerve exit zone.

The mean BAS-1 and BDS-1 scores of the patients prior to the Botox treatment were higher compared to the control group. The mean post-treatment BAS-2 scores of patients with HS as disease type were significantly lower compared to those with BS as disease type. It was observed that the frequency of anxiety decreased even further after botulinum toxin treatment in HS patients compared to the BS group. While blepharospasm is reported to be more common in some psychiatric disorders, such as obsessive-compulsive disorder (OCD), it is not certain that the etiology and clinical findings of the disease are directly associated with psychiatric disorders[10]. The emergence of involuntary movements in facial muscles in both BS and HS can indirectly affect the patients' interpersonal communication negatively and lead to depressive mood and feelings of stigma in the patient[11,12]. Self-stigmatization can result in decreased self-esteem and reduced quality of life[12]. In a study of HS patients, visual symptoms and social inhibition due to involuntary movements in the face were observed in 41% of the patients[13]. In rural areas and traditional societies, these involuntary movements in the face will sometimes be misinterpreted which are expressed as causes of anxiety and depression in the patients[11]. Especially in HS patients, since voluntary facial movements exacerbate facial spasms, impairment in vision and speech and even, in more severe cases, mental functions may be affected as a result of these symptoms[14]. These issues can affect the patient's perception and relationship with the external world, leading to secondary social anxiety and sometimes feelings of shame[14]. In furtherance of this information, the anxiety and depression scores of our HS patients were higher than those of the normal population.

Previous studies have mentioned a higher prevalence of OCD and depressive symptoms in blepharospasm patients[10]. Additionally, the social and physical barriers related to these conditions are other reasons of the underlying psychopathology. Another study conducted on patients with blepharospasm and hemifacial spasm also yielded similar results[15]. It is observed in the blepharospasm group that psychiatric symptoms were significantly more prevalent. Likewise, in our cohort, the anxiety and depression scores were found to be higher in BS patients compared to the normal population, similar to the HS patient group.

There is a statistically significant difference between the first measurement (Pre-treatment) and the second measurement (Post-treatment) of BAS and BDS scores, and the BAS and BDS

scores have decreased in the second measurement. A regression was observed in the anxiety and depression score points of post-treatment patients. Furthermore, in correlation analyses among variables in the group receiving Botox treatment, it was found that as the disease duration increased, age, duration of treatment, and BDS-1 scores also increased, and it is considered that factors such as the necessity of continuous hospital visits and long-term treatment concerns have a negative effect on depressive mood as the current process becomes chronic. The fact that observing an increase in BDS-1 scores as the duration of treatment increases during the chronic process in parallel to increased disease duration, it is considered that patients continuing the current treatment for a long time during the chronic phase of the disease and living with the disease anxiety may be a contributing factor to such increase.

Conclusion

In conclusion, anxiety and depression may be more prevalent in HS and BS patients compared to the normal population. Since these conditions involve involuntary contractions of the muscles around the eyes and facial nerves, they can negatively impact the patients both in terms of health and social anxiety, triggering anxiety and depressive mood in the long term. Long-term follow-up and well-managed treatment can not only improve patients' physical well-being but also help protect them from potential concerns, worry, anxiety, and depressive mood associated with the disease from a mental perspective.

From our perspective, recording the severity of HS and BS disease in patients and providing a more detailed description of treatment response could have made the study more understandable and informative.

Ethical Committee Approval: The study was conducted in accordance with all procedures, ethical principles, and Helsinki pursuant to the decision of Van Yüzüncü Yıl University Hospital Clinical Research Ethics Committee (Date: 21.09.2022, Decision No.: 03).

Patient Consent: Detailed informed consent of the patients were obtained in accordance with the Helsinki Declaration.

Peer Review: Reviewed by both the editorial board and off editorial board individuals.

Financial Support: No financial support was received from any institution or individual for the study.

Note: The preliminary data of the current study, evaluated with a smaller number of patients, were presented as an oral presentation at the "3rd International and 7th Medicine and Treatment Congress" held in Bafra/Turkish Republic of Northern Cyprus between September 21-25, 2022.

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International Archives of Medical Research 16:1 (2024) 11-17

ORIGINAL RESEARCH

Six-month Follow-up of Hepatitis A Antibodies in Newborn Infants in Diyarbakir Province and Its Region

Received Date: 23.03.2024, Accepted Date: 16.04.2024 **DOI: 10.56484/iamr.1457184**

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Abstract

Objective: *In this study, we aimed to determine the frequency and persistence of maternally transmitted anti-HAV antibodies in healthy newborn infants of people living in Diyarbakır province, which is located in a high HAV endemicity area, and its neighbourhood.*

Material and Method: *In our study, infants born between October 1999 and January 2000 in the Gynaecology and Obstetrics Clinic of Diyarbakır Dicle University and registered in the Department of Paediatrics were followed up for 12 months. Blood samples were collected from all babies at birth, third and sixth months.*

Results: *A total of 112 healthy newborns were included in the study. Of the infants, 62 (55.3%) were boys and 50 (44.7%) were girls. Demographic and medical information was obtained from the parents. Seropositivity was 90.2% at birth, 87.5% at 1 month, 39.3% at 6 months and 28.6% at one year.*

Conclusion: *It was emphasised that our region has a high endemicity for HAV and in order to reduce HAV infection, socioeconomic level should be increased, hygiene should be given importance and immunisation with vaccine should be performed when appropriate conditions are met.*

Keywords: *Hepatitis A, newborn, hepatitis A vaccine, Diyarbakır*

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Introduction

Hepatitis A virus (HAV) infection is among the most common viral infections in the world. It is still endemic in some regions of developing countries such as our country but can sometimes cause increases. Hepatitis A infection without symptoms, especially in childhood, causes some difficulties in diagnosis. The seroprevalence of hepatitis A infection can be affected by various factors such as geographical location, sociodemographic characteristics, and age distribution[1,2]. Due to improvements in hygiene with increasing socioeconomic conditions, the incidence of HAV infections continues to decrease in many developing countries, including Turkey[1,3].

In terms of passive immunity, transplacental transfer of maternal IgG antibodies may protect against infectious diseases during infancy. However, the presence of maternal antibodies at the time of vaccination may reduce the vaccine-induced immune response[4-6]. The duration of passive immunity provided by maternal antibodies varies among populations. Therefore, seroepidemiological studies provide important data regarding the decrease in maternal antibodies in a specific population.

Seroepidemiological studies have shown that maternally derived anti-HAV antibody titers remain high during the first six months of life but decline significantly after 12 months. With data indicating that only 6.1 percent of 18-month-old babies in Turkey have maternal antibodies, two-thirds of babies older than 12 months have a high risk of contracting HAV infection.

In our study, we aim to evaluate the persistence of naturally acquired maternal antibodies against HAV in a group of newborns aged between 0 and 6 months.

Materials and Methods

In our study, babies born in Diyarbakır Dicle University Gynecology and Obstetrics Clinic and registered in the Department of Child Health and Diseases were followed up for 12 months. Verbal and written consent was obtained from the families for the study. Blood samples were taken from all babies at birth and the third, 6th, and 12th months.

Infants born prematurely, experiencing a complicated delivery, or whose mothers had acute hepatitis, along with those unable to attend scheduled follow-ups, were excluded from the study cohort. Additionally, infants whose parents declined participation were also excluded.

ELISA

Blood samples for the detection of anti-HAV antibodies were taken at birth, at the first month, and at the sixth month. After cleaning the babies' forearms with antiseptic solutions, blood samples were taken from superficial veins in sterile straight tubes in 3 ml quantities. After the

serums were separated, they were brought to the ELISA unit of the Central Laboratory of Dicle University Faculty of Medicine Research Hospital on the same day.

IgM and IgG antibodies against the Hepatitis A virus were evaluated using the enzyme immunoassay method. For this purpose, EQUIPAR Diagnostic HA IgM, HAV Ab III. Belt kits (Equipar srl, Via Power Ferrari Sarenno (va) Italy) were used. The test demonstrated high levels of sensitivity and specificity.. The fresh serum samples taken were stored at 2-8 oC and studied with the Tecan Minilyser ELISA device in the ELISA unit on the same day. All processes were performed at room temperature (20-250C). We conducted all analyses following the manufacturer's instructions, utilizing commercial kits and systems.Sample and threshold values for hepatitis A were determined using the average adsorbance value of the calibrator. Individuals whose diagnostic findings for Hepatitis A surpassed a value of >1.1 S/CO were deemed positive. Our study focused on qualitative analysis of antibodies to HAV, without conducting additional quantitative evaluation.

Statistical analysis

Descriptive and comparative statistical assessments were carried out using the Social Sciences Statistical Package for Windows (SPSS). Nominal variables were delineated by quantity and percentage values.. Quantitative variables are presented in the tables as mean ± std. (standard deviation) and categorical variables are given as n (%). In comparing four dependent repeated measurements with each other, The Cochran's Q test was evaluated based on Monte Carlo simulation outcomes, and the Dun's Test was employed for the Post hoc analysis. Variables were assessed with a 95% confidence interval, and significance was determined for p-values below 0.05.

Results

The study comprised 112 healthy newborns with a mean gestational age of 38.7 ± 0.6 weeks. Of these, 62 (55.2%) were boys and 50 (44.7%) were girls. 38.2% of the fathers and 16.8% of the mothers of the babies included in the study were high school or university graduates. 20.2% of the babies were their mothers' first child. 41.2% of the babies lived in the city center (76.8% in Diyarbakır city center, 23.2% in the surrounding province centers), 58.8% in rural areas (71.2% in the rural areas of Diyarbakır province, 28.8% in the rural areas of the surrounding provinces) (Table 1).

Table 1. *Demographic characteristics of babies.*

	mean ± SD.
Gestational age (weeks)	38.7±0.6
	n (%)
Gender	
Male	62 (55.2)
Female	50 (44.7)
Mother's Educational Status	
Illiterate	43 (38.4)
Elementary School	40 (35.7)
High School	13 (11,6)
University and above	6 (5.3)
Father's Educational Status	
Illiterate	32 (28.6)
Elementary School	37 (33.0)
High School	32 (28.6)
University and above	11 (9.8)
Diyarbakır Province	82 (73.2)
City Center	35 (42.7)
Countryside	47 (57.3)
Surrounding Cities	30 (26.8)
City Center	7 (23.3)
Countryside	23 (76.7)

SD.: Standard Deviation

112 selected for the study successfully completed it.Anti-HAV antibodies persistence is set out in table 2.

Anti-HAV IgG positivity in newborns tested at birth was detected in 90.2% (n=101). The acceleration in the decrease in this positivity until the sixth month became more evident in the first year. Anti-HAV-IgG (+) was detected in 44 (39.3%) babies in the sixth month and in 32 (28.6%) babies in the 12th month (Table 2).

Table 1. *Changes in HAV serology in infants*

Time (n)	**Anti-HAV IgG (+) n (%)**	**Anti-HAV IgG (-) n (%)**	**p**
0. Day (n=112)	101 (90.2)	11 (9.8)	
1. Month (n=112)	98 (87.5)	14 (12.5)	**<0.001**
6. Month (n=112)	44 (39.3)	68 (60.7)	
12. Month (n=112)	32 (28.6)	80 (71.4)	

Cochran's Q test (Monte Carlo), Post Hoc Test: Dun's Test

Anti-HAV IgM antibodies (7.5%) were detected as positive in a male baby who was anti-HAV IgG negative in the neonatal period and two female babies who were anti-HAV IgG positive

until the sixth month but became negative in the sixth month, and in the laboratory examinations, the babies' ALT and AST values were found to be high. No clinical icterus was observed in these babies.

Based on these results, it was concluded that the babies had subclinical HAV infection. The seropositivity rate in the sixth month was significantly lower than those detected in previous months ($p<0.001$) (Table 2) (Figure 1). This value did not become seropositive in any of the anti-HAV IgG seronegative babies during the follow-up period.

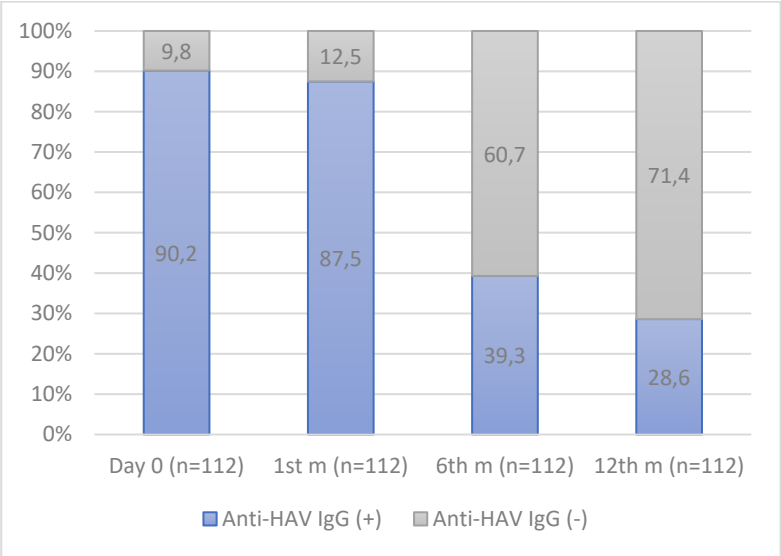

Figure 1. *Changes in anti-HAV-IgG positivity.*

Discussion

Newborns in developing countries are at risk for hepatitis. HAV infection has a high incidence, especially in regions where sanitation conditions are inadequate, and there are no appropriate vaccination programs. Since HAV infection in children is generally asymptomatic, regular seroprevalence studies can provide more clear information to ascertain disease occurrence .

In recent years, there has been no homogeneous distribution among seroepidemiological data following rapidly changing sanitation conditions, awareness about infection, and widespread vaccination programs.

In the context of HAV infections, the occurrence of maternal antibodies and the duration of their decline are pivotal in determining the optimal timing for vaccination across diverse populations[4,7].

The hepatitis A vaccine effectively interrupts virus transmission, resulting in a notable decrease in hepatitis A infection rates within the general populace. While immunizing infants represents an ideal preventive measure, in regions with moderate to high endemicity, a significant

proportion of women of childbearing age possess anti-HAV antibodies, which are passed on to their offspring during pregnancy. For instance, research by Alabaz et al.[8] in Turkey revealed that 138 out of 147 newborns and their mothers were hepatitis A seropositive. Similarly, Kanra et al.[9] demonstrated HAV seroprevalence rates of 70.2% in infants under one year old and 73.2% in women aged 30 or younger. These studies underscored the high incidence of maternal antibody transmission[10,11]. High HAV seropositivity was expected because the patients we included in our study consisted of people living in Diyarbakır city center and rural areas, where sanitation conditions and access to primary health care were difficult at the time of the studyPrior research indicates that maternal antibodies targeting HAV may endure in infants for as long as one year, and may even persist until the second year in moderately endemic regions such as Turkey[10,12]. However, although HAV IgG (+) was previously detected in two babies during the study period, it was observed that their antibodies became negative after the sixth month, and HAV-IgM (+) was detected. This result may be evidence that the protection of maternal antibodies is short-lived, especially in children living in high-endemicity regions.

Alabaz et al. observed HAV seroprevalence rates of 93.9%, 90.5%, 84.4%, 62.6%, 36.1%, and 13.6% at 3, 6, 9, 12, 15, and 18 months, respectively. Meanwhile, Lieberman et al. documented HAV seropositivity rates in 4, 6, and 12-month-old infants as 100%, 95%, and 39%, respectively. In our study, it was found that antibodies became negative at a higher rate in the first six months of postnatal follow-up compared to other studies. This difference in HAV seropositivity rates can be explained by socioeconomic status, sanitation conditions, geographical location, and changes in HAV epidemiology[13]. While more than 90% of HAV infections are asymptomatic in childhood, up to 70-80% of them are symptomatic in adults[1,2]. We assumed that most mothers were exposed to HAV pre-pregnancy and that during pregnancy, antibodies had been transmitted to the fetüs.

It was found that in a population not vaccinated and with no previous history of HAV infection , HAV IgG seropositivity rates decreased to 39.3% in 6-month-old children and 28.6% in the first year. In particular, in our research, the effect of sociodemographic characteristics on rates of seropositivity could not be adequately evaluated due to the similar middle/high socioeconomic status between the study groups. Furthermore, there is a lack of documentation regarding the impact of maternal antibodies on cell-mediated immune responses to HAV. In this investigation, the discovery of 90.2% seropositivity for HAV IgG in newborns suggests that mothers may have been exposed to HAV infection and passed on their antibodies to their offspring. Therefore, the decreasing trend in these seropositivity rates in children during the 6-month follow-up most likely reflects the existence of anti-HAV antibodies acquired from the mother, and the low protection rates

indicate that the vaccination program after the sixth month is accurate.

Maternal antibodies have been shown to inhibit the effectiveness of all inactivated vaccines, live attenuated vaccines, and most DNA vaccines[7,14]. Hence, the timing of primary vaccination is influenced by various factors related to the infant's developing immune system, including the necessity to provide protection before potential exposure to diseases, the potential interference of passively acquired maternal antibodies with vaccine-induced immunity, and other considerations (4,7). By the age of 12 months, passively transferred antibodies from the mother can be detected in only a small minority of infants, and it decreases more dramatically from 6 months onwards[15].

Although the hepatitis vaccine was not yet administered between 2000 and 2012, a significant decrease in seropositivity was observed. This decrease is probably due to improvements in infrastructure and sanitation conditions in Turkey[16,17]. In the subsequent period, vaccination also played a role in this decline. Research undertaken in Turkey before widespread vaccination recommendations reported varying rates due to socioeconomic differences between regions. With the acceptance of widespread vaccination after 2012, it is observed that the differences between regions in Turkey have decreased significantly[18,19]. However, vaccination at an early age has an important place in reducing HAV infection, which causes high morbidity and mortality in adulthood.

The decline in maternal antibodies may create a vulnerable period during which the infant becomes susceptible to relevant infections[4,7,20]. According to Brinkhof et al., the half-life of antibodies is estimated at 40 days, with 95% of infants projected to lose their passive immunity by around 13.2 months[21,22]. Similarly, Alabaz et al. found that roughly two-thirds of infants are susceptible to HAV infection at approximately 12 months of age[8]. Consistent with these findings, our study indicates that one out of every two children becomes susceptible to HAV infection starting from the 6th month. . We think that babies become susceptible to HAV in their first year in terms of decreased antibodies in the mother.

Our study has some inevitable shortcomings. Given that our reserach was undertaken in a medium-high endemicity region for HAV is the most important reason for high HAV-IgG positivity in mothers and therefore in babies. National vaccination programs for HAV in Turkey were started after our study and after 2012. Hence, the data gathered in our study depict the pre-vaccination era among a cohort of unvaccinated children, thus aiding in the identification of the ideal vaccination schedule. The fact that the HAV vaccine was not part of the widespread vaccination program at the time of the study caused the HAV seroprevalence in adults and newborns to have significant differences from current results.

In conclusion, although the transfer of maternal anti-HAV IgG antibodies in the placenta seems protective in the first six months of the baby, it has been determined that one in every two babies is vulnerable to HAV in the following period. Furthermore, given the rapid decline in HAV occurrence among adults as against previous years, the transmission of maternal antibodies is expected to decrease significantly. For this reason, we think that it is appropriate to start widespread vaccination programs for HAV in early infancy.

Acknowledgment

Some portions of this article constitute Dr. Hakan Onur's Graduation thesis for the requirement of the degree in Specialization in Pediatrics at Dicle University, Medical Faculty, Diyarbakir, Türkiye

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International Archives of Medical Research 16:1 (2024) 18-25

ORIGINAL RESEARCH

The Effect of Cold-Water Immersion Application on Biochemical Parameters in Athletes

Received Date: 19.03.2024, Accepted Date: 26.04.2024 **DOI: 10.56484/iamr.1455752**

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Abstract

Objective: *The purpose of this study was to see what influence cold water immersion had on the athletes' biochemical parameters.*

Method: *The study included 20 elite level (Experimental 10, Control 10) male athletes who were licensed in the athletics branch and competed in national and international events. For four weeks, six days a week, the research group was subjected to a ninety-minute long-distance running regimen. Blood samples were collected from the research group's athletes twice, at the start and finish of the training session. CK, ALT, AST and LDH levels were determined in the taken blood samples. The data were analyzed using the SPSS package program. Significance level was accepted as $p<0.05$.*

Results: *According to the findings obtained in the research; According to the research results; It was determined that the trainings applied created significant changes in the CK, ALT, AST and LDH levels of the athletes in the control and experimental groups.*

Conclusion: *Furthermore, it was discovered that the cold water immersion treatment used on the athletes in the experimental group had a greater favorable effect on CK, ALT, AST, and LDH levels than the athletes in the control group.*

Keywords: *Cold water immersion (CWI), Athletics, Biochemistry, Muscle damage, Recovery.*

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Introduction

The primary national and international competitions in most team sports follow a tournament schedule. On consecutive days, teams must play multiple matches. The athletes playing in these competitions all have the same problem: the time allotted for full physiological recovery between matches is short, and hence physical efficiency may suffer. Indeed, recent study has demonstrated that cumulative exhaustion from multiple encounters can have a deleterious impact on team sport performance. Many sportsmen and trainers believe that water immersion provides a cooling effect after a hard training or competition[1].

Blood lactate concentration is typically measured using portable instruments to monitor and plan exercise. Although some studies question the usefulness of blood lactate concentration as a determinant of muscle recovery after exercise, this biochemical marker is extensively employed for this purpose[2].

Strenuous athletic activities might cause muscle injury. Changes in CK plasma enzyme activity in response to activity may signal the onset of muscle injury. Strenuous exercise has been linked to increased CK activity. Athletes had higher plasma CK activity at rest than untrained people, but their CK activity increases less after exercise than non-athletes[3].

It is said that cold water immersion application speeds the biochemical process in order to get rid of these destructions created by hard exercises in athlete's metabolism with the least amount of harm and to recover quickly. Again, cold water immersion (CWIT) is a method that involves immersing a body portion in water that is less than 15°C. It is one of the most widely used therapy techniques for improving muscle recovery following high-intensity exercise. However, there is just anecdotal scientific evidence to support the efficacy of this treatment. Intense exercise disrupts many physiological processes, including muscle injury, hyperthermia, dehydration, and glycogen depletion. Inadequate/late restoration of these physiological alterations may result in poor performance in following training sessions, whereas chronic imbalance between training stress and recovery may result in overreach or overtraining syndrome[4].

Cold water immersion (CWI) after exercise is gaining popularity among athletes as a means of reducing tiredness and speeding post-exercise recovery. CWI is claimed to facilitate recovery by reducing cardiovascular strain by improving hyperthermia and subsequent changes in the central nervous system (CNS), removing accumulated muscle metabolic byproducts, reducing exercise-induced muscle damage (EIMD), and improving autonomic nervous system function. The current study seeks to provide a thorough and extensive examination of the processes that promote acute and long-term improvements in exercise performance following post-exercise CWI[5]. CWIT is vital

for recovery in sports with short rest intervals and extensive tournaments, such as athletics, football, volleyball, tennis, handball, and other sports. Despite the inexpensive cost of CWIT, the time necessary for therapists to prepare CWIT is lengthy. Furthermore, the water and ice used in CWIT can only be used once, and temperature control during treatment is problematic. LEDT devices, on the other hand, can be used multiple times without requiring lengthy preparations, but they are somewhat expensive when compared to water and ice[6]. In this situation, it is critical to recuperate from a sporting standpoint, particularly in terms of enhancing athletic performance to the highest degree or repeating it in the following competition and competition. The purpose of this study was to see what influence cold water immersion had on the athletes' biochemical parameters.

Materials and Methods

Research Group

20 elite level male athletes (Experimental 10, Control 10) licensed in the athletics branch and participating in national and international competitions voluntarily participated in the research group.

Control Group (n:10): the group doing athletics training

Experimental Group (n:10): the group in which cold water immersion was applied in addition to athletic training.

Training Program

For four weeks, six days a week, the research group was subjected to a ninety-minute long-distance running schedule. A 10-minute warm-up phase and an average of 40 stretching cooling exercises were conducted at the end of the training, in addition to the ninety-minute training program.

Collection and Analysis of Samples

CK, LDH, AST, and ALT blood samples were obtained at rest from all athletes participating in the study right before the training program for cold water immersion. Following the training routine, the experimental group was immersed in water at an average temperature of -2^{o}C for 8 minutes, with the neck of the body left exposed. To maintain a steady temperature, the water was measured with a thermometer and ice was added in between. 4 hours after the cold water immersion, CK, LDH, AST and ALT blood samples were taken from the experimental group again and analyzed. The blood samples taken from the athletes were taken in the private hospital laboratory by the experts in the sitting position and resting state by means of a fully automatic hemogram called “Coulter Stks” and analyzed.

Statistical Analysis

SPSS statistical package program was utilized in the analysis of the data. Normality analysis of the data was made and parametric tests were used for the data determined to be normally distributed. In the study, "Paired Samples t" test was used for in-group comparisons and "Independent Samples t" test was used for intergroup comparisons. The significance level was accepted as $p<0.05$.

Results

When Table 1 was assessed, it was determined that there was a statistically significant difference between the pretest-posttest values of the control group's CK, ALT, AST and LDH levels ($p<0.05$).

Table1. *Biochemical Changes of the Control Group Before and After Training*

Parameters	Pre test	Post test	t	p
CK	285,00±7,45	274,10±8,90	8,970	0,00*
ALT	34,90±3,51	31,10±2,23	4,670	0,00*
AST	37,30±2,66	30,10±1,96	7,298	0,00*
LDH	186,90±3,90	179,40±3,50	7,479	0,00*

*p<0,05

When Table 2 was examined, it was determined that there was a statistically significant difference between the pretest-posttest values of the experimental group's CK, ALT, AST and LDH levels ($p<0.05$).

Table 2. *Biochemical Changes of the Experimental Group Before and After Training*

Parameters	Pre test	Post test	t	p
CK	282,50±6,34	255,00±5,77	9,153	0,00*
ALT	34,20±4,70	27,60±3,23	7,802	0,00*
AST	37,10±3,98	26,50±1,71	6,805	0,00*
LDH	187,90±7,86	173,80±6,66	9,083	0,00*

*p<0,05

When Table 3 was examined, it was determined that there was a significant difference between the CK, ALT, AST and LDH levels of the control and experimental groups in the post-test values ($p<0.05$), and there was no significant difference between the pre-test values of the CK, ALT, AST and LDH levels ($p>0$). .05).

Table 3*. Intergroup Comparison Analysis Results*

Parameters		Control Group	Experiment Group	t	p
CK	**Pre test**	285,00±7,45	282,50±6,34	,808	0,43
	Post test	274,10±8,90	255,00±5,77	5,693	0,00*
ALT	**Pre test**	34,90±3,51	34,20±4,70	,377	0,71
	Post test	31,10±2,23	27,60±3,23	2,813	0,01*
AST	**Pre test**	37,30±2,66	37,10±3,98	,132	0,89
	Post test	30,10±1,96	26,50±1,71	4,359	0,00*
LDH	**Pre test**	186,90±3,90	187,90±7,86	-,360	0,72
	Post test	179,40±3,50	173,80±6,66	2,352	0,03*

*p<0,05

Discussion

Exercises performed on a regular basis, within the context of a specific program, and at a given intensity are known to cause changes in the organism. One of them is the organism's metabolic alterations, which are changing.

It has a negative impact on athletes and causes them to recover more slowly. Cold water immersion is one of the strategies used to prepare athletes for the upcoming events and tournaments. The purpose of this study was to see what influence cold water immersion has on athletes' biochemical parameters for post-exercise recovery. According to the research results; It was determined that the trainings applied created significant changes in the CK, ALT, AST and LDH levels of the athletes in the control and experimental groups. In addition, it was observed that the cold water immersion application applied to the athletes in the experimental group positively affected CK, ALT, AST and LDH levels more than the athletes in the control group. When the studies are examined, de Oliveira Ottone et al., (2014) discovered that CWI (15°C) was a suitable strategy to provide rapid parasympathetic reactivation after exercise, TWI (28°C), and They stated that HWI (38°C) should not be used for this special purpose[7]. Wiewelhove et al., (2018) determined in their study that CWI and massage method were more effective than active and passive listening in recovery after long-term jogging exercises[8]. In a different study, Kwiecien and McHugh (2021) noted that traditional cryotherapy procedures often alleviate pain after soft tissue injury and reduce pain after harmful activity[9]. Guo et al. (2022) discovered that cold water immersion (CWI) was more effective than contrast water therapy (CWT) in reducing blood Interleukin-6 and Prostaglandin E2 levels as well as muscle soreness after exercise[10]. In their study, Matsumura et al. (2022) discovered that applying liquid ice 48 hours after high-intensity activities reduced muscular

stiffness more than ice application[11]. In another study, Laia et al. (2022) found that wearing a cooling vest after exercise helped to lower body temperature, lower blood lactate concentrations above resting levels, and improve recovery[12]. Tabben et al. (2018) investigated physical performance, hematological stress markers, and 10-meter-long physical performance after 24 hours of cold water immersion (CWI) applied following a simulated mixed combat tournament (3x5 minute mixed fights separated by 1 minute passive rest). They discovered that sprint performance has a beneficial effect[13]. Bouzid et al. (2018) discovered in their study that 10 minutes of cold water immersion (CWI-10°C) and thermo-neutral water immersion (TWI-28°C) following an intermittent shuttle run reduced muscle injury and felt muscle pain in professional football players. They discovered that it increased physical performance recovery[14]. Durmaz et al. (2017) found in their study that the training program they implemented caused changes in some biochemical values of the athletes[15]. Sánchez-Urea et al. (2017) discovered that long-term and intermittent cold water immersion methods used on basketball players were helpful in lowering tiredness symptoms and, in particular, delaying the development of muscle discomfort[16]. Schimpchen et al. (2017) reported in a different study that cold water immersion (CWI) as a result of 3-day rigorous exercises had no favorable effect on the athletes[17]. Cold water immersion (CWI) has an effect on improving performance and reducing muscle soreness in athletes, but not on muscle strength, according to Alshoweir (2016)[18]. A study by C. Bleakley and G. Davison (2009) states that immersion in cold water for 5 minutes or less has significant effects on the body. These effects include increased heart rate, increased blood pressure, changes in respiratory minute volume and acceleration of metabolism, which may lead to various physiological and biochemical changes in the body.[19] In the study conducted by Gregson et al (2011), it was stated that lower water temperatures have a potential effect on the treatment of exercise-induced muscle damage and injury rehabilitation, and this is associated with a decrease in blood flow in the muscles. It has been suggested that this may reduce inflammation by accelerating the recovery process.[20] The study by Bleakley et al (2012) indicates that post-exercise cold water immersion significantly reduces muscle pain and fatigue compared to passive intervention.[21]

Conclusion

Finally, the study found that cold water immersion (CWI) had a favorable effect on muscle injury markers and metabolic parameters in athletes when compared to passive rest. According to this information, we believe that the CWI application to be used after the exercises will improve the athletes' early recovery and athletic performance.

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International Archives of Medical Research 16:1 (2024) 26-34

CASE REPORT

A Very Rare Relaps Type in Multiple Myeloma: Leptomenıngeal and Cranial Involvement

Received Date: 19.03.2024, Accepted Date: 26.04.2024 **DOI: 10.56484/iamr.1455752**

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Abstract

Multiple myeloma is a hematological malignancy that develops as a result of clonal proliferation of plasma cells and progresses with remissions and relapses. It is clinically characterized by many symptoms and signs such as osteolytic bone lesions, hypercalcemia, renal dysfunction, hypergammaglobulinemia and anemia. However, involvement of the central nervous system, especially the leptomeningeal/cranial region, is a rare and prognostically important form of relapse of the disease. This case report discusses this rare clinical presentation, diagnostic approach, and treatment strategies of extramedullary involvement of multiple myeloma.

Keywords: *Multipl Myeloma, Cranial involvement, Leptomeningeal involvement*

Introduction

Multiple myeloma (MM) is a B cell malignancy characterized by clonal proliferation of plasma cells. One of the most distinctive features of MM is abnormal plasma cell accumulation in the bone marrow and high levels of monoclonal immunoglobulin (M protein) accumulation in the serum[1]. At the genetic and molecular level, critical chromosomal changes play a role in the development and progression of MM. Specific chromosomal translocations and deletions, especially t(11;14), t(4;14) and del(17p), are important in the pathogenesis of this disease[2]. The interactions of MM in the bone marrow microenvironment, especially its interactions with bone marrow stromal cells, are critical for the development of the disease. Interactions between MM cells and bone marrow stromal cells trigger the release of various cytokines and growth factors. Cytokines, especially IL-6, Vascular Endothelial Growth Factor (VEGF) and Tumor Necrosis Factor alpha (TNF-α), while supporting the proliferation and differentiation of MM cells, may also contribute to the development of resistance to protease inhibitors[3]. The bone marrow

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microenvironment of MM stimulates osteoclast activity while inhibiting osteoblast activity. The interaction of MM cells with bone marrow stromal cells stimulates the production of RANKL (receptor activator of nuclear factor kappa-B ligand). This stimulates osteoclastogenesis by activating osteoclast precursor cells bearing the RANK receptor[4]. At the same time, MM cells can inhibit the production of osteoprotegerin (OPG), a molecule that antagonizes the effects of RANKL. This imbalance causes increased osteoclast activation and bone resorption[5].

MM has a prevalence rate of 1-2% among hematological malignancies[6]. An increased incidence has been observed in the population aged 65 and over, with approximately 6 new cases per 100,000 people reported annually in western societies[7]. It has been stated that the incidence of MM is higher in men and individuals of African origin than in women and individuals of Caucasian origin[8]. MM has a significant impact on the skeletal system, especially due to osteolytic lesions, pathological fractures and osteoporosis[9]. Renal involvement can occur both by the direct nephrotoxic effects of monoclonal light chain accumulation and by the combination of other factors such as hypercalcemia, dehydration and nephrotoxic drug use[10]. Additional organ involvement such as cardiomyopathy, amyloidosis and pulmonary complications can also be observed in MM patients[11].

Although MM is primarily known as the malignant proliferation of plasma cells within the bone marrow, extramedullary involvement can also be frequently observed in the later stages of the disease. While the incidence of extramedullary involvement varies between 7-18% at the time of diagnosis, it has been reported that this rate can increase to 20-40% in the later stages of the disease [12].

Nervous system involvement, seen as exramedullary involvement in MM, is a condition that should be taken into consideration both clinically and prognostically. Among the neurological complications of MM, such as radiculopathy, peripheral neuropathy and spinal cord compression are frequently observed clinical findings. However, although leptomeningeal involvement in central nervous system complications is relatively rare, it is of critical importance in terms of clinical course and treatment strategies[13]. Leptomeningeal involvement is characterized by the infiltration of malignant plasma cells into the subarachnoid space. This can occur independently of the classic MM symptoms of Bence Jones proteinuria, hypercalcemia, anemia, and bone lesions. This involvement can include a wide clinical spectrum, such as signs of meningeal irritation, neurological deficits, and cranial nerve palsies. Early diagnosis and management of leptomeningeal involvement has a decisive role on the clinical outcomes of the patient. Therefore, in addition to clinical and radiological evaluations, cerebrospinal fluid analysis is recommended in MM patients

with suspected involvement of leptomeninges. Intrathecal treatment and radiotherapy are among the potentially effective methods in the treatment of these patients[14].

Cranial involvement is an advanced-stage complication that can be observed in MM patients, and this condition poses significant challenges for both diagnostic and therapeutic approaches. Cranial involvement associated with MM usually occurs through osteolytic lesions or, more rarely, through direct invasion into the central nervous system (CNS)[4]. Clinically, this involvement can lead to various symptoms such as headache, neurological deficits and cranial nerve palsies[7].

Magnetic resonance imaging (MRI) is particularly valuable in the diagnosis of cranial involvement. MRI allows detailed evaluation of intracranial structure, as well as lesions within the skull and meninges, and plays a critical role in monitoring treatment response[4]. Treatment usually involves a combination of systemic chemotherapy regimens and regional radiotherapy. As in leptomeningeal involvement, the potential benefits of intrathecal chemotherapy and molecular targeted therapies in the treatment of cranial involvement are being investigated[14].

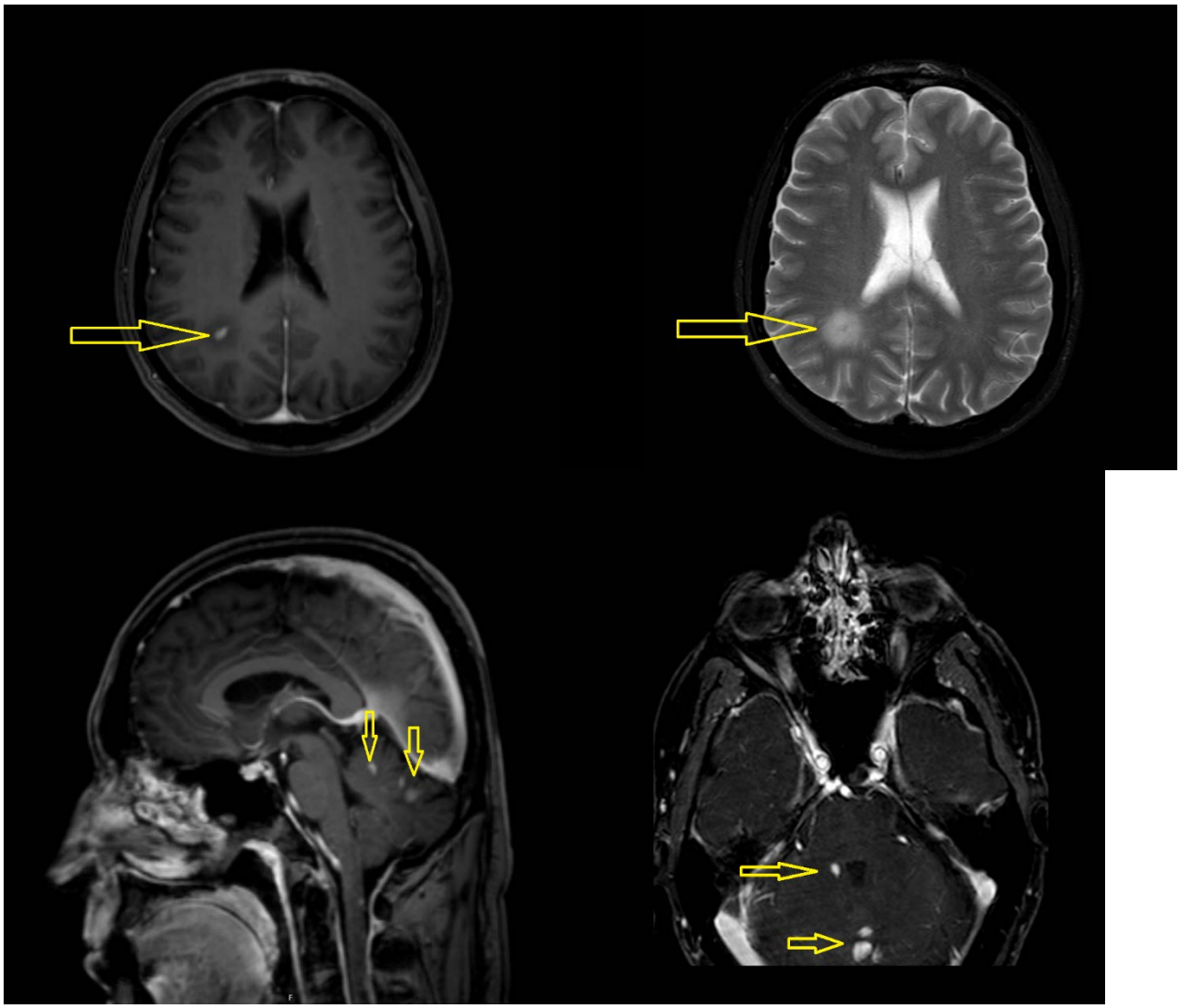
In conclusion, both leptomeningeal and cranial involvements of multiple myeloma are serious complications seen in aggressive and advanced forms of the disease. Early diagnosis and effective management of these complications can significantly improve patients' quality of life and potentially prolong survival. Therefore, it is recommended to carefully evaluate neurological symptoms in MM patients and apply aggressive treatment strategies in the early period when necessary.

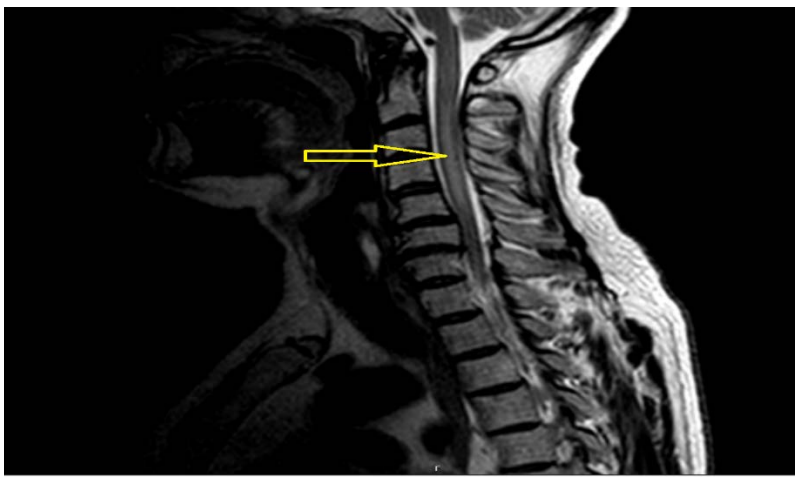
CASE REPORT:

53-year-old male patient, no known chronic disease or medication use. The patient applied with the complaint of double vision in 2020. As a result of the cranial imaging, a diagnosis of meningioma was made and accordingly, the patient received cranial gamma knife radiotherapy (RT) in March 2020. In the same year, in the additional evaluations made for the patient who re-applied with complaints of pain in the low back and left hip area, a biopsy of the mass located in the subtrochantiric region of the left femur was taken on October 13, 2020. The biopsy result was reported as plasma cell myeloma of bone. According to the results of the bone marrow aspiration biopsy performed on November 2, 2020, the patient was diagnosed with multiple myeloma. At diagnosis, the patient exhibits findings compatible with only "B" of the CRAB criteria of multiple myeloma, that is, a bone lesion. Anemia, hypercalcemia and renal dysfunction were not observed in this patient. Immunoglobulin values (IgA, IgG, IgM) were found to be within normal limits.

However, the presence of lambda light chains as a result of serum immunofixation was considered a sign of MM. Immediately after the diagnosis of multiple myeloma, the patient received palliative radiotherapy (RT) for the lesion detected in the left femur. In November 2020, a course of chemotherapy with a combination of cyclophosphamide, velcade, and dexamethasone (CyBorD) was started. Autologous peripheral stem cell transplantation (APSCT) was performed in February 2021. After the transplantation, the patient was followed up with Lenalidomide maintenance. While the patient was being followed up with a full response under maintenance treatment, he applied with complaints of vision loss in the left eye and severe neck pain in June 2023. Cranial computed tomography (CT) examination was performed after the patient presented with complaints of vision loss in the left eye and neck pain. No abnormal findings were detected in this examination. However, for a more detailed examination, contrast-enhanced cranial and cervical magnetic resonance imaging (MRI) was performed. In MR imaging, lesions showing contrast enhancement after intravenous contrast material (IVCM) were seen in the right parietal region at the corona radiata level, in the right middle cerebellum peduncle, in the cerebellar vermis and in the left cerebellar hemisphere, and increased contrast enhancement was detected in the cerebellar folia. Two nodular lesions with meningeal contrast enhancement were observed in the cervical spinal cord. Edema was detected in the spinal cord between the C2-6 vertebral levels [Figure 1-5]. Visual field examination revealed papilledema and vision loss in the left eye [Figure 6-7]. Following the observed radiological findings, cerebrospinal fluid (CSF) examination was performed to determine neurological involvement. In this examination, the presence of diffuse plasma cells was detected and these findings were evaluated as leptomeningeal involvement [Figure 8].

In June 2023, DR-PACE (Dexamethasone, Lenalidomide, Cisplatin, Etoposide, Cyclophosphamide, Doxorubicin) chemotherapy protocol and cranial RT were applied, and in addition to this protocol, intrathecal treatment was also performed. Following this treatment approach, a significant regression was detected in the patient's complaints, his life comfort improved, and a clinical improvement was observed in the visual function of his left eye. It was reported that he passed away in the intensive care unit where he was hospitalized due to pneumonia in the city where he lived, although his hematological parameters were good.





Figures-1-5: Cranial MR Findings

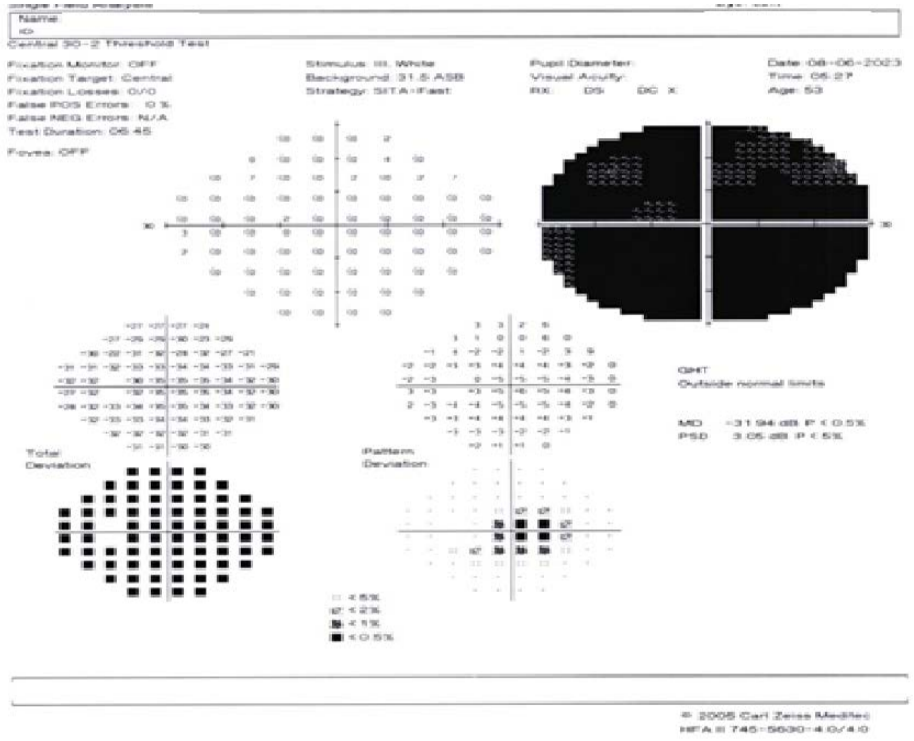


Figure-6: Left eye visual field

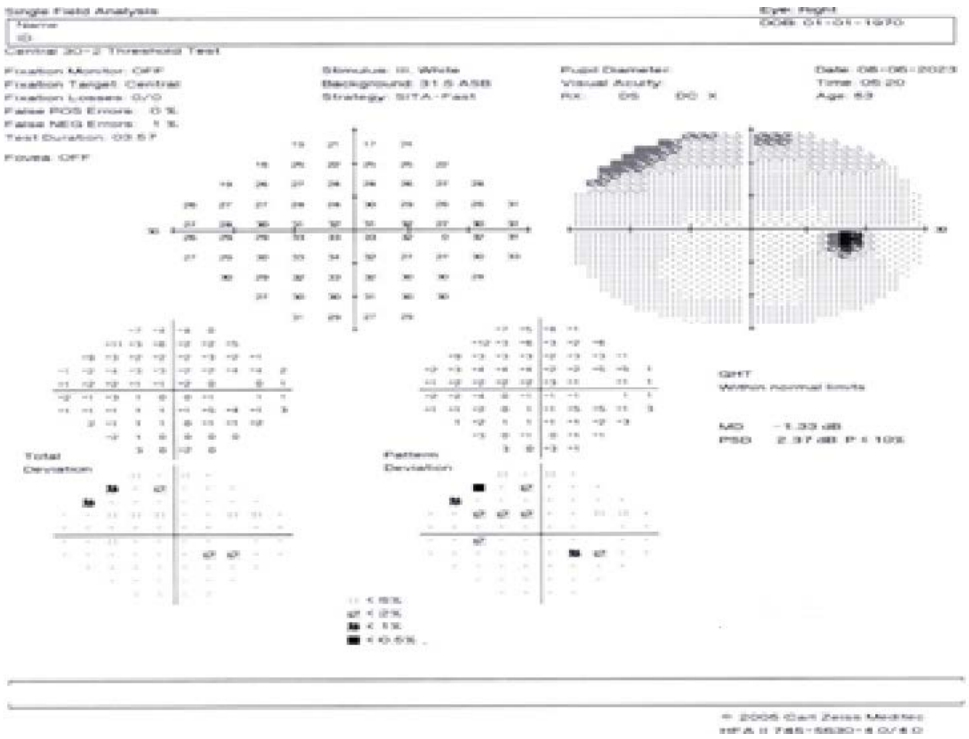


Figure-7: Right eye visual field

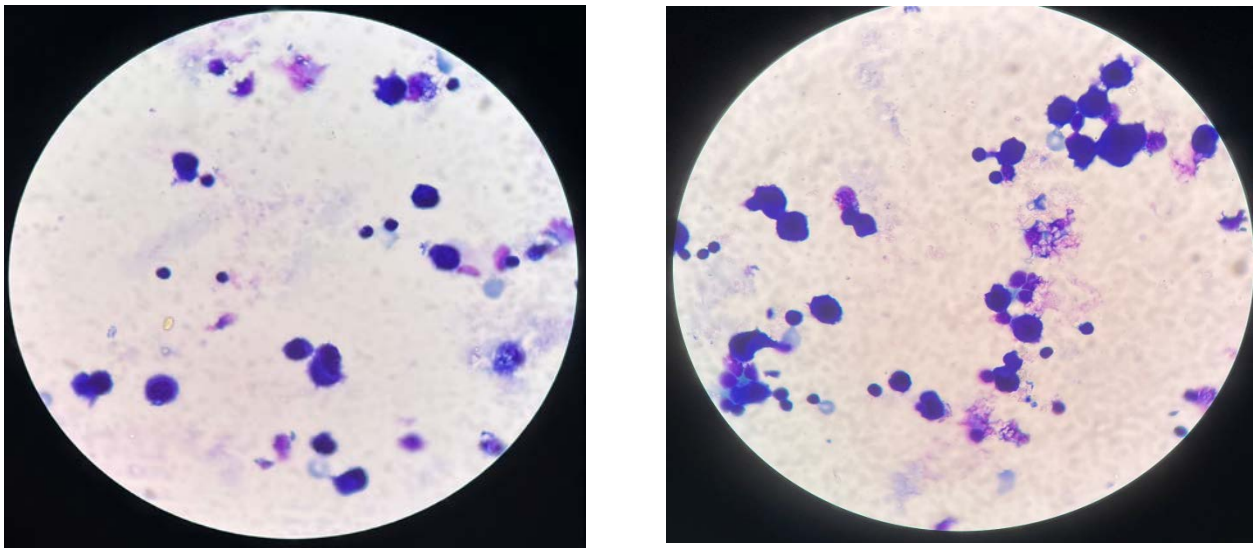


Figure-8: Plasma cells in cerebrospinal fluid

Discussion

Multiple myeloma (MM) is a hematological malignancy that develops due to malignant proliferation of plasma cells and is characterized mainly by involvement in the bone marrow. However, there is also the potential for spread to extramedullary regions in the course of the disease. Leptomeningeal involvement, which is among the neurological complications of MM and has been reported in a limited number of cases in the literature, has been brought to the fore once again with this case. Extramedullary involvements of MM are generally observed in the advanced stages of the disease or in case of relapse, and can sometimes be observed at initial presentation. The main reasons for these involvements include worsening of the patient's general condition, development of resistance to treatment, and the presence of some genetic mutations. Such complications often indicate aggressive forms of MM and require re-evaluation of treatment strategies. Neurological involvements occur especially as a result of the infiltration of plasma cells in neural tissues. This situation can both negatively affect the patient's quality of life and be a negative indicator for prognosis. Leptomeningeal involvement is a rare neurological complication of MM and often negatively affects prognosis. Management of leptomeningeal involvement requires early diagnosis and aggressive treatment strategies because this condition often occurs in advanced stages of the disease and can have serious clinical consequences. In the literature, studies addressing leptomeningeal involvement of MM emphasize the importance of this complication, despite its rarity, and the difficulties of response to treatment. In one study, Gozzetti et al. (2012) stated that intracranial and leptomeningeal involvements of MM may require different treatment approaches compared to standard MM treatments[14]. This study showed that intrathecal chemotherapy and radiotherapy may be effective in the management of leptomeningeal

involvement14. Additionally, research on the genetic and molecular mechanisms associated with the neurological manifestations of MM allows personalization of treatment strategies. Fonseca et al. Genetic and cytogenetic analyzes conducted by (2004) showed that certain chromosomal changes and mutations play an important role in the aggressiveness of MM and response to treatment[2]. In conclusion, leptomeningeal and cranial involvements of MM may have a significant impact on the course of the disease and response to treatment. Management of these complications requires a multidisciplinary approach and personalized treatment strategies based on the genetic and molecular characteristics of the disease.

This case report aims to draw attention to the rare neurological involvements of MM. It reminds us of the need to evaluate such rare complications in MM patients presenting with atypical neurological symptoms. Early diagnosis of the underlying causes of atypical symptoms, especially those encountered in the clinic, is essential in determining the prognosis and planning the most appropriate treatment approach for patients.

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