**Hypsarrhythmia and spasms resolution after Valproic acid discontinuation in an infantile spasm patient**

Mohammed S. Alsallumi, MBBS, SB-PN, SFEE.

**ABSTRACT**

Several studies have reported a variable benefit of valproic acid for the treatment of infantile spasm. However, valproic acid can also worsen spasms, as occurred with this child who presented with post-traumatic seizure which evolved to spasms. The child was started on antiepileptic medications, including valproic acid, despite that spasms persisted. For this reason, she was admitted for adrenocorticotropic hormone therapy. The baseline electroencephalogram showed modified hypsarrhythmia, and the laboratory workup showed thrombocytopenia, which was attributed to the valproic acid. After the valproic acid cessation, the spasms and the hypsarrhythmic pattern resolved dramatically next day, and the intended adrenocorticotropic hormone therapy was not started. Eight months later, she was still free of spasms. In conclusion, though valproic acid might have a beneficial effect in some patients with infantile spasm, it might have a negative impact on spasms in some patients which warrants its discontinuation sooner than later during spasms treatment.

Infantile spasm was first described in 1841 by James West in his own son. It is an age-specific epileptic disorder that mostly affects infants aged between 4 to 8 months, and the majority present before the age of 24 months. Classically, the spasms are characterized by bilateral, symmetric contraction of the axial muscles lasting for less than 2 seconds followed by less intense tonic contraction lasting between 2-10 seconds. The spasms occur in clusters separated by intervals of 5-30 seconds. As they are mostly occurring in infants with developmental delay, infants with infantile spasms are inevitably experience regression in their development and demonstrate a characteristic pattern of hypsarrhythmia on electroencephalogram (EEG).

The spasms are usually refractory to most of the conventional antiepileptic medications, and are usually associated with poor long-term prognosis. Although the treatment guidelines for infantile spasm are limited, hormonal therapy and vigabatrin have higher evidence of effectiveness in the treatment of infantile spasms. Other medications including topiramate, zonisamide, valproic acid, pyridoxine and ketogenic diet might...
help to reduce spasms frequency and are often used after ACTH and vigabatrin.\(^2,3\) Although the valproic acid produced benefits in spasms reduction,\(^6\) I am reporting this interesting case in which the valproic acid resulted in the perpetuation of the clinical spasms and electrographic hypsarrhythmia in a child with refractory epilepsy secondary to post-traumatic injury. Immediately after discontinuation of the drug, spasms and hypsarrhythmia resolved completely.

**Case Report.** *Patient's information.* A 24 months old girl a case of global developmental delay and symptomatic epilepsy secondary to severe traumatic brain injury due to a vehicle traffic accident at the age of 3 months. At that time, she was admitted and had several surgeries including a ventriculoperitoneal shunt for post hemorrhagic hydrocephalus. Post-discharge from the hospital, she continued to have unprovoked partial and generalized seizures. This evolved into spasms in the form of the whole body stiffening with flexion of arms and head deviation to the right side. Her eyes would be staring ahead during the event. She had these fits in 4-5 clusters per day, and these were more prominent upon awakening from sleep. She was initially treated with phenobarbital for the partial and generalized seizures, but when spasms developed, she was given valproic acid since the age of 4 months.

According to history, there was no clear change in the frequency of spasms after starting the valproic acid, however, no documentation from previous reports. Vigabatrin was given for 6 months without response. There was no clear documentation of EEG at the time of diagnosis nor during the course of illness. She was also prescribed levetiracetam without success. She was referred to our hospital for further management.

**Clinical findings.** On examination, she is markedly failing to thrive. She has Spasticity in all her limbs, deep tendon reflexes were exaggerated with clonus and planter reflex was upgoing. She is weaker in the left side in comparison to the right side. Systemic examination was unremarkable.

**Diagnostic assessment.** She was admitted at age of 24 months for ACTH therapy. A baseline EEG was carried out which showed modified hypsarrhythmia due to asymmetry in the form of hemihypsarrhythmia (Figure 1).

During the admission, she was found to have thrombocytopenia, at which point the valproic acid was discontinued. On the day after valproic acid was discontinued, the spasms stopped, although ACTH was not given. Repeat EEG 1 week later showed focal slowing over the right side with the resolution of the hypsarrhythmic pattern (Figure 2).

**Therapeutic intervention.** Because of the dramatic improvement of the spasms after valproic acid discontinuation, no therapeutic intervention was

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**Figure 1** - The baseline EEG, (Bipolar montage, sensitivity: 7 mV/mm, HF: 70 Hz, LF: 1 Hz) shows a disorganized, chaotic activity intermixed with high amplitude, multifocal spike and slow wave discharges in the right hemisphere, consistent with “Modified hypsarrhythmia”.

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Infantile spasms worsen with valproate … Alsallumi

Follow up and outcomes. The child was discharged home on no antiepileptic drugs and remained seizure free for 8 months post discharge. However, she developed focal seizures, which were treated with topiramate, with partial response. At the age of 5 years, she was still having focal seizures, and her development was severely delayed with spastic quadriplegia (Figure 3).

Discussion. Valproic acid is a broad-spectrum antiepileptic drug that is used for multiple types of epilepsy. Although there are no controlled trials supporting the use of valproic acid in the infantile spasm, the reported benefit of valproic acid in the infantile spasm patients is variable, with the degree of spasms reduction, ranging between 40% to 70% among patients who do not respond to ACTH. In another prospective study, 91 children were started on valproate, 39.5% of them showed a good response, but seven later relapsed while on the same dose of valproate.

In this case, the patient had a post traumatic partial and generalized seizures which evolved to the spasms semiology. Valproic acid was started and despite that, the spasms persisted. Once the valproic acid was stopped, the clinical spasms and the hypsarrhythmia pattern in the EEG resolved dramatically. Opposite to previous reports, in this case, the valproic acid acted as an exacerbating or emerging factor for her spasms. It is possible that resolution of spasms is a spontaneous remission due to increasing age of the patient; however, it is plausible to claim that it is related to discontinuation of VPA for the following 2 reasons; first, the spasms in this patient is symptomatic secondary to old traumatic brain injury which makes the spontaneous resolution less likely and, second, the time lock of cessation of...
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spasms immediately post discontinuation of the drug.

During the literature review for infantile spasms exacerbated by valproic acid, I identified one reported case by Itonaga et al. In this case, the spasms were exacerbated after the valproic acid administration. As per the authors, it induced a novel complex partial seizure, suggesting that the patient had distinctive clinical seizures due to non-ketotic hyperglycinemia.

In addition to the clinical spasms exacerbation, other adverse effects could occur when the valproic acid is introduced to the infantile spasm patients. Sivathanu et al. reported an infant with infantile spasm that started on sodium valproate, clonazepam and ACTH. After a period of improvement, she developed signs of encephalopathy including vomiting, altered level of sensorium and increased the seizures frequency which was dramatically improved after the valproic acid stopped. The encephalopathy was attributed to the valproate-induced hyperammonaemia or hepatic encephalopathy.

Unfortunately, the ammonia level in our patient was not ordered when the patient was receiving valproic acid which could cause hyperammonemia. However, such induced hyperammonemia is usually associated with encephalopathic clinical features rather than the spasms emergence or aggravation. The epilepsy etiology for the patient is post traumatic which had evolved later to the spasms. However, the reason of the dramatic spasms resolution after the valproic cessation remains unclear.

In conclusion, though valproic acid might have a beneficial effect in some patients with infantile spasm, a negative impact on spasms might also be encountered, which warrants discontinuation of this drug sooner than later during spasms treatment.

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References

Multiple Sclerosis Patients Knowledge in Saudi Arabia

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ABSTRACT

Objectives: To assess Multiple Sclerosis (MS) patients' knowledge in Saudi Arabia (SA) and in which aspect of the disease do patients need more awareness.

Methods: A cross-sectional web-based survey has been conducted between June and August 2017. It consisted of 2 parts: sociodemographic and 23 multiple choice questions chosen from the previously validated MS Knowledge Questionnaire (MSKQ). The survey has been sent to 500 MS patients.

Results: A total of 218 MS patients filled the questionnaire where only 200 included in the study. Female MS patient represents 66% of all the participants. More than half of the patients had achieved their bachelor degree. The total mean of the correct answer for both male and female found to be 58.98% (±SD 15.06%). Most patients were aware that MS is a disease of central nervous system (93%), autoimmune disease (79%), not contagious (90.5%), or inherited (64.5%). However, few patients were aware that there is no single test to diagnose MS (28.5%), and intravenous injection of contrast during MRI reveals new lesions (18.5%). Only (37%) knew what is "Relapsing–remitting" MS. The MS knowledge is positively correlated with the educational level.

Conclusion: Patients with MS in SA have less knowledge in the disease's types, workups, and treatment efficacy. While in contrast, they have more awareness of the disease's pathophysiology. Patient's awareness programs should aid more knowledge among MS patients in SA.

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MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune, chronic, inflammatory disease of the central nervous system; its behavior is highly varied and unpredictable, and the cause, until now, is not known. Nevertheless, it appears to be multifactorial; it involves a combination of genetic and environmental factors. Moreover, it is a common autoimmune disease of the central nervous system.

The prevalence of MS in the Middle East is low to medium. Incidences of MS in the Gulf countries including Saudi Arabia, in particular, suggest an indication of its increase. The prevalence of the disease in Saudi Arabia has not been studied yet. Not to mention that MS awareness and knowledge is sub-optimal in the country.

Patients’ knowledge of pathophysiology, types, diagnostic modalities, and medication effectiveness is critical to facilitate decision-making, achieving emotional stability, and help the patient cope with the disease. Because of the lack of published research in this area, as the literature review of this study indicates, the aim of this study is to measure patients’ knowledge of MS.

Methods. This study has conducted a web-based survey in Arabic, “MS Patients Knowledge in Saudi Arabia,” where patients recruited with the help of ARFA” patient support group for MS in Saudi Arabia.” “www.arfams.org.sa” is an authenticated society by Ministry of Social Affairs in Saudi Arabia. Its base is in Saudi Arabia, and it is a non-profit organization that helps people affected by MS by facilitating professional education and providing programs and services that are of help to them and their families. This cross-sectional survey has been conducted over a period of 3 months, between June 2017 and August 2017. It consists of 23-multiple choice items, following a validated questionnaire carried out in Italy, MSKQ-25, to assess the current survey. There has been an exception of 2 questions, which was about the disease's prevalence in Italy (Q3), and it has been deleted in the current survey because there has been no study in Saudi Arabia to determine the prevalence accurately yet. The second deleted question (Q20) was about MS diagnosis because of unclarity of the question.

We included MS patients with age from 18 years old or above. Unconfirmed or suspected cases were excluded. The questionnaire is divided into 2 sections; the first section is a sociodemographic information that consists of 6 items including gender, age, marital status, educational level, occupation, and residence. The second section is 23 Questions from the MSKQ-25 (Multiple Sclerosis Knowledge Questionnaire) self-administered instrument. Permission to use this tool has been taken from the corresponding author. We used the Statistical Package for Social Sciences (SPSS

www.nsj.org.sa Neurosciences 2018; Vol. 24 (4) 327
Inc, Chicago, IL, USA) version 16 to do the analysis. Chi-square, ANOVA, and T-test were used to calculate the P-value. Differences were considered statistically significant at a level of <0.05.

**Results.** The response rate was 43.6% (218 from 500). 18 cases were excluded because 13 were not sure about the diagnosis of MS and 5 were duplicated cases. A total of 200 cases included in the analysis. The average MSKQ score of the whole group is 13.57±SD 3.46 (58.98%±SD15.06) out of the 23 questions. The minimum score is 4 (17.4%), and the maximum score is 21(91.3%) out of 23. The median is 14(60.9%), and the mode is 16 (69.6%).

Table 1 shows the demographics of all the patients with their average MSKQ score. Only 19 (9.5%) with the educational level of less than a high school and the rest are equivalent or higher. 99 (49.5%) were unemployed. The majority of the participants 74(37%) were from the central region of Saudi Arabia.

Table 1 shows the average MSKQ score across various demographics. The mean score of the female was slightly higher than the male without statistical significance.

There is no difference in the average score concerning the age, residence and the social status of the patients. There is an increase in the average MSKQ score with the increase of the level of education. However, it did not reach the statistical significance. Looking into the occupation part, patient working in the healthcare
scored higher with statistically significant p-value (0.003).

Table 2 show the percentage of the correct answer regarding each question. We divided them into three groups according to their score. 90 patients scored less than 60% while only 25 scored more than or equal to 75%. Questions 1, 6, 15, and 24 were the most correctly answered by the participants. Questions 7, 9, and 16 were answered only by a small proportion (i.e., less than 25%).

From the pathophysiological aspect, 93% of patients answered that MS is a disease of central nervous system. 60.5% of them are aware that central nervous system consists of the brain, spinal cord, and optic nerves. 79% of patients know that it is an autoimmune disease. 69.5% answered that MS injures the myelin. 71% know that myelin facilitates and speeds up the signals transmission between neurons, while the rest, 22.5%, selected “I do not know”. Most of the participants recognize correctly the most affected age 77.5% and the gender ratio as well 86% (Table 2).

Considering the reasons for the disease, the majority of patients (68%) do not know what the actual cause of illness is, 19% think that Diet and smoking cause the disease, while (13%) believe that genetic together with infection play a major role in having the disease. Most of them believe it is not a contagious illness (90.5%), while only 2% believe it is, the rest did not know (7.5%).

In regard to the awareness of Genetic rule, some participants (5.5%) believe that the disease can be transmitted via the chromosome from parents to their children, the majority, (64.5%), believe it is not, while the rest (30%) do not know. Around one fifth 21% of the patient participated recognized correctly that having a relative with MS put the person at slightly higher risk of developing MS. On the other hand, 4.5% think that having a relative with MS will increase the risk significantly. 27% of the patient believe that it does not change the risk and 47.5% choose “I don’t know.”

Around one third (28.5%) know that there is no single test to diagnose MS and almost (56.5%) believe...
that there is a single diagnostic test to confirm the diagnosis of MS. Nearly all (96.5%) agree that MRI is the examination most commonly used to confirm the diagnosis of MS. By comparing MRI with Intravenous injection (gadolinium), only 18.5% of the participants know that gadolinium during MRI reveals new lesions, 1.5% believe it reveals old lesion, while the rest of them either don't know 27.5% or think it reveals both old and the new lesion 52.5%. Eighty-two and five percent are aware that MRI at repeated intervals is better to follow the disease course over time, while 4.5% think the repeated MRI is not a better way to monitor the disease course and 13% do not know. In comparison, 42% are aware that Lumbar puncture at repeated intervals is not a better way to follow disease course over time, 49.5% do not know if it is better to follow disease course over time, and 8.5% think it is better to follow disease course over time. Fifty-one percent of the participants do not know that Lumbar puncture sample shows immunological reaction, while 44.5% do know. Only 4.5% are sure that Lumbar puncture sample does not demonstrate any immunological response.

Considering “Relapsing–remitting” MS, which is the most common type, 37% know that it is a form of repeated relapses at more or less frequent intervals. One third (32.5%) think it is a slow and progressive deterioration in functioning and 30.5% do not know. Regarding “Benign” MS, 54% of patients do not know what “Benign” MS is. Thirty-two and five percent know it is a minimal deterioration in functioning in 15–20 years after disease onset, while only 13.5% think it is a decline in functioning in one year after disease onset.

Considering Treatment efficacy, 91% of the patient knows that there is no cure for MS. Moreover, 34.5% think treatment is only effective in “Relapsing–remitting” MS, only 2.5% believe that it is effective in “Primary progressive” MS, and 44.5% think it is effective in both.

Considering disease prognosis in general 60.5% of the patients know that MS does not shorten lifespan significantly, while 7% believe it does, the rest do not know 32.5%. About the effect of pregnancy on MS, 63% know it does not get worse during pregnancy, 5.5% think it does, while 31.5% do not know.

Discussion. The average MSKQ score of the whole group is 13.57±SD 3.46 out of the 23 questions. The minimum score is 4 (17.4%), and the maximum score is 21(91.3%) out of 23. This result is comparable to another cohort of MS patient filled the same MSKQ. Their average was 15.6±3.9. The minimum and highest scores were 3 and 24 out of 25. We used the same questionnaire except deleting 2 questions (see reasons above).

If we further compare the result of the 2 surveys, they are exactly the same in questions with highest correct answers (Table 2). These were questions about: “MS as a contagious disease,” “organ involved in MS,” “role of MRI in the diagnosis of MS” and “absence of curative treatment” (Q6, Q1, Q15, and Q24 respectively). On the other hand, the lowest answered questions differ largely. They only share the item number 16 about “the role of Gadolinium injection during MRI” (Table 2). Other lowest score were in the Q7 “MS etiology” and Q9 “MS transmission to other family members.”

There are only a few other studies carried out assessing patient knowledge. The mean score knowledge about the interferon in one study was low. In another study the mean score of knowledge was 6.4 (SD 2.4) corresponding to a 34% of possible correct answers. This also applies to knowledge about the risk of treatment with MS medication. A survey showed that only 21% of the MS patient have adequate knowledge about treatment risk before engagement in any basic education program.

Although in one old survey the younger patient tends to know more about the disease, there was no association between the patient knowledge and with the length of illness or level of disability. The majority of the patient in this survey did not consider MS as an infectious (97.2%). On the other hand (86.1%) agree that it is not a hereditary disease. In our group, 90.5% agree that MS is not contagious. On the other hand, only 64.5% and 21% answered correctly when asked about the MS transmission to offspring and other family members (Q8 and Q9 respectively).

In our cohort, there was no statistically significant difference in the knowledge among different age group. On the other hand, one knowledge assessment study among MS patient found a negative correlation between the knowledge and age.

One of the limitations of our study is that we lack the disease duration. Although there are discrepancies between the studies carried out in the past, one found no correlation and one concluded that the highest knowledge about the disease found in a patient with short disease duration.

Patient knowledge about the disease is crucial especially dealing with a lifelong chronic illness. It can help them in various aspect of the disease. Patient, good understanding about the illness is essential also to avoid the fear of the future as one study found that good patients’ knowledge was associated with less fear of disease progression. There are many elements regarding MS that need more education. However, the
most chosen area of interest for MS patient include symptomatic treatment, MRI, relapses, and role of complementary medicine.11

In Conclusion, MS patients in Saudi Arabia have less knowledge about some aspects of the disease's types, investigation modality, treatment efficacy and genetic role, while, in contrast, they have more awareness of the disease's mechanism and nature. Patient awareness programs should aid more knowledge among MS patients in Saudi Arabia and be delivered by medical health providers. Having more knowledge of the disease leads to a sense of understanding. This will help in achieving the emotional stability and aid more compliance to medications.

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References

Pediatric intracranial hypertension

Experience from 2 Tertiary Centers

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ABSTRACT

Objectives: To review the experience of 2 tertiary centers in Saudi Arabia with intracranial hypertension (IH) in the pediatric population.

Methods: We retrospectively reviewed and analyzed pediatric patients diagnosed with IH from June 2002 to May 2017 in 2 institutes.

Results: We identified 53 patients (30 females and 23 males) with a mean age of 7 years at the time of presentation. Among them, 41 patients were younger than 12 years, and 12 were older. Obese and overweight patients constituted 27.00% (n = 14) of all cases, 8 (66.7%) of whom were older than 12 years. The most common presenting feature was papilledema followed by headache. Vitamin D deficiency, which constituted the most common associated condition, was identified in 12 (22.6%) patients. Acetazolamide was the treatment option in 98.11% of patients, and only 5.7% underwent surgical interventions. The length of follow-up ranged from 6 months to 8 years.

Conclusion: Intracranial hypertension is rare in children and commonly seen in overweight females older than 12 years similar to adults. Patients younger than 12 years tend to develop secondary IH. More studies are needed to characterize the clinical presentation and guide the management plan.

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Intracranial hypertension (IH) is rarely reported in children. It is characterized by increased intracranial pressure (ICP) without any evidence of underlying brain pathology, structural abnormalities, hydrocephalus, or any abnormal meningeal enhancement.¹ The incidence of IH differs from region to region due to variations in the prevalence of obesity and other secondary causes. The annual incidence of IH in children is 0.9 per 100,000 in the United States,² 0.5 per 100,000 in Germany,³ 0.6 per 100,000 in Nova Scotia and Prince Edward Island in Eastern Canada,⁴ and 1.2 per 100,000 in Croatia.⁵ A study carried out in Oman estimated the incidence of IH to be 1.9 per 100,000 in children below 15 years of age; with it being higher in female children.⁶ The present study aimed to review the clinical presentation, possible aetiological factors, diagnosis, management, and outcomes in children with IH in 2 tertiary institutes in Saudi Arabia.

Methods. After approval of the study proposal by the Research Ethics Committee at King Saud University, and King Abdullah Research Center, we did a retrospective review of all pediatric patients diagnosed with IH between June 2002 to May 2017 at King Saud University Medical City and King Abdullah Children Specialist Hospital, National Guard Health Affairs. Patients with identified aetiologies were classified as having secondary IH (SIH), and patients without identified aetiologies were classified as having idiopathic or primary IH (PIH). The following parameters were recorded: patients’ characteristics, age at the time of presentation, presenting symptoms and signs, associated conditions, diagnostic procedures, brain images, treatment, and outcome. IH was defined based on the modified Dandy criteria.⁷ The inclusion criteria were: patients aged between 6 months and 18 years, normal brain magnetic resonance imaging (MRI) and/or computed tomographic (CT) scan, a cerebrospinal fluid (CSF) opening pressure greater than 250 mm H₂O with normal CSF analysis, bilateral papilledema, and intact neurologic examination except for isolated abducens, trochlear or oculomotor paresis. We excluded patients who had abnormal CSF study results, normal or undocumented ICP pressure, brain imaging showing structural abnormalities, and abnormal neurological examination other than sixth nerve palsy or papilledema.

We identified a total of 64 cases; 11 were excluded for missing data, lack of documentation, or inability to meet the inclusion criteria, thus resulting in the inclusion of a final 53 patients. We classified the patients as either prepubertal or pubertal. The use of secondary sexual characteristics is often the proper method to classify children as either pubertal or prepubertal. However, due to the retrospective nature of this study, we instead chose an average age. Therefore, patients younger than 12 years were considered prepubertal, while patients older than 12 years were considered pubertal. Based on their body mass index (BMI), we further classified the patients into three groups: obese, overweight, or normal body weight. A child was described as obese if the BMI was more than 30 and overweight if the BMI ranged between 25 and 29.9.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 19 (IBM Corp., Armonk, N.Y., USA).

Results. A total of 53 children with IH were analyzed in this study. The mean age of the patients at presentation was 7.7 years, ranging from 8 months to 16 years. Twenty-three children were male and thirty were female. Most individuals (n=36 [69.2%]) had normal weight, 7 (13.5%) were overweight, and 7 (13.5%) were obese. The demographics of the participants are shown in Table 1. In the present study, 12 patients were 12 years and older (pubertal group) and 41 patients were younger than 12 years (prepubertal group). The mean age at presentation in the pubertal group was 13.66±1.66 years (range=12-16 years) and 5.9±3.38 years (range=8 months -11 years) in the prepubertal group. The percentage of females in the prepubertal group was 52.63% and pubertal group was 66.66%. Obese and overweight patients constituted 27.00% (n=14) of all cases, and 66.7% (n=8) of those in the

### Table 1 - Demographics of the participants.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td><strong>Age (prepubertal group)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>3 (7.31)</td>
</tr>
<tr>
<td>1-6 years</td>
<td>20 (48.78)</td>
</tr>
<tr>
<td>&gt;6 years</td>
<td>18 (43.9)</td>
</tr>
<tr>
<td><strong>Sex (total group)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (43.4)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (56.6)</td>
</tr>
<tr>
<td><strong>BMI (total group)</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>36 (69.2)</td>
</tr>
<tr>
<td>Overweight</td>
<td>7 (13.5)</td>
</tr>
<tr>
<td>Obese</td>
<td>7 (13.5)</td>
</tr>
<tr>
<td>Asymptomatic Papilledema</td>
<td>16 (30.2)</td>
</tr>
<tr>
<td>Symptomatic Papilledema</td>
<td>35 (66.0)</td>
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</tbody>
</table>

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Table 1 - Associated conditions and medications (Secondary Intracranial Hypertension).

<table>
<thead>
<tr>
<th>Associated conditions</th>
<th>n (%)</th>
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</thead>
<tbody>
<tr>
<td>Vitamin D deficiency</td>
<td>12 (22.6)</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>4 (7.5)</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>4 (7.5)</td>
</tr>
<tr>
<td>ADHD</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>2 (3.8)</td>
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<tr>
<td>Achondroplasia</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Acute lymphoblastic leukaemia</td>
<td>1 (1.9)</td>
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<tr>
<td>Atrioseptal Defect</td>
<td>1 (1.9)</td>
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<tr>
<td>Autoimmune thyroiditis</td>
<td>1 (1.9)</td>
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<tr>
<td>Bronchial asthma</td>
<td>1 (1.9)</td>
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<tr>
<td>Cataaract</td>
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<tr>
<td>Mucopolysaccharidosis type VI</td>
<td>1 (1.9)</td>
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<tr>
<td>Middle East Syndrome</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Minimal change disease</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>MLC 1 gene mutation</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Epilepsy during infancy</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Retinitis pigmentosa</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Skeletal dysplasia</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Subaortic stenosis</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Sagittal “Dural” sinus thrombosis</td>
<td>1 (1.9)</td>
</tr>
</tbody>
</table>

Medications

<table>
<thead>
<tr>
<th>Medications</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>2 (3.77)</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Steroid</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1 (1.9)</td>
</tr>
</tbody>
</table>

ADHD - Attention deficit hyperactivity disorder

Table 2 - Surgical treatment and recurrence.

<table>
<thead>
<tr>
<th>Surgical treatment &amp; recurrence</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical treatment</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (5.7)</td>
</tr>
<tr>
<td>No</td>
<td>50 (94.3)</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (13.2)</td>
</tr>
<tr>
<td>No</td>
<td>46 (86.8)</td>
</tr>
</tbody>
</table>

Papilledema was asymptomatic in 16 (30.2%) patients. Other common symptoms included visual problems such as photophobia, diplopia, and blurred vision. Neurologic examination was reported as normal in 29 (54.71%) patients, and sixth nerve palsy was present in 4 (7.54%) patients. All the patients had an insignificant perinatal history, except 2 who were born prematurely at 30 and 34 weeks of gestation. The clinical features of the patients are shown in Table 1. Figure 1 & 2 demonstrates papilledema in some of the patients.

Out of the 53 patients, 13 patients had PIH (idiopathic) and 40 patients had SIH (Table 2). There were no significant differences in gender, age at presentation, or BMI between the PIH and SIH patients. Interestingly, 16 (44.4%) patients with SIH required additional lumbar puncture (LP). In terms of outcome, the recurrence in the SIH group was high (n=6 [19.4%]), whereas only one patient had a recurrence in the PIH group. At the time of presentation, majority of the patients (n=47 [88.7%]) were not on any medications except for 2 (3.77%) who were on carbamazepine, one (1.9%) who received growth hormone therapy, one (1.9%) on steroids and cyclosporine, and one (1.9%) on methotrexate (Table 2). Lumbar puncture was carried out in all cases. Opening pressure was high in all patients. Cerebrospinal fluid analysis was normal in all patients. All patients underwent neuroimaging studies, including CT and/or MRI brain scans. Four (7.5%) patients had craniosynostosis. Magnetic resonance venography (MRV) had been performed in 37 (69.8%) patients. Sagittal dural sinus thrombosis was evident in one patient. The MRI showed typical IH features in more than half of the patients 36 (67.9%). Figure 3 demonstrates the findings in one of the patients. Further laboratory tests were performed in most patients and included the thyroid function test, antinuclear antibody test, and C3, C4 and 25 (OH) vitamin D levels. All these tests showed normal results except for 25 (OH) vitamin D levels, which were low in 12 (22.6%) patients.

The majority of patients (n=52 [98.1%]) were treated with acetazolamide as first-line therapy. Only one patient was treated with topiramate alone. Out of the 52 patients who received acetazolamide, 29 (54.71%) did not require further treatment. Most patients (n=50 [94.3%]) did not require surgical intervention, and only 3 (5.7%) patients underwent surgical treatment (lumboperitoneal shunt). According to the long term outcome, there were no relapses in 46 (86.8%) patients. None of our patients had optic nerve fenestration. The surgical treatment and recurrence are summarized in Table 3. The length of follow-up ranged from 6 months to 8 years.
Discussion. The IH is typically present in overweight women; however, it can occur at any age. Unlike in adults, several studies have found that IH in prepubertal children is less commonly associated with obesity, and has no female predominance. On the other hand, IH in postpubertal children is usually similar to that in adults, and is associated with overweight and commonly occurs in women. In our study, obese and overweight patients constituted 27.00% (n=14) of all cases, a majority of whom were pubertal. This classification is rarely done in pediatric IH cases reported in the literature.

As the name implies, the pathophysiology of IH is not fully understood. There are several proposed hypotheses such as increased CSF production, decreased CSF outflow, increase in cerebral blood volume, increase in water content, venous obstruction, chronic inflammation, and metabolic causes. Obesity is an important risk factor for IH in postpubertal females. However, the absence of obesity and sex predilection in some prepubertal children and adolescents with IH suggests a different pathogenesis in these patients. Hence, a secondary cause should be carefully investigated and ruled out before making a diagnosis.

Additionally, IH can also be secondary to an underlying medical condition or use of certain medications. In a recent study of IH in the pediatric population, 30% of the cases were found to have a secondary cause. Several factors have been associated with IH in pediatric patients. These include hyperparathyroidism, thyroid replacement therapy, treatment with recombinant human growth hormone, Chiari malformation, meningitis, hydrocephalus, craniosynostosis, traumatic brain injury, superior sagittal sinus thrombosis, leukemia, congestive heart failure, renal failure, and kidney transplantation. In a recent study, vitamin D deficiency was found in 26.3% of pediatric IH patients, with none of them having hypocalcemia or signs and symptoms of rickets. In our study, 12 (22.6%) cases were found to be associated with vitamin D deficiency. The exact pathophysiology of increased intracranial pressure in relation to vitamin D deficiency is not fully known. In the present study, one case of hypoparathyroidism-retardation-dysmorphism syndrome, also known as Middle east syndrome or Sanjad-Sakati syndrome (OMIM # 241410), had IH possibly resulting from the associated hypoparathyroidism, a recognized risk factor of IH.

The most common clinical presentation in children is headache. Other clinical features include nausea and vomiting, blurred vision, and double vision. The neurological examination of children with IH is usually normal except for papilledema, decreased visual acuity, visual fields defects, neck stiffness, and sixth nerve palsy. Although papilledema is an important sign in children...
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with IH, the absence of papilledema does not rule out IH.\textsuperscript{17,18} A previous study reported that papilledema was absent in 48% of the patients. Interestingly, one of our patients (1.9%) did not have papilledema at the time of presentation.

Imaging studies are essential in the diagnosis of this condition. A CT scan should be done first, and if the findings are normal, then a lumbar puncture with opening pressure should be performed.\textsuperscript{19} Further tests should be considered to rule out secondary causes. Brain MRI is used to rule out intraparenchymal lesions, abnormal meningeal enhancement, or hydrocephalus.\textsuperscript{20} The MRV is used to rule out cerebral venous sinus thrombosis.\textsuperscript{20} MRI findings suggestive of IH in children include: posterior globe flattening, intraocular protrusion of the optic nerve, horizontal tortuosity of the optic nerve, optic nerve sheath enlargement, and decreased size of the pituitary gland.\textsuperscript{21,22} Lumbar puncture is indicated to measure the CSF opening pressure and to exclude meningitis.\textsuperscript{1,23} Diagnosis of IH is made according to the modified Dandy criteria.\textsuperscript{1} However, new criteria in children involving a specific CSF opening pressure have been introduced into the literature by Friedman and his colleagues.\textsuperscript{24} The criteria also take into consideration the diagnosis of IH when the presentation is not clear or atypical. In this study, SIH was more common than PIH, especially in children under 12 years. Moreover, IH was strongly associated with syndromes such as craniosynostosis and Down syndrome or other medical problems such as vitamin D deficiency. Different treatment modalities have been indicated;\textsuperscript{25,26} however, the selection of medical, surgical, or combined treatments relies on the severity of the visible signs and symptoms. Medical treatment, including carbonic anhydrase inhibitors, which have been used to lower ICP, is initially indicated. The most commonly used carbonic anhydrase inhibitor is acetazolamide, which is usually used as first-line therapy.\textsuperscript{1} Its use has been thoroughly studied and is thought to decrease production of CSF in the choroid plexus. However, the use of topiramate has not been as thoroughly examined as a monotherapy agent for IH in adults or children. Topiramate is used for the treatment of IH through its inhibitory effect on carbonic anhydrase enzyme, which also causes mixed renal tubular acidosis. Moreover, its side effect of appetite suppression makes it an effective adjunct agent for individuals with obesity.\textsuperscript{27} In our study, medical treatment was effective in most cases (86.8%), with four cases being treated by topiramate. Additionally, steroids can be used to reduce intracranial pressure rapidly. Nonetheless, it is only recommended for short-term use in severe cases where surgical intervention is not immediately possible.\textsuperscript{28} In our study, steroids were only used in 4 cases.

Surgical treatment in the form of optic nerve sheath fenestration (ONSF) and CSF diversion is indicated when medical treatment fails to lower ICP.

Figure 3 - MRI Brain and orbit for a 10-year-old girl with primary IH. MRI sagittal T1WI brain. A) showing partial empty sella (white arrow). Axial T2 fat saturation for orbits, B&C) showing flattening of posterior sclera and prominence of the optic nerve head (black arrow) as well as tortuosity of optic nerve and prominent perioptic nerve sheath (white arrow).
or when the visual impairment is deteriorating. The most commonly used CSF diversion procedures are lumboperitoneal and ventriculoperitoneal shunting, with lumboperitoneal shunting being reported as the most successful in relieving symptoms. Only three patients in this study required surgical management in the form of lumboperitoneal shunting. ONSF is indicated for acute, severe, or progressive vision loss despite maximum medical treatment. None of our patients underwent ONSF.

Additionally, lifestyle modifications such as weight reduction in overweight and obese patients can decrease the symptoms associated with IH in adults. However, in the presence of visual deterioration, weight loss alone is insufficient to reduce ICP within the appropriate time. Interestingly, bariatric surgery can be considered in morbidly obese IH children who failed multiple trials of weight loss, with favorable outcome. During the follow-up period, 7 (13.2%) cases had a recurrence. Previous studies have reported an IH recurrence rate in children of up to 18-22%. Although visual loss in pediatric patients with IH has been previously reported, permanent vision loss in is usually rare. In our study, most patients did not have any signs or symptoms of visual deterioration.

Study limitation. This study has several limitations, including its retrospective nature and small sample size. In conclusion, IH in children is rare and differs from that in adults. Unlike in adults, IH in pre-pubertal children is less commonly associated with obesity, has no female predominance, and more commonly manifests as SIH. On the other hand, IH in postpubertal children is usually similar to that in adults, and is associated with overweightness as well as female predominance. Our study adds to the body of evidence by reporting on our institutions’ experience with IH in the pediatric population.

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References

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Authorship entitlement

Excerpts from the Uniform Requirements for Manuscripts Submitted to Biomedical Journals updated November 2003.
Available from www.icmje.org

The international Committee of Medical Journal Editors has recommended the following criteria for authorship; these criteria are still appropriate for those journals that distinguish authors from other contributors.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
An author should be prepared to explain the order in which authors are listed.
Clinical Notes

Unilateral headache and convulsive-like movements as a manifestation of pontine warning syndrome

Hussein A. Algahtani, MD, FRCPC, Bader H. Shirah, MS, Yehya A. Seddeq, MD, Sarah A. Alshehri, MD.

Stroke is considered as the third most common cause of death and the single most common cause of disability worldwide.1 Headache often accompanies stroke with a prevalence varying between 7% and 65% depending on different data sources.2 In 1664, Thomas Willis described the autopsy finding of a patient who reported a right-sided headache and was found to have asymptomatic ipsilateral carotid artery occlusion. He also found dilatation of the left carotid and vertebral arteries up to 3 times the normal size.3 Since then, numerous papers were published regarding headache caused by different cerebrovascular lesions and the relationship between migraine and stroke.4 In this report, we present a case of a man who developed a new headache occurring for the first time with close temporal relation to vertebrobasilar insufficiency. In addition, a convulsive motor phenomenon is described in this case report which was difficult to differentiate from epileptogenic seizures. The case was challenging due to several difficulties including the delay in diagnosis, timing of neuroimaging, and the subsequent development of ischemic pontine stroke with no thrombolysis offered.

A 73-year-old male who was previously healthy until the day of presentation to the Emergency Department when he complained of sudden severe left temporal and retro-orbital headache that lasted minutes followed by dysarthria, facial asymmetry, and dense right hemiplegia. His weakness lasted only 20 minutes with full recovery. He was admitted to the hospital and was started on dual antiplatelet therapy including aspirin 81 mg daily and clopidogrel 75 mg daily. He was diagnosed as a case of transient ischemic attack. An extensive workup was carried out including electrocardiogram, echocardiography, computed tomography (CT) scan of the head, Doppler carotid, and all results came back unremarkable. On the third day following admission, he had 3 more similar attacks with each lasting 30 to 60 minutes. Interestingly, he developed brief intermittent right leg jerky movement that was described as a recurrent clonic movement of the right leg with each attack of transient ischemic attack with resolution once the symptoms disappear. The right leg jerky movement was not associated with loss of consciousness and not responding to 2 anti-epileptic medications (Levetiracetam and Lamotrigine). Routine electroencephalogram failed to show any abnormality. Both CT perfusion and magnetic resonance imaging (MRI) of the brain with diffusion were done which were absolutely normal. On the fifth day of admission, he developed another similar attack with persistence of dysarthria and hemiplegia. Neuroimaging was not repeated due to a refusal of the neuroradiologist to perform any further studies given the numerous normal previous examinations. Two days later and after a lengthy discussion, MRI of the brain was repeated, which demonstrated an acute infarction of the left medial aspect of the pons (Figure 1A). Magnetic resonance angiography of cerebral vasculatures demonstrated irregularity involving the left vertebral artery and basilar artery with mild luminal stenosis suggestive of atherosclerosis (Figure 1B). His past medical history was only remarkable for hypertension with no history of migraine, dyslipidemia, cardiac disease, trauma, and neck pain. Family and social history were all unremarkable. Clinically, the patient had right facial asymmetry, dysarthria, and dense hemiplegia. Upper extremities showed a power of 0/5 and the lower extremities showed a power of 3/5. He had right Babinski sign, and the rest of the examination was unremarkable. Thrombolysis was not offered to the patient, and he was transferred to a rehabilitation center for further management including physiotherapy and occupational therapy. The patient was seen in the clinic 6 months following discharge with remarkable improvement in his motor functions and speech.

Headache attributed to ischemic stroke is described as “a new headache developing simultaneously with or in close temporal relationship to signs or other evidence of ischemic stroke associated with neuroimaging confirmation of ischemic infarction”. When a new headache occurs for the first time in close temporal relation to symptoms and signs suggestive of a vascular disorder, it should be considered and coded as a secondary headache disorder until proven otherwise. This is also true if the headache has the clinical characteristics of primary headache disorders such as migraine or cluster headache. Factors that support adding the diagnosis of a secondary headache disorder (vascular) include a close temporal relation to the vascular disorder, marked worsening of the pre-existing headache, good evidence that the vascular disorder can aggravate the headache, and improvement of the headache after the acute phase of the vascular disorder.5 In our patient, the headache was new with a close
temporal relation with the signs and symptoms of stroke including dysarthria and hemiplegia. Unfortunately, frequently performed neuroimaging including CT and MRI were unremarkable, which made the treating team diagnose him as a primary headache disorder, mainly hemiplegic migraine. For this reason, he was not offered thrombolytic therapy despite labeling him in our rounds as the gentleman with “Willis Headache”.

The headache of ischemic cerebrovascular disease is usually unilateral, focal, of mild to moderate severity, and likely to be abrupt or gradual in onset. In 1940, Ray and Wolff observed that stimulation of a single vessel in the meninges and at the base of the brain resulted in an ipsilateral headache, which is in accordance with several recent and extensive studies. In 1962, Williams and Wilson\(^3\) reported that 21-53% of patients with vertebrobasilar insufficiency developed occipital headache that was either lateralized or nonlateralized. It was described as throbbing or bursting in nature that is frequently accentuated by stooping and straining. Rarely, headache was localized to occipitofrontal or frontal distributions (lateralized or nonlateralized) and was described as band-like. Several studies reported that anterior circulation stroke (carotid) usually give rise to frontal headache and that posterior circulation strokes cause occipital headache.\(^2\)

The capsular and pontine warning syndromes are defined as a subset of crescendo transient ischemic attacks and characterized by repetitive episodes of motor dysfunction due to ischemia in the region of internal capsule and pons, respectively. Since its first description by Donnan et al\(^4\) in the 1980s, several reports were published regarding this vascular entity. Upon reviewing the literature, none of these reports described headache as part of the symptoms of this syndrome.

The pathophysiological mechanisms behind the development of headache in association with acute ischemic stroke include hemorrhagic transformation, edema, and changes in the trigeminovascular system. The headache symptoms is more likely to occur in the posterior circulation strokes compared to strokes in other vascular territories. This could be due to the heavy innervation of the cerebral vasculature of meninges in the posterior circulation by nociceptive afferents. Another possible explanation includes vasodilation of arteries following emboli or thrombus formation in the base of the brain or occlusion of several arterial branches leading to change in the vascular perfusion. A further mechanism may be the release of vasoactive substances (e.g. serotonin and prostaglandin) from activated platelets.\(^1,2\) The trigeminal nerve has an important role in pain transmission and blood flow control. This is indicated by the circumscribed unilateral headache and pain referred to the cutaneous receptive field of the first trigeminal division. The pial nerve fibers are of trigeminal origin, and the perivascular nerve fibers contain vasoactive neuropeptides (e.g. calcitonin gene-related peptide and substance P), which on release into the vessel wall, increase blood flow and vascular permeability. The origin and distribution of the perivascular afferent fibers explain several unique features of vascular headache. For example, the predominantly ipsilateral distribution of trigeminal fibers explains the strictly ipsilateral distribution in many vascular headaches. In addition, the bilateral innervation of certain vessels (e.g. anterior cerebral artery) explains the bilateral or even contralateral location of the headache in diseases affecting these vessels. Moreover, the dual innervation of the superior cerebellar artery and the rostral basilar artery (i.e. from the upper cervical roots and the trigeminal fibers) provides an anatomical explanation for the coexistence of occipital and frontal headaches.\(^1\)

In general, headache disorder has no specific diagnostic workup. However, if a red flag exists and
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an underlying secondary etiology is suspected, careful diagnostic evaluation is warranted. In cryptogenic strokes or strokes in young patients, further tests should be considered including anticardiolipin antibodies, antithrombin III, lupus anticoagulant, and protein C and S. Neuroimaging studies (CT, MRI, MRA, or CTA) are necessary to evaluate the possibility of aneurysm, subarachnoid hemorrhage, intracerebral hemorrhage, cerebral neoplasm, or ischemic infarct. Cerebrospinal fluid analysis may be considered to rule out subarachnoid hemorrhage, central nervous system angitis, or central nervous system infection. Cardiac evaluation may exclude or confirm a cardiogenic or aortic source of cerebral embolism and should include electrocardiography, Holter monitor, and transesophageal echocardiography.

There is no particular information available for the management of headache associated with an ischemic cerebrovascular disease. Headache can be treated with acetylsalicylic acid or acetaminophen (when hemorrhage is excluded). Triptans and dihydroergotamine are contraindicated. Beta-blockers or calcium-channel blockers may be used if antihypertensive treatment is indicated.

Patients with brainstem strokes may develop involuntary convulsive-like movements that vary in nature, frequency, and trigger. This phenomenon was reported in few articles in the literature with all patients having normal electroencephalogram, preserved consciousness, and no effect of anti-epileptic medications. The mechanism behind the occurrence of such movements could be due to ischemia of the corticospinal tract bilaterally or disruption of the inhibitory projection of the cortex to the spine or brainstem.

In conclusion, this paper reported a rare case of vertebrobasilar insufficiency associated with unilateral headache and convulsive-like movements. This case indicates that a frontal headache with dysarthria, hemiplegia, and convulsive-like movements are warning signs for posterior circulation stroke that should be taken seriously. Elderly patients presenting a new headache for the first time that is recurrent, not responding to treatment, or presenting with a clinical red flag should be fully investigated to rule out a vascular disorder, mainly stroke. Early identification of a stroke within the therapeutic window of thrombolytic therapy will lead to better outcomes and may be life-saving. We are reporting two new symptoms to be added to the list of symptoms of pontine warning syndrome. Received 3rd April 2019. Accepted 10th June 2019.

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References

Frequency, risk factors, and outcomes in patients with significant carotid artery disease admitted to King Abdulaziz Medical City, Riyadh with Ischemic Stroke

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ABSTRACT

Objectives: To determine the frequency, risk factors, and outcomes of significant carotid artery disease (CAD) in patients with ischemic stroke.

Methods: The frequency of significant CAD in patients admitted to the Stroke Unit between January 2014 and December 2015 was determined from radiological data. Outcomes were determined clinically and radiologically.

Results: Among 435 patients, 273 were men (62.8%), with a mean age of 57.4±12.2 years. Significant CAD was found in 48 vessels in 40 (9.2%) patients, of which 30 patients were symptomatic. Nine of these patients were treated with carotid artery stenting, one underwent carotid endarterectomy, and 3 underwent an urgent thrombectomy, without stenting. Seventeen symptomatic patients were not treated for the following reasons: patient/family refusal (n=2), contraindications (n=5), and complete occlusion (n=10). One (7.7%) of the 13 treated patients had an ipsilateral stroke on follow up, one (7.7%) had contralateral transient ischemic attack (TIA), 9 (69.2%) had no recurrence, and no clinical data were available for 2 patients. Among the 17 untreated patients, one (5.9%) had an ipsilateral stroke, 7 (41.2%) had no recurrence, and 9 (52.9%) were lost to follow up.

Conclusions: Significant carotid artery disease is uncommon in our cohort found in less than 10% of patients. Vascular risk factors are more or less similar between patients with or without CAD except obesity which appears to have inverse relation with CAD. A small number of patients received carotid intervention with no recurrence of stroke at limited follow up.

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Strokes are the second leading cause of death worldwide. According to data from the Institute of Neurological and Communicative Disorders and Stroke, 22% of strokes can be attributed to carotid artery disease (CAD). Carotid artery disease is classified as extracranial or intracranial. There appear to be racial variations in the distribution of the 2 types of CAD, with a relatively higher incidence of intracranial disease in black and Hispanic individuals and a relatively higher incidence of extracranial atherosclerotic disease among Caucasians. Extracranial atherosclerosis has long been identified as a common source of emboli that can travel to the brain and cause a stroke. Intracranial atherosclerotic disease accounts for 30-50% of strokes in Asia. Carotid artery disease is classified into symptomatic and asymptomatic disease. Symptomatic patients with carotid stenosis experience a focal neurological deficit ipsilateral to stenosis. Asymptomatic carotid stenosis is not a life-threatening condition, with a mortality rate of 0.05% and a stroke recurrence rate of 1–2% or less annually. However, it is significantly associated with the development of life-threatening cardiovascular events, as it co-exists with coronary artery disease in 40% of cases. Symptomatic CAD can be managed by medications alone, or medications with carotid artery stenting or carotid endarterectomy, depending on the individual patient. In acute cases, carotid thrombectomy without carotid artery stenting can be performed as part of endovascular treatment of an acute stroke, although this has not been well studied in randomized trials. A study by Al Rajeh et al on 500 Saudi stroke patients found that ischemic strokes accounted for 76.2% of the stroke cases. Determining the degree of carotid stenosis and type of CAD (i.e., symptomatic or asymptomatic) is crucial for patients’ management and prognosis. Data on significant CAD among stroke patients in the Saudi population are lacking. The scarcity of data is cause for concern. In this study, we determined the frequency, risk factors, management and outcomes of significant CAD in ischemic stroke patients. We also determined the prevalence of symptomatic or asymptomatic disease.

Methods. This study was conducted in the stroke unit of King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Kingdom of Saudi Arabia. Patients admitted to the stroke unit between January 2014 and December 2015 were included. Significant CAD was defined as more than 50% stenosis confirmed on vascular imaging. If the patient had suffered an ischemic stroke or transient ischemic attack (TIA) and the ipsilateral vessel showed significant stenosis (>50%), CAD was considered symptomatic.

The inclusion criteria included all ischemic stroke patients aged 18 years and older of both genders. Patients admitted to the neurology department were included in the study. Stroke patients admitted to any other department in the hospital were excluded. Additional exclusion criteria included patients with intracerebral hemorrhages, a final diagnosis other than a stroke, and missing important data.

Demographic, clinical, and radiological data were collected using a standard prespecified form. The descriptive statistics for the demographic and clinical characteristics are presented as the mean (median), with standard deviations for continuous variables and counts and percentages for categorical variables.

The study was approved by the Institutional Review Board of King Abdullah International Medical Research Center (KAIMRC) and King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Riyadh, Kingdom of Saudi Arabia. Due to retrospective, chart review nature of the study, the IRB waived the need for informed consent from the included patients.

Statistical analysis. Pearson’s chi-square test or Fisher’s exact test was used to detect clinical associations between the categorical variables and the outcome variable. To assess the association of demographics and clinical variables with the outcome variable, a general linear model, generalized estimation equation, and mixed methods were utilized as the study cohort was longitudinal. The significance level α was considered 0.05 if the probabilistic p-value was less than the assumed significance level. The statistical software packages SAS version 9.4 (SAS Institute Inc. Cary, NC, USA) or R version 3.4 (The R Project for Statistical Computing: free software) was used for data analysis. The data were analyzed using SPSS Statistics (SPSS Inc., Chicago, IL, USA) version 22.0. Fisher’s exact test, the χ² test, an independent sample t-test, Mann–Whitney test, one-way analysis of variance, and multiple logistic regression analysis were conducted.

Results. Of 726 stroke patients included in the study, 435 patients were included in the final analysis. The other patients were excluded for the following reasons: a hemorrhagic stroke (n=57 patients), final

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There were 273 men (62.8%) and 162 women (37.2%), with a mean age of 57.4±12.2 years. In terms of stroke-related risk factors, 315 (72.4%) patients had hypertension, 276 (63.4%) patients had diabetes, and 171 (39.3%) patients were obese (Table 1). A comparison of risk factors between patients with significant and nonsignificant CAD is shown in Table 2, with the estimated parameters, standard errors, p-values, and odds ratios, with their 95% confidence intervals. In the univariate analysis, obesity showed an inverse relationship with significant CAD \( p=0.022 \) (Table 1). This finding persisted in the logistic regression analysis, with obesity showing an inverse relation with significant CAD \( p=0.0087 \). There were no between-group differences in any of the other risk factors (Table 2, Figure 1). Obesity as a risk factor for significant CAD was associated with lower odds (36%) as compared to nonobese individuals. Significant CAD was found in 48 vessels in 40 (9.2%) patients, of which 30 (6.9%) patients were symptomatic. Of these 30 symptomatic patients, 9 (30%) were treated with carotid artery stenting, one (3.3%) underwent endarterectomy, and 3 (10%) underwent an urgent thrombectomy, without stenting. The other 17 (56%) symptomatic patients were not treated for the following reasons: patient/family refusal (\( n=2, 11.8\% \)), contraindications to the intervention (\( n=5, 29.4\% \)), and complete occlusion (\( n=10, 58.8\% \)). These results are summarized in Figure 2.

As shown by the clinical and radiological follow up of the treated (\( n=13 \)) and untreated (\( n=17 \)) patients, one (7.7%) patient had an ipsilateral stroke on follow up, and one (7.7%) patient had a contralateral TIA at the 6-months follow up. Nine (69.2%) patients had no recurrence, and no clinical data were available on 2 (16.9%) patients. Among the untreated 17 vessels, one (5.9%) patient had an ipsilateral stroke, 7 (41.2%) patients had no recurrence, and 9 (52.9%) patients were lost to follow up.

**Discussion.** In the West, CAD is a strong risk factor for a stroke, accounting for approximately 20–22% of stroke cases. A recent study in Pakistan showed that CAD was present in 56% of stroke patients, making it a significant risk factor in this population. In contrast to the literature, the frequency of significant CAD was only 9% in our cohort, of which 6.9% of patients were symptomatic. A study in Taiwan reported a similar low frequency, where ischemic strokes resulting from CAD were found in only 6% of the cohort. A recent Saudi study that compared diabetic and nondiabetic patients detected significant carotid artery stenosis in 13.4% of all patients. A study in Iran found that most large vessel strokes (69%) were attributable to extracranial CAD. These wide variations in the frequency of significant CAD are difficult to explain and warrant large multicenter, multinational studies to ascertain the reasons for the disparity in different populations.

Among the symptomatic patients in our cohort, less than 50% underwent a carotid intervention, with the other patients either having contraindications or the patient or family refusing an intervention. We also found that a large number of symptomatic vessels were completely occluded, which may suggest long-standing
Carotid artery disease in stroke ... Shaheen et al

Table 2 - A comparison of risk factors in patients with significant and nonsignificant carotid artery disease (CAD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Analysis of Penalized Maximum Likelihood Estimates</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>DF</td>
<td>Estimate</td>
<td>Standard Error</td>
<td>Wald chi-square</td>
<td>Pr &gt; chi-square</td>
<td>Odds ratio (95% confidence intervals)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Female vs. Male</td>
<td>1</td>
<td>0.5363</td>
<td>0.3941</td>
<td>1.8518</td>
<td>0.1736</td>
<td>1.71 (0.76-3.77)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes vs. No</td>
<td>1</td>
<td>0.5828</td>
<td>0.4132</td>
<td>1.9058</td>
<td>0.1584</td>
<td>1.79 (0.81-4.28)</td>
</tr>
<tr>
<td>Obesity</td>
<td>Yes vs. No</td>
<td>1</td>
<td>-1.0310</td>
<td>0.3931</td>
<td>6.8782</td>
<td>0.0087</td>
<td>0.36 (0.15-0.76)</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes vs. No</td>
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<td>0.6932</td>
<td>0.4250</td>
<td>2.6612</td>
<td>0.1028</td>
<td>2.00 (0.84-4.58)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>Yes vs. No</td>
<td>1</td>
<td>0.3198</td>
<td>0.4374</td>
<td>0.5346</td>
<td>0.6467</td>
<td>1.38 (0.55-3.16)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Yes vs. No</td>
<td>1</td>
<td>0.3369</td>
<td>0.3418</td>
<td>0.9713</td>
<td>0.3244</td>
<td>1.40 (0.71-2.76)</td>
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<td>Migraine</td>
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<td>0.9752</td>
<td>1.0577</td>
<td>0.8501</td>
<td>0.3565</td>
<td>2.65 (0.25-15.33)</td>
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<tr>
<td>Hypertension</td>
<td>Yes vs. No</td>
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<td>0.4218</td>
<td>0.4593</td>
<td>0.8434</td>
<td>0.3584</td>
<td>1.53 (0.63-4.05)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>Yes vs. No</td>
<td>1</td>
<td>0.2843</td>
<td>0.4339</td>
<td>0.4295</td>
<td>0.5122</td>
<td>1.33 (0.54-3.01)</td>
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<tr>
<td>Transient ischemic attack</td>
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<td>0.6300</td>
<td>0.7940</td>
<td>0.6297</td>
<td>0.4275</td>
<td>1.88 (0.33-7.43)</td>
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<tr>
<td>Atrial fibrillation</td>
<td>Yes vs. No</td>
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<td>0.6420</td>
<td>1.9259</td>
<td>0.1652</td>
<td>2.44 (0.60-7.67)</td>
</tr>
</tbody>
</table>

Figure 1 - Likelihood ratios of risk factors in patients with significant and nonsignificant carotid artery disease (CAD).

Figure 2 - Pattern of intervention in the significant group, treated group (dark black bars), and nontreated group (dotted bars).

We found a significant increase in the frequency of vascular risk factors in our cohort as compared with that reported in 2 previous studies conducted in Saudi Arabia in the 1990s. These studies reported hypertension in 41–56% of their cohorts as compared with 72.4% in our cohort. This finding may suggest an overall increase in the prevalence of hypertension or a higher number of untreated patients in the Saudi population. Zafar et al also found an increased frequency of vascular risk factors among stroke patients. A recent national survey in Saudi Arabia of more than 10,000 individuals older than 15 years found that approximately 55% of the population had hypertension or borderline hypertension. In our cohort, the prevalence of diabetes was 63.5%, which points to a significant increase in comparison to the previous frequencies of 42% and 25% reported in Saudi populations. The incidence of ischemic heart disease...
has also increased (14.7%) as compared with that found in the previous Saudi study (10%). \(^1^5\) The median age of our patients was 57 years, which was somewhat younger than the mean ages of 61 and 63 years reported in the earlier studies. \(^9^,1^5\) A marked increase in cerebrovascular risk factors may explain the younger age of the patients in our cohort.

Other than established cerebrovascular risk factors, various other factors, such as obesity and lifestyle changes, can play a role in stroke risk. In 1992, the obesity rate in Saudi Arabia was estimated to be 16.4%, whereas it was 52.9% in 2016. \(^1^7\) In our study, 39.3% of the patients were obese. In general, obesity has a negative impact on cardiovascular morbidity. However, we found an interesting paradox, with obesity appearing to play a protective role against significant CAD in our cohort. Obesity was inversely related to significant carotid artery stenosis in stroke patients, reducing the risk of CAD up to 36% \((p=0.0087)\). A previous study also reported that obesity was associated with reduced mortality in stroke patients and with a reduced risk of readmission for recurrent strokes. \(^1^8\)

**Our study has several limitations.** It was a retrospective cohort study, and most data were extracted from the hospital files. Some CAD patients were excluded due to missing files and others were excluded due to missing or incomplete data. The documentation for all stroke patients was also not standardized. In addition, our cohort was from a single tertiary care center, which caters mostly to members of the Saudi National Guard, although emergency care is provided to all patients, regardless of their affiliation with the National Guard. Thus, our data are likely not generalizable to the entire Saudi population. Among the patients diagnosed with CAD, many patients were lost to follow up, and longitudinal data on outcomes were not available.

In conclusion, carotid artery disease was an uncommon cause of ischemic stroke in our population with less than 10% of ischemic stroke patients having significant CAD. Although traditional vascular risk factors did not differ among patients with or without CAD, obesity showed an interesting and as yet unexplained paradoxical role with CAD, providing possible protection against carotid disease among stroke patients. A small number of patients with symptomatic CAD underwent intervention with no recurrence of stroke at last follow up.

We recommend multicenter studies in Saudi Arabia to determine the frequency of significant CAD, as well as the reasons for the apparent discrepancy in the frequency as compared with that in other regions of the world. There is an urgent need for action to address vascular risk factors in the Saudi population to decrease the risk of strokes and stroke-related morbidity and mortality.

**References**

Hashimoto’s Encephalopathy Presenting with Progressive Cerebellar Ataxia

Hussein A. Algahtani, MD, FRCPC, MMed, Anmar N. Fatani, MD, Bader H. Shirah, MS, Raghad H. Algahtani, MS.

ABSTRACT

Hashimoto’s encephalopathy is a rare neurological syndrome occurring in patients with autoimmune thyroid disease. The diagnosis of Hashimoto’s encephalopathy is based on the clinical picture with the presence of serum anti-thyroid antibodies regardless of the thyroid disorder. Acquired cerebellar ataxia associated with Hashimoto’s disease is a rare occurrence. In this article, we present a case who had progressive non-familial autoimmune pancerebellar disease in association with an increased level of thyroid peroxidase and thyroglobulin antibodies. The patient was managed aggressively with both intravenous immunoglobulins and plasma exchange, which stopped the progression of the disease and allowed for slow improvement.

Case Report. Patient Information. A 25-year-old female presented to the neurology clinic with gradually progressive dizziness, imbalance, right-hand tremor and clumsiness, and difficulty walking 2 months after delivery. She delivered a healthy girl through uncomplicated spontaneous vaginal delivery. She is

Disclosure. The authors declare no conflicting interests, support or funding from any drug company.
a mother of a 3-year-old boy with a previous history of one abortion and ABO incompatibility in her first pregnancy. There was no history of seizures, forgetfulness, sensory symptoms, weakness, or bowel/bladder involvement. Her family history was unremarkable for any neurological diseases including hereditary ataxias. Her symptoms were progressive with difficulty mobilizing without support, and she required a wheelchair 6 months after the onset of her disease. Her speech was slurred and her tremor caused difficulty in feeding and other activities of daily living. She also developed severe visual impairment due to oscillopsia.

**Clinical Findings.** Her neurological examination showed normal higher mental functions. Her cranial nerve examination showed normal visual acuity, pupils size and reactivity, and hearing were all normal. Her motor examination showed generalized hypotonia (mild) with normal power and reflexes. Her coordination examination showed severe postural and intentional tremor with dysmetria and dysdiadochokinesia. Her gait was severely impaired, which was broad-based and tremulous. She was unable to perform tandem gait. Scale for the assessment and rating of ataxia (SARA) was used, and she scored 33/40, which indicates severe ataxia. Her cerebellar findings were symmetrical bilaterally. All sensory modalities were normal.

**Diagnostic Assessment.** MRI of the brain showed significant symmetrical cerebellar atrophy involving both cerebellar hemispheres and the vermis with a prominence of the fourth ventricle and cerebellopontine angle cisterns (Figure 1). The cerebral hemisphere, basal ganglia, and brainstem structures were normal. Systemic investigations, connective tissue screen, celiac disease autoantibodies, and thyroid function tests were all normal. Workup for Wilson disease and organic acid disorders were negative. Anti-thyroid peroxidase and anti-thyroglobulin were highly elevated at >1000 and 10.03, respectively, which is consistent with the diagnosis of Hashimoto’s disease. Serial investigations for malignancy and paraneoplastic syndrome were unremarkable including computed tomography scan of the chest, abdomen, and pelvis, tumor markers, and paraneoplastic serological tests (e.g. anti-Ri, anti-Hu, anti-Yo). Serum protein electrophoresis did not show an increase in IgM and no monoclonal spikes. Genetic testing panel for hereditary ataxia was negative. Investigations for connective tissue disease was negative including anti-nuclear antibody, rheumatoid factor, and antibodies for Sjogren’s syndrome (anti-SS-A and anti-SS-B). Investigations for other immune-mediated cerebellar ataxia including anti-GAD, anti-NMDA receptor antibodies, anti-Purkinje, and anti-neuronal nuclear were negative. Cerebrospinal fluid (CSF) assessment was unremarkable with negative oligoclonal bands. The CSF was not tested for anti-thyroid peroxidase and anti-thyroglobulin antibodies.

During the admission, she was found to have thrombocytopenia, at which point the valproic acid was discontinued. On the day after valproic acid was discontinued, the spasms stopped, although ACTH was not given. Repeat EEG 1 week later showed focal slowing over the right side with the resolution of the hypersynchronous pattern (Figure 2).

**Therapeutic Intervention.** The patient was treated with pulse steroid therapy followed by oral prednisolone with no significant improvement. She was then treated with a 5-day course of plasma exchange followed by intravenous immunoglobulin with some improvement of her symptoms and SARA scale assessment (25/40) for 6 months. She was also treated with 4-aminopyridine for one month with no improvement in her condition. 4-aminopyridine was discontinued due to lack of efficacy according to the patient.

**Follow-up and Outcomes.** Unfortunately, we had to repeat the immunomodulatory therapy due to relapse of her symptoms, but again with some improvement. The patient was discharged home with a strong physiotherapy and occupational therapy program and was seen in the clinic in a stable condition (Figure 2).
**Discussion.** Disorders of the thyroid gland accompanied by neurological complications are common with a frequency of 1-2% of unsellected general medical, geriatric, and psychiatric in-patients. Neurologists should be aware of the common, rare, and unusual neurological complications of thyroid disease. This is because neurological complications may be the presenting features of thyroid disorders and they are usually readily treatable with appropriate early therapy. The neurological complications of thyroid disease may result from an immune-mediated mechanism or from an alteration in the levels of circulating thyroid hormones. Hormonal alterations may exacerbate a pre-existing neurological disorder, increase the severity of a subclinical problem, or produce a new neurological disorder. Other mechanisms resulting in neurological complications include local compression of adjacent structures from enlargement of the thyroid gland, development of cerebral metastasis from thyroid carcinoma, and raised intracranial pressure in patients with hypothyroidism.

The first description of the possible association between Hashimoto’s thyroiditis and the development of an autoimmune encephalopathy was suggested by Brain and colleagues in 1966 and was subsequently
confirmed by other authors. The majority of reported patients were euthyroid at the time of neurological presentation, and alteration in the thyroid metabolic status clearly did not explain the encephalopathy in these patients. Hashimoto's encephalopathy, also called steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), is characterized by subacute onset of altered level of consciousness, cognitive impairment, stroke-like episodes, and focal or generalized seizures. There is a preponderance of female patients with a female to male ratio of 10:1, and the course of the disease is usually relapsing that should alert the physician to the diagnostic possibility of Hashimoto's encephalopathy. Hypothyroidism is a common disorder and anti-thyroid peroxidase antibodies can occur in the general population. Therefore, the diagnosis of Hashimoto's encephalopathy may be challenging due to the lack of causality and the possible coincidence of separate diseases. In addition, many other antibodies (most notably anti-mGluR1 antibodies) can be found in patients with autoimmune ataxia. If extensive antibody screening has not been made in the CSF, the presence of autoantibodies more specific than anti-thyroid peroxidase antibodies cannot be excluded.

Thyroid peroxidase and thyroglobulin, the main thyroid autoantigens, are the enzyme-substrate pair involved in thyroid hormone production. Thyroid peroxidase is a 933-amino-acid, which carries out the iodination and the intramolecular coupling of tyrosine residues of thyroglobulin to form thyroid hormones. Several thyroid-related auto-antibodies may react against these autoantigens with subsequent development of widespread systemic manifestations. It is estimated that around one-fourth of patients with Hashimoto's thyroiditis have associated systemic disease. These include pernicious anemia, myasthenia gravis, Addison's disease, and ulcerative colitis. Immune-mediated cerebellar ataxia due to anti-peroxidase antibody has been associated with autoantibodies to cerebellar structures, specifically, cerebellar astrocytes expressing glial fibrillary acid protein. The exact epitope that causes cross-reaction is not yet identified. In that study, the anti-thyroid peroxidase antibodies from patients' CSF reacted with monkey astrocytes, while anti-thyroid peroxidase antibodies from patients with thyroiditis and no neurological symptom did not. This may suggest that either anti-thyroid peroxidase antibodies from Hashimoto's encephalitis patients are somewhat different from the usual anti-thyroid peroxidase antibodies. It may also suggest that there is actually another antibody involved. Further basic science research is required to address these questions. Studies with reported patients having a high level of anti-thyroid peroxidase showed a good response to steroids, but in these cases, the level never reached 700. In our case, the anti-thyroid peroxidase level was very high (more than 1000), which may explain little or no response to steroid therapy, and aggressive therapy such as intravenous immunoglobulins or plasma exchange should be used on top of steroid therapy. The presence of normal thyroid function and very high autoantibodies have excluded hormonal deficiency or alteration as the etiology. Other features that argue in favor of autoimmune ataxia include young female patient, acute and subacute progression, and good response to immunomodulation.

4-aminopyridine (prolonged-release fampridine) is a lipid-soluble selective potassium channel blocker that readily crosses the blood-brain barrier and is currently indicated for walking improvement in adult patients with multiple sclerosis. It acts on the surface of nerve fibers to reduce the leakage of ionic current from potassium channels in demyelinated axons, thereby inhibiting repolarization and prolonging the duration of action potentials, presumably allowing for more action potential propagation along the cell membrane. This medication is used off-label for walking improvement in patients with hereditary ataxia with success in some patients. This is a single case report, and although our experience suggests that this medication is not effective in the management of autoimmune cerebellar ataxia, large scale studies should be done for an accurate recommendation.

Conclusion. Early diagnosis of Hashimoto's encephalopathy with autoimmune cerebellar ataxia and intervention with immunomodulatory therapy are of paramount importance. Close monitoring after steroid therapy is important since some patients with this rare disease might be resistant to steroid therapy and require aggressive immunomodulatory therapy. The presence of cerebellar atrophy and high levels of anti-thyroid peroxidase (more than 1000) may suggest the need to start aggressive therapy with steroids and other immunomodulatory therapy such as intravenous immunoglobulins or plasma exchange. The presence of cerebellar atrophy should not prevent the treating team from being aggressive in the management of this disease. 4-aminopyridine is not effective in the management of autoimmune cerebellar ataxia. However, more studies need to be done for this rare disease especially those which carry longitudinal data of several cases instead of one case report. Clinic-laboratory correlation (clinical improvement with the magnitude of autoantibody titer) is important.
References


Clinical Practice Guidelines

Clinical Practice Guidelines must include a short abstract. There should be an Introduction section addressing the objective of producing the guideline, what the guideline is about and who will benefit from the guideline. It should describe the population, conditions, health care setting and clinical management/diagnostic test. Authors should adequately describe the methods used to collect and analyze evidence, recommendations and validation. If it is adapted, authors should include the source, how, and why it is adapted? The guidelines should include not more than 50 references, 2-4 illustrations/tables, and an algorithm.
Examination of the effects of coordination and balance problems on gait in ataxic multiple sclerosis patients

Fatma Erdeo, Pt, Phd, Yeliz Salcı, Pt, Phd, Ali Ulvi Uca, MD, Phd, Kadriye Armutlu, PhD, Prof.

ABSTRACT

Objectives: To investigate the effects of coordination and balance problems on gait in multiple sclerosis patients.

Methods: This was an observational, cross-sectional study. It was conducted at Necmettin Erbakan University between March and December 2017. Twenty-four individuals with coordination problems, 36 individuals with balance problems and 32 healthy individuals were included in the study. The EDSS, Functional Reach Test, Dynamic Gait Index, baropodometry and stabilometry evaluations were performed.

Results: There were significant differences between the groups (velocity \( p=0.000 \), cadence \( p=0.000 \), step width \( p=0.018 \), step length \( p=0.000 \), foot angle \( p=0.000 \)). Multiple comparisons demonstrated that the velocities and cadences of the coordination group were lower, while their step widths were found to be higher, compared to the balance group \((p=0.012, p=0.004, p=0.017, \text{respectively})\). In static plantar pressure distribution, lateral forefoot pressure, lateral hindfoot pressure and medial hindfoot pressure were significantly different between the groups \((p=0.002, p=0.000, \text{respectively})\). Multiple comparisons showed that the pressure on the lateral part of the hindfoot in the coordination group was found to be significantly higher compared to the balance group \((p=0.002)\). According to the dynamic plantar pressure distribution, lateral forefoot, medial forefoot, lateral hindfoot and medial hindfoot pressures were significantly different between the groups \((p<0.05)\).

Conclusion: Coordination and balance problems affect gait and plantar pressure distribution. The identification of these changes will help physiotherapists determine specific therapeutic targets.
Multiple sclerosis (MS) is an infectious disease of the central nervous system of unknown etiology. Typically, patients initially experience a relapse and remission course (RRMS). In many cases, secondary progressive MS (SPMS) is observed, causing the slow and insidious development of disability. One of the common symptoms of MS is ataxia. Ataxia, which is characterised by postural control, balance and coordination impairment that causes limitation in MS, is one of the most important causes of disability. Coordination problems are common due to problems in the cerebellum and its connections. Cerebellar pathology causes nystagmus, dysarthria and tremor with limb, trunk and gait ataxia depending on the lesion area. In about 80% of MS patients, different types of ataxia emerge as significant symptoms.

Ataxia is one of the most critical factors affecting gait. Gait ataxia emerges with balance and coordination problems or a combination of these. While previous studies have clearly displayed the effect of balance on gait, the effects of coordination problems on gait are not apparent. In a limited number of studies, the effect of coordination on gait was investigated, and conflicting results were found. Limb coordination, standing and balance control and locomotion were the subjects that the researchers emphasised frequently. Morton and Bastian reported that balance in patients with cerebellar ataxia caused an impairment in the spatiotemporal parameters of gait, but coordination did not affect the spatiotemporal parameters of gait. Winfried et al. reported that coordination problems affect gait. This study aimed to investigate the effect of balance and coordination problems on gait and plantar pressure in MS patients and to compare its effects with balance problems.

**Methods.** **Study design.** An observational, cross-sectional study design was applied. This study, which was planned in order to investigate the effect of balance and coordination problems on gait in ataxic MS patients, was conducted in Turkey at Necmettin Erbakan University between March 2017 and December 2017.

**Participants.** A total of 60 MS patients and 32 healthy volunteers were included in the study.

**Inclusion criteria.** Being older than 18 years, having an EDSS score between 3 and 5, not taking corticosteroids within the 3 months before the study, having an EDSS pyramidal system score < 3 and being diagnosed with definite MS by a neurologist were the inclusion criteria.

**Exclusion criteria.** Patients who had a history of MS attacks in the last 3 months, who had orthopaedic or systemic problems that prevented their participation in the evaluations, who had peripheral vestibular problems and who were using gait orthosis/aids were excluded from the study.

**Disclosure.** Authors have no conflict of interests, and the work was not supported or funded by any drug company.

**Ethics committee approval.** Permission for the study was received from Necmettin Erbakan University’s Non-Interventional Clinical Research Ethics Committee (ON: 2017/850). The MS patients were divided into 2 groups: those with marked balance problems (balance group) and those with marked coordination problems (coordination group).

**Balance group (BG).** According to the cerebellar evaluation of the EDSS, patients with trunk ataxia signs only and more patients whose Romberg tests were mild and more and patients whose functional reach tests were less than 25 cm were included in this group.

**Coordination group (CG).** According to the cerebellar evaluation of the EDSS, patients whose lower limb ataxia was sign only and more and patients whose functional reach tests were less than 25 cm were included in this group.

If the functional reach test was lower than 25 cm, the patient was included in the BG even if he/she had mild coordination problems. Patients with functional reach tests higher than 25 cm and mild coordination problems were included in the CG even if they had mild trunk ataxia.

**Healthy group (HG).** The inclusion criteria for healthy individuals were determined as not being diagnosed with any neurological disease, not having vertigo or loss of sensation in the foot and not having any wound or foot or ankle problems that would affect plantar sensation.

Individuals were informed about the purpose and methods of the study. Their written consent for participation in the study was obtained. The patients’ ages, heights, weights, disease durations, dates of last attack, drugs used, dates of last corticosteroid use, number of attacks experienced, physiotherapy and rehabilitation programs previously participated in and presence of systemic and orthopaedic diseases were recorded in detail.
Evaluation procedure. Before the gait evaluation, clinical evaluations of the patients were made.

**Expanded disability status scale (EDSS).** This test was developed to follow up the disease stage in MS patients by evaluating pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and other systems. The scores obtained from all these functional systems evaluations are converted into a single score, and the disease is graded between 0 and 10. As the score increases, the severity of the disability increases.\(^\text{12}\) The EDSS assessment was performed by a certified physiotherapist.

**International Cooperative Ataxia Rating Scale (ICARS).** This scale was developed for ataxic patients and is also valid and reliable for MS patients.\(^\text{13}\) In this test, in which postural and gait disorders, kinetic functions, speech disorders and oculomotor disorders are evaluated under four headings, the score distributions of the sections are 34, 52, 6 and 8, respectively. Of the 34 points that represent the sum of posture and gait disorders, 12 points are used for gait evaluation and 22 points are used for posture evaluation. The scale is scored on a total of 100 points, and the score increases as the severity of the ataxia increases.\(^\text{14}\)

**Stabilometric test.** In the stabilometric evaluation, a STABYLO platform, which is produced by Diagnostic Support, is used. A 40x80 cm sensing surface with 12,800 active sensors is used for the examination of body oscillations in the upright position (the foot at 30°) and for the evaluation of body strategies in a specific time frame (maximum 51.2 sec) by maintaining the eyes in the open and closed positions. In the present study, the body oscillations with open and closed eyes were calculated as an area in cm².\(^\text{15}\)

**Functional Reach Test (FRT).** The patients, who were positioned in the upright position without touching the wall, were asked to lift their hands at 90 degrees by keeping the elbow of the dominant arms straight, to make fists and to reach forward without any loss of balance. The third metacarpophalangeal joint’s projection on the wall was marked before and after the measurement, and the distance between these measurements was recorded in cm.\(^\text{16}\)

**Evaluation of Gait Problems in MS.** Evaluation of the spatiotemporal parameters of gait: The spatiotemporal parameters of gait were evaluated using the Diagnostic Support Baropodometer Footscan® 3D system. The system consists of a pressure-sensing platform, power unit, cameras (high-speed and video), printer, monitor and connections between the printer and the platform and between the monitor and the platform. A dynamic analysis was performed with the gaits of patients at normal gait speeds on the platform, which perceives pressure and is 4 m in length and 40 cm in width. First, the patients were made to walk in order to ensure their adaptation to the base of the platform. In order to be reliable, the gait cycle was completed with 3 trials of going and returning. Specific parameters of gait, such as cadence, acceleration, step width and step length, were obtained. Static analysis was carried out in a stationary standing position on the work platform, which is 45 cm x 45 cm and which has 4,024 sensors and a frequency of 300 MHz. The spatial parameters of gait, step length (cm), step width (cm) and foot angle (degrees) and the temporal parameters of gait, speed (m/min), cadence (step/min) and stance time (sec) were recorded.\(^\text{15,17}\)

Evaluation of the plantar pressure distribution: By using the Diagnostic Support Baropodometer Footscan® 3D system, besides the dynamic evaluation and recording of the spatiotemporal parameters, the data on the total load on the forefoot, midfoot and hindfoot; the average pressure; and the distribution of load in the forefoot, midfoot and hindfoot were also obtained. Moreover, with static evaluation, on the work platform, data such as the total load on the forefoot

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CG (n=24)</th>
<th>BG (n=36)</th>
<th>HG (n=32)</th>
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<td>0.483</td>
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<td>Gender n(%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (33.3)</td>
<td>9 (25.0)</td>
<td>13 (40.6)</td>
<td>0.389</td>
</tr>
<tr>
<td>Female</td>
<td>16 (66.7)</td>
<td>27 (75.0)</td>
<td>19 (59.4)</td>
<td></td>
</tr>
</tbody>
</table>

SD - standard deviation, BMI - Body Mass Index, CG - coordination group, BG - balance group, HG - healthy group.\(^\text{\*}p<0.005\)
and midfoot, hindfoot, right and left foot weight ratios, average pressure on the feet, and maximum pressure were obtained as percentages. Static pressure and dynamic pressure were evaluated over the percentages.\textsuperscript{17}

**Dynamic gait index.** The DGI, which is a valid and reliable scale in the evaluation of gait in MS patients, consists of 8 items.\textsuperscript{18,19} The highest score that can be obtained from the test is 24. The highest score demonstrates the best physical condition.

**Statistical analyses.** Statistical analyses were performed using the SPSS 20 (IBM Corp., Armonk, NY, USA) analysis program. For descriptive statistics, number, percentage, mean and standard deviation were presented, and the homogeneity of the descriptive characteristics of the groups was evaluated with Pearson's chi-square test in categorical variables and with a one-way analysis of variance in independent groups in numerical variables. The aim was to determine the sample size required for the study, and the G*Power (G*Power Ver. 3.0.10, Franz Faul, Kiel University, Germany) software package was used.\textsuperscript{20} In the power analysis carried out before the study in order to determine the number of patients in the groups, the study by Morton and Bastian was taken as a reference.\textsuperscript{9} It was calculated that a sample size of 90 patients (30 patients in each group) would achieve 80% power ($d=0.50$ effect width, $\alpha=0.05$ type I error, $\beta=0.20$ type II error).

In the comparison of the mean scores of the dependent variables (dynamic foot analyses and gait analyses) of the 3 study groups, in the independent groups, the one-way analysis of variance (Tukey's honestly significant difference (HSD) for post hoc analysis) was used for normally distributed variables, and the Kruskal-Wallis test (the Bonferroni-corrected Mann-Whitney U test for post hoc analysis) was used for non-normally distributed variables. The comparison of the dependent variables was performed according to the type of ataxia (balance or coordination). The t-test was used in the independent groups. The relationship between the dependent variables was evaluated by the Pearson correlation analysis.\textsuperscript{21} The normal distribution of the data was examined with Skewness-Kurtosis values and the Kolmogorov-Smirnov test. The statistical significance level was accepted as $p<0.05$.\textsuperscript{22}

The average of the plantar pressure distribution was evaluated by comparing it with the one-way analysis of

### Table 2 - Comparison of descriptive measurements results between groups.

<table>
<thead>
<tr>
<th>Descriptive measurements</th>
<th>CG N=24</th>
<th>BG N=36</th>
<th>HG N=32</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDSS</td>
<td>3.92±0.69</td>
<td>3.89±0.76</td>
<td>-----</td>
<td>0.804</td>
</tr>
<tr>
<td>Functional Reach(cm)</td>
<td>27.38±3.55</td>
<td>19.80±3.99</td>
<td>5.908</td>
<td>0.000*</td>
</tr>
<tr>
<td>ICARS Total</td>
<td>26.42±8.38</td>
<td>24.86±5.94</td>
<td>-----</td>
<td>0.540</td>
</tr>
<tr>
<td>Oscillation Length: Eyes open (mm)</td>
<td>303.53±189.99</td>
<td>431.58±220.00</td>
<td>196.63±144.77</td>
<td>0.000*</td>
</tr>
<tr>
<td>Oscillation Length: Eyes closed (mm)</td>
<td>359.77±204.92</td>
<td>609.28±552.61</td>
<td>218.45±158.27</td>
<td>0.000*</td>
</tr>
<tr>
<td>Romberg</td>
<td>105.98±81.64</td>
<td>299.74±228.14</td>
<td>154.02±206.09</td>
<td>0.000*</td>
</tr>
<tr>
<td>DGI</td>
<td>16.25±5.64</td>
<td>13.14±5.46</td>
<td>-----</td>
<td>0.037*</td>
</tr>
</tbody>
</table>

SD - standard deviation, EDSS - Expanded Disability Status Scale, DGI - Dinamik Gait Index, CG - coordination group, BG - balance group, HG - healthy group, *$p<0.005$

### Table 3 - Comparison of the spatiotemporal parameters of Gait.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CG N=40 feet</th>
<th>BG N=72 feet</th>
<th>HG N=64 feet</th>
<th>*P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity (m/s)</td>
<td>0.44±0.28</td>
<td>0.59±0.26</td>
<td>0.71±1.13</td>
<td>0.000*</td>
</tr>
<tr>
<td>Foot angle (°)</td>
<td>10.63±4.68</td>
<td>12.31±4.63</td>
<td>14.13±3.80</td>
<td>0.000*</td>
</tr>
<tr>
<td>Step width (cm)</td>
<td>13.50±5.64</td>
<td>11.27±4.34</td>
<td>10.46±2.86</td>
<td>0.018*</td>
</tr>
<tr>
<td>Step length (cm)</td>
<td>29.92±18.42</td>
<td>32.89±15.56</td>
<td>44.46±8.10</td>
<td>0.000*</td>
</tr>
<tr>
<td>Cadence (step/per min)</td>
<td>31.87±17.66</td>
<td>40.33±17.76</td>
<td>52.06±16.94</td>
<td>0.000*</td>
</tr>
<tr>
<td>Stance time (s)</td>
<td>0.74±0.52</td>
<td>0.74±0.28</td>
<td>0.77±0.12</td>
<td>0.529</td>
</tr>
</tbody>
</table>

SD - standard deviation, *$p<0.005$, CG - coordination group, BG - balance group, HG - healthy group.
Limb and trunk ataxia on gait in MS ... Erdeo et al

**Results.** For this study that included 24 individuals (8 males and 16 females) in the CG, 36 individuals (9 males and 27 females) in the BG and 32 individuals (13 males and 19 females) in the HG, the demographic characteristics of the groups and their characteristics related to the course of the disease are summarised in Table 1 & 2.

**Spatiotemporal parameters of gait.** All spatiotemporal parameters of gait, except for stance time, were significantly different between the groups ($p<0.05$). When multiple comparisons were performed, it was found that velocity$_1$ and cadence$_2$ were lower in the CG than in the BG ($p_1=0.012$, $p_2=0.004$). Step

---

**Table 4** - Pairwise comparison of the spatiotemporal parameters of Gait in healthy individuals and ataxia types.

<table>
<thead>
<tr>
<th>Parameters (Dependent variables)</th>
<th>Group 1(I)</th>
<th>Group 2(J)</th>
<th>Mean Difference (group 1-2)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity (m/s)</td>
<td>CG</td>
<td>BG</td>
<td>-0.15</td>
<td>0.012*</td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>HG</td>
<td>-0.27</td>
<td>0.000*</td>
</tr>
<tr>
<td></td>
<td>BG</td>
<td>HG</td>
<td>-0.12</td>
<td>0.011*</td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>BG</td>
<td>-1.68</td>
<td>0.126</td>
</tr>
<tr>
<td>Foot angle (°)</td>
<td>CG</td>
<td>HG</td>
<td>-3.50°</td>
<td>0.000*</td>
</tr>
<tr>
<td></td>
<td>BG</td>
<td>HG</td>
<td>-1.82°</td>
<td>0.043*</td>
</tr>
<tr>
<td>Step width (cm)</td>
<td>CG</td>
<td>BG</td>
<td>2.23</td>
<td>0.017*</td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>HG</td>
<td>3.04</td>
<td>0.003*</td>
</tr>
<tr>
<td></td>
<td>BG</td>
<td>HG</td>
<td>0.81</td>
<td>0.887</td>
</tr>
<tr>
<td>Step length (cm)</td>
<td>CG</td>
<td>BG</td>
<td>-2.98</td>
<td>0.614</td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>HG</td>
<td>-14.55</td>
<td>0.000*</td>
</tr>
<tr>
<td></td>
<td>BG</td>
<td>HG</td>
<td>-11.57</td>
<td>0.035*</td>
</tr>
<tr>
<td>Cadence (step/per min)</td>
<td>CG</td>
<td>BG</td>
<td>-8.46</td>
<td>0.004*</td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>HG</td>
<td>-20.19</td>
<td>0.000*</td>
</tr>
<tr>
<td></td>
<td>BG</td>
<td>HG</td>
<td>-11.73</td>
<td>0.000*</td>
</tr>
</tbody>
</table>
| Stance time (s)                 | Post hoc analysis was not performed since a difference was not found in the primary analysis

$p<0.005$, CG - coordination group, BG - balance group, HG - healthy group

**Table 5** - Comparison of dynamic and static plantar pressure of individuals with MS and healthy individuals.

<table>
<thead>
<tr>
<th>Dynamic foot analysis</th>
<th>CG n=40 feet</th>
<th>BG n=72 feet</th>
<th>HG n=64 feet</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forefoot pressure: Lateral (g/cm²)</td>
<td>40.80±2.32</td>
<td>40.42±2.73</td>
<td>43.56±5.05</td>
<td>0.002*</td>
</tr>
<tr>
<td>Forefoot pressure: Medial (g/cm²)</td>
<td>55.05±5.29</td>
<td>54.07±6.44</td>
<td>58.87±4.24</td>
<td>0.000*</td>
</tr>
<tr>
<td>Midfoot pressure: Lateral (g/cm²)</td>
<td>73.73±13.92</td>
<td>73.43±13.69</td>
<td>68.69±14.73</td>
<td>0.136</td>
</tr>
<tr>
<td>Midfoot pressure: Medial (g/cm²)</td>
<td>27.52±13.72</td>
<td>26.57±13.69</td>
<td>29.14±14.36</td>
<td>0.584</td>
</tr>
<tr>
<td>Hindfoot pressure: Lateral (g/cm²)</td>
<td>53.34±3.51</td>
<td>54.66±5.00</td>
<td>50.99±4.96</td>
<td>0.001*</td>
</tr>
<tr>
<td>Hindfoot pressure: Medial (g/cm²)</td>
<td>49.98±5.59</td>
<td>48.00±4.99</td>
<td>45.79±4.51</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Static foot analysis</th>
<th>CG n=40 feet</th>
<th>BG n=72 feet</th>
<th>HG n=64 feet</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forefoot pressure: Lateral (g/cm²)</td>
<td>44.40±7.69</td>
<td>43.36±12.33</td>
<td>52.64±13.97</td>
<td>0.002*</td>
</tr>
<tr>
<td>Forefoot pressure: Medial (g/cm²)</td>
<td>54.55±9.07</td>
<td>49.90±17.09</td>
<td>48.96±13.26</td>
<td>0.218</td>
</tr>
<tr>
<td>Midfoot pressure: Lateral (g/cm²)</td>
<td>50.53±46.66</td>
<td>54.53±46.36</td>
<td>61.60±41.62</td>
<td>0.584</td>
</tr>
<tr>
<td>Midfoot pressure: Medial (g/cm²)</td>
<td>6.45±14.76</td>
<td>6.06±12.93</td>
<td>10.15±16.03</td>
<td>0.359</td>
</tr>
<tr>
<td>Hindfoot pressure: Lateral (g/cm²)</td>
<td>52.78±7.35</td>
<td>44.15±15.57</td>
<td>44.09±12.17</td>
<td>0.000*</td>
</tr>
<tr>
<td>Hindfoot pressure: Medial (g/cm²)</td>
<td>47.17±9.93</td>
<td>49.43±12.97</td>
<td>55.83±10.61</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

SD - standard deviation, *$p<0.005$, CG - coordination group, BG - balance group, HG - healthy group
width was found to be higher in the CG than in the BG ($p=0.017$). Step length, and foot angle, were lower than in the HG ($p<0.05$) but were similar in the BG and CG ($p_1=0.614, p_2=0.126$) (Tables 3-4).

**Plantar pressure distributions.** In a static plantar pressure distribution, lateral forefoot pressure, lateral hindfoot pressure and medial hindfoot pressure were significantly different between groups ($p=0.002, p=0.000, p=0.000$, respectively). Multiple comparisons showed that the pressure on the lateral part of the hindfoot of the CG was found to be significantly higher compared to the BG ($p=0.002$). According to the dynamic plantar pressure distribution, lateral forefoot, medial forefoot, lateral hindfoot and medial hindfoot pressures were significantly different between groups ($p <0.005$). Multiple comparisons showed that there were no differences between the BG and the CG ($p>0.005$) (Tables 5-6).

**Dynamic gait index:** The DGI average of the BG was significantly lower compared to the CG ($p=0.037$) (Tables 2).

**Discussion.** This study sought to investigate the effects of coordination and balance problems on gait and the plantar pressure distribution in ataxic MS patients and to determine the differences between them. This study is different from other studies in terms of gait and plantar pressure assessment in different ataxia types, such as trunk and extremity. The most important results of the present study are that the velocity and cadence of MS individuals with coordination problems are lower than those of individuals with balance problems, while the step width is higher. The foot angle, step length and stance time were found to be similar. The static pressure distribution in the lateral hindfoot for the CG was found to be significantly higher compared to the BG, while dynamic plantar distribution was similar between both ataxic groups. In other words, MS patients with coordination problems walk with more short steps and more slowly; at the same time, they cannot make normal plantigrade contact.

Many studies have demonstrated a slower gait, short step-taking (decreased step length), slow step-taking (decreased cadence) and less joint motion in MS patients in comparison with control groups and variabilities in many gait parameters. However, it is not clear to what extent these balance and coordination problems affect the spatiotemporal

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**Table 6 -** Pairwise comparison of the dynamic footh analyses.

<table>
<thead>
<tr>
<th>Dynamic foot analysis</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Mean difference (group 1-2)</th>
<th>*p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forefoot pressure: Lateral</td>
<td>CG</td>
<td>BG</td>
<td>.38</td>
<td>0.732</td>
</tr>
<tr>
<td>CG</td>
<td>HG</td>
<td>-2.75</td>
<td>0.012*</td>
<td></td>
</tr>
<tr>
<td>BG</td>
<td>HG</td>
<td>-3.14</td>
<td>0.001*</td>
<td></td>
</tr>
<tr>
<td>CG</td>
<td>BG</td>
<td>.97</td>
<td>0.782</td>
<td></td>
</tr>
<tr>
<td>Forefoot pressure: Medial</td>
<td>CG</td>
<td>HG</td>
<td>-3.82</td>
<td>0.000*</td>
</tr>
<tr>
<td>BG</td>
<td>HG</td>
<td>-4.79</td>
<td>0.000*</td>
<td></td>
</tr>
<tr>
<td>Hindfoot pressure: Lateral</td>
<td>CG</td>
<td>BG</td>
<td>-1.31</td>
<td>0.410</td>
</tr>
<tr>
<td>CG</td>
<td>HG</td>
<td>2.35</td>
<td>0.005*</td>
<td></td>
</tr>
<tr>
<td>BG</td>
<td>HG</td>
<td>3.66</td>
<td>0.000*</td>
<td></td>
</tr>
<tr>
<td>CG</td>
<td>BG</td>
<td>1.98</td>
<td>0.089</td>
<td></td>
</tr>
<tr>
<td>Hindfoot pressure: Medial</td>
<td>CG</td>
<td>HG</td>
<td>4.19</td>
<td>0.001*</td>
</tr>
<tr>
<td>BG</td>
<td>HG</td>
<td>2.20</td>
<td>0.016*</td>
<td></td>
</tr>
<tr>
<td>Static foot analysis</td>
<td>Forefoot pressure: Lateral</td>
<td>CG</td>
<td>BG</td>
<td>1.04</td>
</tr>
<tr>
<td>CG</td>
<td>HG</td>
<td>-8.24</td>
<td>0.005*</td>
<td></td>
</tr>
<tr>
<td>BG</td>
<td>HG</td>
<td>-9.28</td>
<td>0.001*</td>
<td></td>
</tr>
<tr>
<td>Hindfoot pressure: Lateral</td>
<td>CG</td>
<td>BG</td>
<td>8.63</td>
<td>0.002*</td>
</tr>
<tr>
<td>CG</td>
<td>HG</td>
<td>8.69</td>
<td>0.000*</td>
<td></td>
</tr>
<tr>
<td>BG</td>
<td>HG</td>
<td>.06</td>
<td>0.403</td>
<td></td>
</tr>
<tr>
<td>Hindfoot pressure: Medial</td>
<td>CG</td>
<td>BG</td>
<td>-2.26</td>
<td>0.069</td>
</tr>
<tr>
<td>CG</td>
<td>HG</td>
<td>-8.66</td>
<td>0.000*</td>
<td></td>
</tr>
<tr>
<td>BG</td>
<td>HG</td>
<td>-6.40</td>
<td>0.018*</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.005, CG - coordination group, BG - balance group, HG - healthy group
Limb and trunk ataxia on gait in MS ... Erdeo et al

parameters of gait in MS individuals. Morton and Bastian evaluated 20 patients with cerebellar damage in order to observe which one of the factors of balance and coordination affects gait, and they found that the step length was shorter, the gait speed was slower and the step width was higher in patients with balance problems in comparison to those with coordination problems. In contrast to the study by Morton and Bastian, in this study, the gait speed and cadence of the group with coordination problems were found to be significantly lower compared to the group with balance problems, while the step width was higher and the step length was similar. It is an expected result that both groups walk more slowly and with shorter steps than healthy individuals. However, the slower walking of individuals with coordination problems than those with balance problems can be explained as follows: individuals may be using the support period more effectively since their trunk and pelvic stabilisations are better. This may be advantageous in terms of single-leg stance. As a result, the joints are locked in the load-bearing leg, and dynamic activity may only be sustained relatively in the subtalar joint. This situation causes mediolateral mobility in the foot but at a position where the ataxic movements of the transferred leg are less observed. This stability may provide more appropriate control of the swing phase. However, there was rapid activity in the BG due to the reduction in trunk and pelvic stabilisation.

These patients may have difficulties in controlling the swing phase and may choose to quickly lift their legs and place them on the floor. The similarity of the stance time in both groups confirms this theory. Since there is no study to support this in the literature, interpretation of the results is limited in this context. However, the results are different from the study by Morton and Bastian since the number of individuals involved in the latter was small, and the disease group was different. The foot angle is the line that connects the calcaneus to the second metatarsal. It is observed that this angle deteriorates in the elderly, Parkinson’s patients, pregnant women and children with Down syndrome. In a study conducted on cerebellar patients, the foot angle was demonstrated to increase in order to ensure stability. In the present study, the average of the foot angle of patients with coordination disorders was similar to those with balance problems, but it was lower in both groups compared to the HG. The ankle angle is affected by many factors, such as spasticity power loss. Although pyramidal symptoms were kept minimal in our patients (only patients with EDSS pyramidal system scores below 3 were included), it is expected that it does not show similarities with the results found in isolated cerebellar patients.

Although there are many studies on plantar pressure in the literature, the number of studies on plantar pressure in MS is limited. Abdurakhmanov demonstrated that the pressure under the first metatarsal and in the heel decreased in MS patients. It is stated that the pressure reduction under the first metatarsal provides trunk stability. In the present study, static and dynamic analyses show that the load was distributed normally, as expected, in healthy individuals, whereas the static hindfoot medial load was distributed less in the other groups. This situation is more pronounced in individuals with coordination problems. The load transfer route is located laterally in the heel in patients with coordination problems. The increase in the lateral hindfoot load and the decrease in the medial may be caused by the inadequacy of normal subtalar joint pronation that occurs during stance. Consequently, foot pronation is restrained due to the coordination difficulty of the distal extremity. Similar results have been reported by Keklicek et al. Additionally, it was seen that the BG performed better foot accommodation to the ground. This may be the result of better extremity control in the BG.

In the dynamic analysis, it was observed that the pressure increases, especially in the heel medial and lateral regions, and decreases in the forefoot medial and lateral regions in individuals with coordination problems and balance problems, and it is higher compared to healthy individuals. However, there is no significant difference between the ataxia groups. This result suggests that there is a compensation mechanism developed to increase ankle joint motion width at the same time that patients with MS use the same compensation mechanisms to ensure balance, even if the ataxia is different. Another thought is that MS patients have a general neuromuscular response even if they are divided into groups. The DGI is a balance and gait evaluation developed by Shumway-Cook and Woollacott for the evaluation of individuals with ambulation and balance problems. In the present study, when the DGI averages were examined according to ataxia type, the DGI averages of the patients with balance problems were significantly lower than for those with coordination problems. Since the DGI also evaluates balance together with gait, the score of the group with balance problems was lower, as expected.

**This study has several limitations.** In the present study, only the spatiotemporal parameters of gait were evaluated. In a study in which kinetic and kinematic analyses were performed, more data on limb and trunk ataxia could be attained. In MS patients, it is difficult...
to separate the symptoms from each other with sharp limits. Just as it is difficult to find patients with only balance problems or only coordination problems, it is also impossible to exclude the pyramidal problem completely. Although in the present study the groups were not separated with sharp limits using clinical tests, we were able to group the patients according to low pyramidal scores, marked balance problems and marked coordination problems. Although this is a limitation, it is also related entirely to the complex nature of the disease.

In conclusion, spatiotemporal parameters of gait and static plantar pressure distribution were different between balance and coordination problems in MS patients. Patients with coordination problems walked with more short steps and more slowly; in both dynamic and static processes, patients with coordination problems carried the load with the hindfoot. Knowing the differences in gait and plantar pressure in patients with balance and coordination problems will guide the development of treatment programs. We believe that performing rehabilitation and orthosis applications considering these differences will improve the quality of gait. Our study may be a guide for future studies for MS and ataxia patients.

Acknowledgment. The authors would like to thank IDEA Translation Office for English language editing.

References

2. Wilkins A. Cerebellar Dysfunction in Multiple Sclerosis. Front Neurol 2017; 8: 312.
Limb and trunk ataxia on gait in MS ... Erdeo et al


References

* References should be primary source and numbered in the order in which they appear in the text. At the end of the article the full list of references should follow the Vancouver style.

* Unpublished data and personal communications should be cited only in the text, not as a formal reference.

* The author is responsible for the accuracy and completeness of references and for their correct textual citation.

* When a citation is referred to in the text by name, the accompanying reference must be from the original source.

* Upon acceptance of a paper all authors must be able to provide the full paper for each reference cited upon request at any time up to publication.

* Only 1-2 up to date references should be used for each particular point in the text.

Sample references are available from:
http://www.nlm.nih.gov/bsd/uniform_requirements.html
Case Reports

Posterior mediastinal neuroblastoma masked as flaccid paraparesis in a 3 year child

Farah S. Yahya, MBCHB, CABP, Hieder A. Al-Shami, MD, EFNS, MRCS.

ABSTRACT

After leukemias and brain tumors, neuroblastoma is the third most common cancer in infants and is the most common extracranial solid tumor in children. It is an embryonal tumor of the sympathetic nervous system. It originates from neuroblasts. Approximately two-thirds of cases present as an abdominal mass. Thoracic (posterior mediastinal) neuroblastomas are asymptomatic and may be diagnosed accidentally by imaging or may become symptomatic after invasion of the neural foramen. In this case report, we highlight the challenges in the early diagnosis of posterior mediastinal neuroblastoma as one of the causes of acute lower limb weakness in young children.

Case Report. Patient information. A 3-year-old female child with no significant past medical problems and unknown immunization history presented with a history of dry cough and gradual onset of dyspnea for 2 weeks without fever or evidence of upper respiratory tract infection. She began to develop significant weight loss and progressive fatigue. Chest X-ray showed a heterogeneous opacity involving most of her right lung.
Neuroblastoma masked as paraparesis … Yahya & Al-Shami

(Figure 1 A&B). The initial diagnosis was pneumonia, for which she was kept on antibiotics (amoxicillin) and bronchodilators. However, this treatment failed to improve her cough or dyspnea. Several days later, the patient developed weakness of both lower limbs which then progressed to a complete inability to walk, with flaccid weakness of her lower limbs over 20 days in addition to dyspnea. She was admitted to a local hospital. The main differential diagnosis at that time was Guillain-Barré syndrome, depending on history and clinical findings, only because the facility for other sophisticated investigation was unfortunately unavailable at that peripheral hospital. Her condition rapidly worsened, including further worsening of her dyspnea and the development of central cyanosis. She was referred to our tertiary center for immediate mechanical ventilation.

Clinical findings. Upon arrival, the patient was severely dyspneic with central cyanosis, respiratory rate of 50 cycles/minute, and peripheral capillary oxygen saturation (SpO2) of 85% on room air. Neurological examination showed loss of sphincter control such that the bladder was palpable up to the level just below the umbilicus; therefore, she underwent catheterization. Further examination showed 2 palpable small right-side supraclavicular lymph nodes. Chest auscultation showed poor air entry in most of her right lung. Neurological examination of her lower limbs revealed flaccid paraparesis with loss of tone and reflexes and equivocal Babinski reflex on both sides. Sensory examination was difficult and non-conclusive and opsoclonus-myoclonus

![Figure 1 - Chest X-ray posterior-anterior view showing rather a well defined large homogenous soft tissue opacity lesion in the right upper zone area (arrow) that have broad based toward mediastinum and making an obtuse angle with it. There are no any detected calcifications seen within the lesion. The mass have overlapped the upper thoracic spine but not Silhouetting the upper cardiac border suggested to be retro-cardiac. Note the widening of the right sided upper posterior rib interspace highly localizing mass lesion to be in the posterior mediastinum.](image)

![Figure 2 - Chest MRI (multiple sections through the chest and mediastinum). The examination showing A) large well defined soft tissue lesion about 8 * 6 * 5 cm (arrow head), have low signal intensity in T1W image with multiple signal void area in favouring of few spots of calcification, This mass being extra pulmonary lesion at the right side para-vertebral area showing extension upward occupying the right side upper postero-superior thoracic gutter connecting to another mass at the right side supraclavicular area in favour of multiple discrete & matted involved lymph nodes (arrow) by metastasis that have the same mass criteria in signal intensity enhancement. B) The whole 2 bulk masses showing heterogeneous enhancement post contrast (arrow). There are no any surrounded bony changes. This large mass abutting the descending thoracic aorta displacing trachea to the left side.](image)
movement of both eyes were observed; however, her pupils were normal in size and reacted to light with no periorbital ecchymosis.

The patient was admitted to the respiratory care unit and ventilated with synchronized mechanical ventilation (SMV) for her declining oxygen saturation and worsening dyspnea.

**Diagnostic assessment.** The patient’s serum electrolyte levels were normal and other blood test results were unremarkable except for respiratory acidosis. Emergency magnetic resonance imaging (MRI) of the chest showed a large right posterio-superior mediastinal mass that had pushed the trachea to the left with heterogeneous enhancement associated with pleural effusion, as well as 2 supraclavicular lymph nodes, direct invasion of the dorsal spine, and canal stenosis. The liver was normal no metastasis (Figure 2 A&B).

Whole-spine MRI showed extension of the tumor to the intraspinal canal at the level of D1-D8 (Figure 3 A&B). The initial differential diagnosis was neuroblastoma. Thereafter, assessment of urine vanillylmandelic acid (VMA) showed high levels. Bone marrow biopsy confirmed infiltration with neuroblastoma tumor cells.

**Therapeutic intervention.** Due to spinal compression, which is an oncologic emergency, the patient underwent thoracotomy and total resection of the mass with spinal decompression and relief of the canal stenosis with pedicle screw instrumentation to fix the spine after long-segment decompression.

**Follow-up and outcome.** Histopathological examination detected a poorly differentiated neuroblastoma as a small, blue, round-cells tumor with a fine chromatin pattern and high mitotic rate with nests of cells (pseudorosettes). Supraclavicular lymph node biopsy detected features of round blue cells consistent with neuroblastoma. According to the revised Shimada grading system, the tumor was a poorly differentiated neuroblastoma. Therefore, according to the International Neuroblastoma Risk Group Staging System (INRSS), the patient was classified as having high-risk neuroblastoma.

The postoperative period passed smoothly with significant improvement of the dyspnea followed by weaning from the ventilator but with residual lower limb weakness, opsoclonus myoclonus eye movement, and loss of bladder control. Then, the patient was administered a course of induction of intensive chemotherapy including the combination of cyclophosphamide, etoposide, and vincristine; however, the patient unfortunately died during the induction phase due to severe pancytopenia, overwhelming septicemia, and renal impairment despite intensive care and management. The timeline of patient case history and follow-up is shown (Figure 4).

**Discussion.** Patient perspective. We reported a case of acute lower limb weakness in a young child which had masked an underlying mediastinal neuroblastoma. Acute
flaccid paralysis is a pediatric emergency which includes many differential diagnoses such as poliomyelitis (which remained non-eradicated in the patient’s locality), Guillain-Barré syndrome (GBS), trauma, transverse myelitis, and periodic hypokalemic paralysis. Every pediatrician should be aware of the common differential diagnoses of acute lower limb weakness in children. However, malignancy is an uncommon underlying cause of acute lower limb weakness in young children. Therefore, prompt evaluation of such cases is essential to exclude uncommon and malignant underlying causes. Our patient was initially misdiagnosed with acute flaccid paraparesis due to GBS due to the poor facilities in the hospital in which she was first managed before referral to our tertiary center. In this case report, we emphasize the importance of awareness of neuroblastoma as one of the potential underlying causes of spinal cord compression in young children. There are a few similar reported cases in the literatures. Between 7 and 15% of children with neuroblastoma present with spinal cord involvement. Chemotherapy and laminectomy are the modalities of choice for spinal compression caused by neuroblastoma. Spinal cord compression signs and symptoms including pain, weakness, sensory disturbances, and sphincter dysfunction are well known by every clinician. However, in young children, the detection of spinal cord compression is very difficult because of the subtle and gradual onset of the neurological symptoms; thus, it is difficult to identify the symptoms in young children, which leads to delayed diagnosis and serious neurological outcomes, as occurred in our patient. Young children refuse to walk and may even lose bowel and/or bladder control when they are ill. Thus, parents may miss early limb weakness. Therefore, the diagnosis is challenging for clinicians unfamiliar with normal motor milestones in children of such a young age. Emergency MRI is the imaging modality of choice to provide adequate clues in suspected cases.

Neurological recovery is correlated with early diagnosis of the initial symptoms. Caretaker or parent neglect and ignorance, unfortunately, leads to delayed diagnosis and advanced stage, resulting in dismal outcomes, as occurred in our patient. Due to the bulk of the tumor with advanced stage, delayed diagnosis, and the use of combination chemotherapy, we unfortunately lost the patient during the induction phase due to refractory pancytopenia, overwhelming septicemia, and renal failure despite careful care and blood product support with broad-spectrum antibiotics and early dialysis.

**Conclusion.** Malignant spinal cord tumors are a disastrous cause of acute lower limb weakness in children. Neuroblastoma is a common extracranial solid malignant pediatric tumor. Posterior mediastinal neuroblastomas comprise 15% of all cases of neuroblastoma as a primary site. The patients at high risk are those older than 18 months of age with disseminated tumors. Spinal cord compression symptoms and signs are subtle and diagnosis is especially challenging in young children. Mediastinal neuroblastoma can be asymptomatic and detected incidentally by imaging; it can also be symptomatic, causing respiratory or neurological symptoms if it grows through the spinal foramen into the spinal canal. Therefore, posterior mediastinal neuroblastoma should be considered in the differential diagnosis of dyspnea and acute paraparesis in young children.

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**References**


Awareness of patients with multiple sclerosis in Saudi Arabia regarding the relationship between smoking and multiple sclerosis

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ABSTRACT

Aims: To assess the awareness of patients with multiple sclerosis about the relationship between smoking and multiple sclerosis in Saudi Arabia.

Methods: A descriptive cross-sectional study was carried out in 2018 for 162 patients who are attending a tertiary hospital in Jeddah, Kingdom of Saudi Arabia. Self-administered questionnaire and telephone-based interview were used to collect the data. The Analysis was carried out through a statistical package for the social sciences (SPSS) software version 21 by using chi-square.

Results: A total of 162 patients responded to the questionnaire (response rate, 58.1%). Among the respondents, 56 were current smokers, and 41 of them were males. Thirty-nine patients had a previous cessation attempt, and in 64.1% of the cases, it was mainly a self-made decision. Doctors counseled only 52.7% of the active smokers regarding the effect of smoking on the progression of their disease.

Conclusion: Results indicate that there is a low level of awareness regarding the risk of smoking on multiple sclerosis. Therefore, educational programs and campaigns would be beneficial to fulfill the gap. Moreover, Health institutions and health care workers should take this issue into account when counseling the patient.

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Multiple sclerosis (MS) is a neurodegenerative, inflammatory, demyelinating disease of the central nervous system that has an increasing incidence.1-2 It is one of the world’s most common neurologic disorders with a prevalence of 30.1 cases affected per 100 000 population worldwide.3 Epidemiological studies have shown that MS has a high prevalence on the Arabian Gulf region.2
Multiple Sclerosis usually starts between the ages of 20 and 50. After trauma, the most common cause of neurological disability in young individuals is MS and it leads to a personal, social, and economic public health burden. The medical costs of MS care rank second after congestive heart failure, with an estimated cost of $8528 to $54,244 per patient per year. Multiple sclerosis has 4 clinical categories: primary progressive MS (PPMS), secondary progressive MS (SPMS), relapsing-remitting MS (RRMS), and progressive relapsing MS (PRMS). Almost 85% of patients present with RRMS.

Multiple Sclerosis is a disease of an unknown cause, but it is believed that it is a multifactorial disease that can be due to genetic susceptibility and environmental factors; both of these play a valuable role in the pathogenesis of the disease. One of the environmental factors that can play a role in the progression of MS is smoking. Worldwide in 2015, 1 in 19 female and 1 in 4 male, smoked cigarettes daily. Furthermore, a cross-sectional study has shown that individuals with MS smoke more than the general population.

A British Cohort Study that was accomplished in 2017 that assessed the effect of smoking cessation on the degree of disability of MS patients found that MS patients who had smoke-free years had decreased risk of disability. In addition, non-smokers had a decreased risk of disability in comparison with current smokers.

Not only cigarette smoking can affect, passive smoking also plays a role as it was found in a case-control study in Iran 2016 where their results notably related MS to Having ever smoked Water-pipe (odds ratio (OR)=1.77 (1.36–2.31), tobacco OR=1.69 (1.24–2.31), or even being exposed to passive smoking OR=1.85 (1.48–2.32). Furthermore, the association between smoking and MS progression has been researched in a 2015 Swedish cross-sectional study, which concluded that after diagnosis with MS, each added year of smoking increased the likelihood of disease transition to SPMS by 4.7%. In addition, smoking does not only cause acceleration of the disease; it also increases the mortality. An American study in 2015 that examined the effect of smoking and other lifestyle factors on the mortality of MS patients showed that baseline smoking was associated with higher mortality. There is a serious lack of information about the knowledge of, attitude to and awareness of smoking-related issues in MS patients. Therefore, this study aims to assess the awareness of any link between smoking and MS in patients with multiple sclerosis at King Abdulaziz University Hospital (KAUH), Jeddah, Kingdom of Saudi Arabia.

Methods. A cross-sectional descriptive study was conducted in 2018 at KAUH, Jeddah, Kingdom of Saudi Arabia. Patients who were diagnosed to have MS of all types of all ages, both genders, and Saudis or non–Saudis were included. The study was approved by the institutional review board (IRB) of King Abdul-Aziz University (KAU). Some data were collected by well-trained medical students through telephone-based interviews using phone numbers from the medical records securely and confidentially. The remaining data were collected through a self-administered questionnaire for patients who attended the MS clinics. The questionnaire was reviewed by 2 consultant neurologists who were experts in the management of MS, and was prepared in multiple-choice question (MCQ) format with an average time allowance of 20 minutes for each person. It was formulated in Arabic and English. Verbal or written consent was obtained from respondents after clarifying the purpose of the study.

The questionnaire was composed of 4 sections: The first and second sections consisted of demographic data and information about the clinical status of the patient’s disease which includes age, gender, income, education level, course of the disease, and duration of it. The third section consisted of questions in respect of their smoking status at the time of diagnosis, their current smoking status and if any smoking cessation attempt has been made and who advised them about cessation. The fourth section consisted of questions in regard to their knowledge about the relationship between smoking and MS. They were questioned if they considered smoking as a risk factor for MS. In addition, they were asked if they were counseled about the impact of smoking in the progression of the disease by their doctors, and about their opinions as if they think that patients with MS do not have to stop smoking as the disease will progress anyhow.

The center for disease control and prevention definitions’ for current smoker, ex-smoker and never smoker were adopted. Current smoker: is an adult who smokes at the present time and who has smoked 100 cigarettes in his/her life. Ex-smoker: is an adult who had quit smoking at the time of interview in whom has smoked greater than 100 cigarettes in his/her life. Never smoker: is an adult who has smoked less than 100 cigarettes in his/her life or who has never smoked.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.
Awareness about smoking relation to MS ... Bashamakh et al

Limitations were expected to be present in the data collection process such as: missing or change in phone numbers of the patients, refusal of the responders to participate in the study and communication issues. Data was entered into Microsoft Excel 2015 and analysis of the data was carried through the statistical package for the social sciences (SPSS) software version 21 using the chi-squared test with a p-value<0.05 considered significant.

Results. Of the 279 patients invited to participate in this study, only 162 filled in the questionnaire, representing a response rate of 58.1%. Of these, 88 (54.3%) were females. Patients in the 31–40 years age bracket were the most represented, comprising 40.7% of the total sample. The highest educational level encountered was a bachelor’s degree/ diploma (69.1%). Clinically, respondents had different types of MS, but approximately 64.8% did not know what type of MS they were diagnosed with (Table1).

The sample consisted of 56 active smokers (34.6%), 19 ex-smokers (11.7%) ex-smokers, and 87 patients who had never smoked (53.7%). Of the 56 active smokers, 41 were males. Additionally, the analysis revealed a significant relationship between the male gender and current smoking status (\( \chi^2 = 52.435, p = 0.001 \)). Conversely, there was no significant relation between age and current smoking status (\( \chi^2 = 7.414, p = 0.116 \)).

Among the 39 patients who had attempted to give up smoking, 64.1% responded that their smoking cessation was mainly a self-made decision. Other patients took the decision to quit smoking based on the advice of a neurologist (4.9%), another physician (2.5%), or friends (0.6%) or from information read on the internet/social media (0.6%).

Close to half of the MS patients (n=75, 46.3%) did not know whether smoking was a risk factor for MS. Fifty-two patients (32.1%) did not agree that smoking was a risk factor, whereas 31 (19.1%) agreed that it was a risk factor for MS. Four patients (2.5%) failed to respond to this question. More details are given in Table 2 based on smoking status.

Of the 39 patients who had previous attempts at smoking cessation, 7 (17.9%) thought that smoking was a risk factor for MS, 17 (43.6%) thought that it was not, and 15 (38.5%) did not know. However, there was no significant relationship between smoking cessation and knowledge of smoking as a risk factor for MS (chi-\( \chi^2 = 1.547, p = 0.461 \)). Among patients who had never attempted to quit smoking, 2 (8.7%) thought smoking was a risk factor for MS, 9 (39.1%) thought it was not a risk factor, and 12 (52.2%) did not know.

When active smokers were asked if they had been counseled by their doctor regarding the effect of smoking on the progression of the disease, approximately half

Table 1 - Demographic characteristics of the patients (n = 162).

<table>
<thead>
<tr>
<th>Variables</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>88 (54.3)</td>
</tr>
<tr>
<td>Male</td>
<td>74 (45.7)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>≤ 30</td>
<td>63 (38.9)</td>
</tr>
<tr>
<td>31–40</td>
<td>66 (40.7)</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>32 (19.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Primary School</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Secondary school (High school)</td>
<td>34 (21)</td>
</tr>
<tr>
<td>Bachelor or diploma</td>
<td>112 (69.1)</td>
</tr>
<tr>
<td>Postgraduate (Master, PhD)</td>
<td>10 (6.2)</td>
</tr>
<tr>
<td>Income</td>
<td></td>
</tr>
<tr>
<td>More than expenditures (High)</td>
<td>31 (19.1)</td>
</tr>
<tr>
<td>Equal to expenditures (Medium)</td>
<td>103 (63.6)</td>
</tr>
<tr>
<td>Less than expenditures (Low)</td>
<td>28 (17.3)</td>
</tr>
<tr>
<td>Disease course</td>
<td></td>
</tr>
<tr>
<td>Relapsing-remitting</td>
<td>43 (26.5)</td>
</tr>
<tr>
<td>Primary progressive</td>
<td>6 (3.7)</td>
</tr>
<tr>
<td>Secondary progressive</td>
<td>5 (3.1)</td>
</tr>
<tr>
<td>Patient does not know</td>
<td>105 (64.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Disease duration</td>
<td></td>
</tr>
<tr>
<td>≤6 months</td>
<td>6 (3.7)</td>
</tr>
<tr>
<td>6 months to &lt;2 years</td>
<td>29 (17.9)</td>
</tr>
<tr>
<td>2 - 5 years</td>
<td>44 (27.2)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>82 (50.6)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

Table 2 - Summary of responses to the question "Do you think smoking is a risk factor for multiple sclerosis?"

<table>
<thead>
<tr>
<th>Variables</th>
<th>Smoking Status</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Current Smoker</td>
<td>Ex-Smoker</td>
</tr>
<tr>
<td>Yes</td>
<td>5 (8.9)</td>
<td>10 (52.6)</td>
</tr>
<tr>
<td>No</td>
<td>25 (44.6)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Does not know</td>
<td>26 (46.4)</td>
<td>7 (36.8)</td>
</tr>
</tbody>
</table>

*Data are presented as frequency (percent within the smoking status) unless otherwise specific. †Number missing=4.
of them (n=29, 52.7%) responded that they had been counseled by the doctor who managed their MS.

As shown in Table 3, 111 patients (71.2%) did not agree with the statement “smokers do not have to stop smoking as their disease will get worse in any case”. However, there was no significant relationship between current smoking status and patients’ perception of the effect of smoking cessation on MS progression ($\chi^2=1.789, p=0.409$).

Of those who had a previous smoking cessation attempt (n=39), 11 (28.2%) thought that smokers did not need to stop smoking as their disease would get worse anyway, while 28 (71.8%) did not agree with this statement. Conversely, 15 (65.2%) out of 23 patients who had never attempted to quit smoking thought it was not necessary for smokers to quit smoking because their disease would get worse in any case.

### Discussion

This study attempted to assess the extent of awareness of the relationship between smoking and their disease in patients with multiple sclerosis (MS). If the awareness can be identified, then an action plan can be put in place to address such an issue. The results of this study proved that there is a higher proportion of male smokers with MS than female smokers with MS. A recent study revealed that the prevalence of smoking among female Saudi residents was 3.9% while it was 32.5% in male residents, which means that males are eight times more likely to use tobacco than females. The male predominance is a worldwide finding, as a 2015 global study found that the prevalence of daily tobacco smoking was only 5-4% in women, compared with 25% in men. This gender-related variation could be due to a combination of several factors including the physiological effects of ovarian hormones, and cultural, and behavioral influences. From a sociology viewpoint, smoking is probably more acceptable in men, based on the traditional portrayal of women as the primary childcare providers. In this context, the possibility of teratogenic effects leading to congenital disorders in the offspring as well as the danger of infants being affected via breastfeeding might be seen as deterrents to the smoking habit in women.

A research that has conducted in the United Kingdom confirmed that the highest percentage of current smokers was in Secondary progressive multiple sclerosis group. In the present study, an association between the course of the disease and smoking status could not be identified as most of the respondents in this study did not know the classification of their disease. Moreover, around half of the participants did not know whether smoking was a risk factor for MS or not and 32.1% did not agree that smoking can cause MS. All of these results highlight the notion that patients in our population had poor knowledge about their disease. In fact, this lack of awareness of MS was found to be a general problem encountered in Saudi Arabia. This emphasizes the importance of providing better education to these patients.

To expand on this, 8.9% of active smokers, 52.6% of ex-smokers, and 19.3% of patients who had never smoked knew that smoking was a risk factor of MS. Nevertheless, patients who had ever attempted to quit smoking were again asked the same question and 43.6% of them thought that smoking was not a risk factor for MS. These conflicting results cannot be easily explained; hence further research aimed at reaching a conclusion on this point is warranted, the results of which might help improve strategies to educate patients with MS.

As previously mentioned smoking cessation contributes significantly to reduction of the level of progression and the degree of disability in MS. Therefore, we studied the factors that might affect the patient’s decision to attempt to give up smoking and we found that the majority of patients who attempted to stop smoking made this decision autonomously. One study suggested that the diagnosis of MS influenced some to consider quitting whereas they were not considering quitting before the diagnosis. Other patients in the present study were considering attempting smoking cessation according to advice from neurologists, other physicians, friends and the internet.

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Yes</th>
<th>No</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td>18 (11.5)</td>
<td>37 (23.7)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>7 (4.5)</td>
<td>12 (7.7)</td>
<td>0.409</td>
</tr>
<tr>
<td>Never-smoker</td>
<td>20 (12.8)</td>
<td>62 (39.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Total†</strong></td>
<td>45 (28.8)</td>
<td>111 (71.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as frequency (percent) unless otherwise specific. Number missing=6.
This finding was not expected as it was assumed that the majority of them would be influenced by advice from a physician. Health professionals have a remarkable role to help patients quit smoking by affording advice about smoking danger: yet, there were lots of obstacles such as lack follow-up resources and training which could prevent that. However, A recent study emphasized that there were lots of opportunities that have been lost.22-23

According to this study, approximately half of the patients were not counseled by their doctors about the role of smoking in the progression of the disease. The clinical guideline emphasized the importance of referring smokers in general to a specially trained physician.24 Research into patients’ perceptions of doctors’ advice to quit smoking revealed why some patients had not been counseled by their physician, and the fact that physicians feel that there is not enough time during their shifts to have this conversation about cessation. A criticism of this inference is that it takes only a few minutes to provide this advice.25 In spite of the fact that any advice regarding giving up smoking may not always result in concerted efforts to quit, it may have a supplementary effect in addition to other measures.

Although, the notion that “stopping smoking was pointless as the disease would get worse anyhow” was not a universal belief, almost a quarter of the sample considered this to be true. Some people went as far as believing that the advantages of smoking outweigh the dangers.26 Even when a disease is caused by smoking, they still have the desire to continue. The need to make several attempts at quitting and the potential frustration of not continuing the habit might be additional deterrents.27

The present study is novel in that it looks at the patient’s perspective regarding the relationship between smoking and MS. However, some difficulties were encountered during this research, as some patients refused to participate and most of the patients were followed up at a tertiary center with an MS specialist so the results may not be appropriate to the wider patient population who may be monitored by a general neurologist. In addition, most parts of the questionnaire were self-administered, and in retrospect, it is felt that a better option would have been a telephone-based questionnaire in order to avoid misunderstanding by patients.

In conclusion, our results indicate that there is a low level awareness regarding the risk of smoking on the progression of MS. In view of this deficiency, educational programs and campaigns aimed at filling this gap would be beneficial. Health institutions and health care workers should take this issue into account. Further research regarding the potential impact of education is needed to overcome the shortage. All of these would raise the level of awareness and improve knowledge within the MS patient community.

Acknowledgment. We want to show our gratitude to (Anwar Saeed AlZahrani, Rota Hameza Albadawi, Shomokh Fahad Alotaibi, Waad Faisal Bokhari) for their important role in collecting the data. We also would like to thank Editage for English language editing.

References


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**Statistics**


Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as the use of P values, which fails to convey important information about effect size. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the computer software used.
ABSTRACT

Tacrolimus is an immunosuppressant agent utilized for solid organ transplantations. It has been associated with rare neurotoxic effects. This case highlights one possible delayed neurotoxic effect. A 52-year-old lady on tacrolimus (3 mg daily) among her immunosuppressive regimen for her kidney transplant 16 year ago. She presented with unilateral left paracentral black dots progressing over a week, associated with periorbital and temporal pain. The patient was diagnosed with left papillitis. Tacrolimus was tapered and then changed to cyclosporine. However, patient did not show any improvement of any parameter. Reports have indicated such neurotoxic effects with Tacrolimus use. Here, the report emphasizes on the unilateral optic neuropathic effect of tacrolimus even after one decade.

Case Report. Patient information. A 52-year-old female underwent renal transplant due to hypertensive renal failure in 2002. The patient had a history of diabetes (post-transplant), hypertension, dyslipidemia, and osteoarthritis. The immunosuppressive regimen comprised of tacrolimus (FK506, 3 mg daily), cellcept (mycophenolate mofetil, 500 mg twice daily), and prednisolone (5 mg daily). Regular follow-ups were carried out with an ophthalmologist with normal fundal examination and no other complaints. Other medication history included anti-diabetic drugs, antihypertensive drugs, atorvastatin, multivitamins, and esomeprazole, and allergy to lisinopril and azithromycin.

Clinical findings. The patient presented with paracentral black dots in the left eye progressing over a week that plateaued later, and motion aggravated periorbital and temporal pain. The ophthalmologist confirmed left papillitis. Tacrolimus was tapered and then changed to cyclosporine. However, patient did not show any improvement of any parameter. Reports have indicated such neurotoxic effects with Tacrolimus use. Here, the report emphasizes on the unilateral optic neuropathic effect of tacrolimus even after one decade.
Tacrolimus induced optic neuropathy … Alnahdi & Al Malik

Diagnostic assessment. Extensive investigations were requested. Tacrolimus (FK506) serum level was at 8.9 ng/mL (target range 5 - 15 ng/mL), and not exceeding 9.4 ng/mL for 5 years. The magnetic resonance imaging (MRI) of orbits and brain was unremarkable for pathological changes, excluding the neoplastic etiologies in the optic pathway, but had multiple white matter foci suggestive of mild chronic ischemic changes (Figure 1). Serology for neuromyelitis optica antibodies, oligo-clonal band antibodies, and cerebrospinal fluid workup tested negative. Laboratory test results showed normal estimated glomerular filtrate rate, C-reactive protein: 9 mg/L (normal range, <8 mg/L), erythrocyte sedimentation rate: 88 with mild chronic elevation for the last 5 years, otherwise normal. Infectious etiologies were excluded, and stains for cytomegalovirus and mycobacterium were negative.

Therapeutic assessment. The patient was first discharged with a tapered dose of tacrolimus of 1.5 mg daily. Then at 3-week follow-up, tacrolimus was switched to cyclosporine by renal transplant team (Figure 2).

Follow-up and outcomes. Three-week follow-up revealed Lt. RAPD, VA Rt. eye 20\20 and Lt. eye 20\120, visual field (VF) Lt. cecocentral scotoma, and Lt. fundal swelling with normal EOM. At the 6-month follow-up, the patient showed no improvement and symptoms remained similar to the previous state.

Figure 1 - Magnetic Resonance Imaging images obtained after 4 weeks of presentation. T2 weighted image reflecting the absence of any pathological evidence in the optic pathway that may correlate with neoplastic, inflammatory, or ischemic etiologies.

Figure 2 - Timetable demonstrating the sequence of events and case progression.
**Discussion.** Tacrolimus, a calcineurin inhibitor, has shown neurotoxic properties causing optic neuropathy in cases of bone, liver, and islet pancreatic transplantations, even at non-toxic levels. In this case, neurotoxic effects of tacrolimus was the most probable differential diagnosis after extensive laboratory and imaging workup dismissed any possible role of neoplastic, inflammatory, infectious, or ischemic etiologies. The other probable diagnosis was giant cell arteritis; however, it was excluded by rheumatology team due to the patient’s immunosuppressive regimen. The interval between tacrolimus initiation and symptoms onset varied ranging from months to years from previous reports.

In this case, the patient was on tacrolimus for 16 years, and had a normal visual follow-up until incidence of painful unilateral optic neuropathy progressing over a week and then plateaued. Therefore, the interval between tacrolimus initiation and visual changes may indicate delayed toxicity. Even after discontinuing the drug no changes were noted in the patients’ symptoms, indicating irreversibility of the toxic effect. Venneti et al. reported a case that showed histopathologic demyelination process due to tacrolimus at non-toxic serum levels. Tacrolimus neurotoxic effect reportedly presented white matter lesions on MRI; however, imaging of our case did not reveal any such lesions consistent with the clinical presentation.

The pathogenesis of tacrolimus-induced optic neuropathy remains unclear, although few reports postulate that ischemia due to vasoconstriction could be the possible etiology. The patient did not regain her previous vision or show any improvement in the visual fields or VA, even after dose tapering or changing to cyclosporine.

In conclusion, tacrolimus has been linked to causing various neurotoxic effects as evident in the case. Unilateral optic neuropathy has been reported throughout the past decade, but the exact etiology remains unclear. However, it is imperative to address the possible delayed toxic role of tacrolimus after long-term use.

**Acknowledgements.** We would like to thank Editage (www. Editage.com) for English language editing.

**References**

The comorbidity of headaches in pediatric epilepsy patients: How common and what types?

Hanin Al-Gethami, MD, Muhammad Talal Alrifai, MD, Ahmed AlRumayyan, MD, Waleed AlTuwaijri, MD, Duaa Baarmah, MD.

ABSTRACT

Objectives: To estimate the prevalence and characteristics of headache in pediatric epileptic patients.

Methods: This cross-sectional study was performed over 6 months period from January 2018 to June 2018 at King Abdullah Specialist Children Hospital, King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia using a structured questionnaire in pediatric patients with epilepsy.

Results: There were 142 patients enrolled (males, 57.7%; average age, 10.7±3.1 years) with idiopathic epilepsy (n=115, 81%) or symptomatic epilepsy (n=27, 19%). Additionally, patients had focal epilepsy (n=102, 72%) or generalized epilepsy (n=40, 28%), and among them, 11 had absence epilepsy. Overall, 65 (45.7%) patients had headaches compared with 3/153 (2%) in the control group (p<0.0001). Among the 65 patients with headaches, 29 (44.6%) had migraine-type, 12 (18.4%) had tension-type, and 24 (36.9%) had unclassified headache. There was no significant difference in age, gender, type of epilepsy syndrome, and antiepileptic used except in patients with or without headache. For migraine patients, there was a lower headache prevalence in the subgroup treated with valproic acid compared with other treatments.

Conclusion: Headache, predominantly migraine, is a common problem in pediatric epileptic patients and choosing valproic acid when possible can be important in preventing migraine in these patients.


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Epilepsy and headache are chronic paroxysmal disorders that affect adult and pediatric patients with episodic manifestations. Headache or (cephalalgia) is defined as a feeling of pain in the region of the head or neck. Primary headaches include migraines, tension-type headache, and cluster headache. Epileptic seizure is a brief episode of signs or symptoms caused by abnormal excessive synchronized neuronal activity. Epilepsy is defined as a condition where the patient has an enduring tendency to have recurrent unprovoked seizures. These two disorders coexist in some patients. There are few studies on the comorbidity of headaches in children with epilepsy. Other studies reported a significant association between migraine and epilepsy. Additionally, the genetic predisposition for both entities was reported in some forms of channelopathy, and others found more prevalence of migraine headache in specific diseases in pediatric like benign epilepsy with centrotemporal spikes and juvenile myoclonic epilepsy. Seizure-associated headache is common, with an incidence of 42–51% in adult epileptic patients. However, for pediatric patients, it is often neglected by parents and physicians because of other neurological manifestations of the seizure such as loss of consciousness and motor components, and approximately 36% of the parents were reported to be unaware that their children experienced headache. It is our experience that headache is a common problem in up to 50% of epilepsy patients but we do not know exactly the prevalence, in addition to what type of headache is most commonly found in epileptic pediatric patients. Because of few reports on this topic have conflicting results, the objective of this study was to evaluate the prevalence and characteristics of headache in children with epilepsy who were seen at one center in Saudi Arabia.

**Methods.** This cross-sectional study was performed over a 6-month period from January 2018 to June 2018 at King Abdullah Specialist Children Hospital, King Abdulaziz Medical City, Riyadh.

Inclusion criteria were as follows: pediatric epilepsy patients (5–16 years of age) and who were mentally normal and could communicate their symptoms with and without other comorbidities like diabetes, asthma, or renal disease. Epilepsy syndrome patients were excluded since most of them mentally affected. Patients with intellectual disability and patients with unclear information supplied by the patient or their family were also excluded. We had up to 20 patients / pediatric neurology clinic, and 8 clinic/ week, so 142 patients met our inclusion criteria and more than 20 patients were excluded. Patients’ parents/guardians provided informed consent and the study was approved by an ethics board at our hospital. Also, the study was according to principles of Helsinki Declaration.

Patients and their family were interviewed by one of the researchers (H.G.) using a structured questionnaire during their visit to the clinic. The questionnaire was structured to include demographic and clinical information about the symptoms of epilepsy and headache when present. Each patient was asked specifically if had headache, and if yes, the exact age of onset, how many attacks/ month, the relationship to seizure in timing, quality of headache, location, severity, other associated symptoms like nausea, vomiting, photophobia, phono-phobia, facial pain, orbital pain, and eye swelling, if had aura before headache, and frequency of headache. Further data regarding neurological exam, electrophysiological and neuroimaging studies were obtained from the patients’ charts.

The control group comprised siblings of the patients with epilepsy who were free from epilepsy and who were 5–16 years of age, otherwise healthy, and could communicate their symptoms.

Headache was diagnosed based on the International Classification of Headache Disorders (ICHD-II) criteria, and epilepsy was diagnosed based on the International League Against Epilepsy (ILAE) criteria. Seizures were considered frequent if they occurred 2 or more times per month; otherwise, they are considered to be infrequent. Seizure-associated headache was defined as a headache starting within 1 hour before or after the seizure. Headache was either classified to be peri-ictal or inter- ictal headache, however, the peri-ictal headache can be classified to pre- ictal, ictal, and post-ictal headache. Pre-ictal headache is a headache that began before the seizure and lasted until its onset. Ictal headache defined as epileptic seizures in which headache is one of the constituents of the epileptic seizure, besides other manifestations like sensory-motor, psychiatric or non-autonomic one. A headache that occurred only after the seizure is called a post-ictal headache. This classification is based on the IHS criteria. Other headaches are considered inter-ictal.

The data were entered into a database and analyzed using SAS (Statistical Analysis Software). Statistical analysis was performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). The significance level was set at 0.05.

**Disclosure.** Authors have no conflict of interests, and the work was not supported or funded by any drug company.
analysis tests for both continuous and categorical variables were used as appropriate. No other systems were used.

We calculated measures of the association between variables expressed as the \( p \)-value, and for each test the level of significance was set at 0.05.

**Results.** There were 142 patients with epilepsy who fulfilled the entry criteria for this study. Among these patients, 82 were males (57.7%) and the overall average age for both male and female was 10.7±3.1 years. Idiopathic epilepsy was present in 115 (81%) patients while symptomatic epilepsy was present in 27 (19%) patients. Focal epilepsy was present in 102 (72%) and generalized epilepsy was present in 40 (28%) patients, 11 of whom had absence epilepsy. Neuroimaging (CT or MRI) was performed in all patients, and 30/142 (21%) of the studies showed abnormal results, such as focal cortical dysplasia and mild ischemic brain insult.

The EEG which is an electrophysiological monitoring method used to record electrical activity of the brain, was also performed for 141 patients, and 59 (41.8%) showed normal results, 73 (51.8%) showed epileptiform activity focal and generalized interictal discharges with majority had generalized discharges, and 9 (6.4%) showed focal or generalized slowing.

Among the 142 patients, 65 (45.7%) had headache compared with 3/153 (2%) of the control group (\( p<0.0001 \)). The 2 groups were matched for age and gender (Table 1).

Among the 65 patients with headache, 29 (44.6%) patients had migraine-type headache, 12 (18.4%) patients had tension-type headache, and 24 (36.9%) patients had headache that was an unclassified type. The headache and epilepsy started at the same year in 28 patients, and headache preceded epilepsy in total of 7 patients, it was 1-year period in 5 patients, 2 years period in 1 patient, and 3 years period in 1 patient.

Epilepsy started 1 year before headache in 10 patients, 2 years before in 3 patients, 3 years before in 6 patients, 4 years before in 5 patients; 5 years before in 2 patients; and 6 years before in 2 patients, 8 years before in one patient, and 11 years before in one patient.

For the timing of headache in relation to seizures, 56 out of 65 (86%) patients had interictal headaches, 5 (7.6%) patients had post-ictal headaches, 17 (26%) patients had preictal headaches, and 3 patients had ictal headache (4.6%). In fact, some patients have mixed

### Table 1 - Demographics and presence of headaches in the patient and control groups.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Patients n=142</th>
<th>Control n=153</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>82 (57.7%)</td>
<td>85 (55.5%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Age (years; mean, standard deviation)</td>
<td>10.7±3.1</td>
<td>10.6±2.9</td>
<td>0.35</td>
</tr>
<tr>
<td>Headache</td>
<td>65 (45.7%)</td>
<td>3 (1.96%)</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

### Table 2 - Comparison of patients with headache to patients without headache.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients with headache n=65</th>
<th>Patients without headache n=77</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male [%])</td>
<td>35 (53.8%)</td>
<td>47 (61%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Age (years; mean ± standard deviation)</td>
<td>11±3.1</td>
<td>10.6±3.2</td>
<td>0.22</td>
</tr>
<tr>
<td>Type of seizures: Partial (%)</td>
<td>47 (72.3%)</td>
<td>55 (71.4%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Generalized (%)</td>
<td>18 (27.6)</td>
<td>22 (28.5)</td>
<td></td>
</tr>
<tr>
<td>Epilepsy syndrome: Idiopathic</td>
<td>54 (83%)</td>
<td>61 (79.2)</td>
<td>0.55</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>11 (16.9)</td>
<td>16 (20.7)</td>
<td></td>
</tr>
<tr>
<td>Frequent seizures</td>
<td>24 (36.9%)</td>
<td>29 (37.6)</td>
<td>0.92</td>
</tr>
<tr>
<td>Lobe type seizure: Occipital lobe seizure</td>
<td>7 (10.7)</td>
<td>9 (11.6)</td>
<td>0.86</td>
</tr>
<tr>
<td>Temporal lobe seizure</td>
<td>19 (29.2)</td>
<td>22 (28.5)</td>
<td>0.93</td>
</tr>
<tr>
<td>Parietal lobe seizure</td>
<td>3 (4.6)</td>
<td>5 (6.4)</td>
<td>0.68</td>
</tr>
<tr>
<td>Frontal lobe seizure</td>
<td>17 (26)</td>
<td>17 (22)</td>
<td>0.57</td>
</tr>
<tr>
<td>Drug used: Carbamazepine</td>
<td>25 (38.4)</td>
<td>30 (38.9)</td>
<td>0.95</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>17 (26)</td>
<td>18 (23.3)</td>
<td>0.70</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>20 (30.7)</td>
<td>24 (31)</td>
<td>0.95</td>
</tr>
<tr>
<td>Topiramate</td>
<td>3 (4.6)</td>
<td>8 (10.3)</td>
<td>0.22</td>
</tr>
<tr>
<td>Poly-therapy</td>
<td>14 (21.5)</td>
<td>11 (14.2)</td>
<td>0.25</td>
</tr>
<tr>
<td>Others anti-epileptic drugs</td>
<td>13 (20)</td>
<td>7 (9)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Headache in pediatric epilepsy patient ... Al-Gethami et al

Table 3 - Comparison of patient subgroups with migraine or non-migraine headaches.

<table>
<thead>
<tr>
<th>Patient subgroups</th>
<th>Migraine n=29</th>
<th>No migraine n=36</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; mean, standard deviation)</td>
<td>10.9 (2.8)</td>
<td>11.1 (3.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>Gender: male</td>
<td>16 (55)</td>
<td>19 (52.7)</td>
<td>0.84</td>
</tr>
<tr>
<td>female</td>
<td>13 (44.8)</td>
<td>17 (47.2)</td>
<td>0.84</td>
</tr>
<tr>
<td>Epilepsy syndrome: Idiopathic</td>
<td>21 (72.4)</td>
<td>22 (61.1)</td>
<td>0.33</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>6 (20.6)</td>
<td>5 (13.8)</td>
<td>0.46</td>
</tr>
<tr>
<td>Type of seizure: Focal</td>
<td>22 (75.8)</td>
<td>25 (69.4)</td>
<td>0.56</td>
</tr>
<tr>
<td>Generalized</td>
<td>7 (24)</td>
<td>11 (30.5)</td>
<td>0.56</td>
</tr>
<tr>
<td>Focal seizure: occipital lobe</td>
<td>3 (10.3)</td>
<td>3 (8.3)</td>
<td>0.78</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>8 (27.5)</td>
<td>10 (27.7)</td>
<td>0.98</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>1 (3.4)</td>
<td>2 (5.5)</td>
<td>0.68</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>10 (34.4)</td>
<td>6 (16.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Medication: Carbamazepine</td>
<td>12 (41.3)</td>
<td>13 (36.1)</td>
<td>0.66</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>9 (31)</td>
<td>8 (22.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>5 (17.2)</td>
<td>15 (41.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Topiramate</td>
<td>0</td>
<td>3 (8.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Poly-therapy</td>
<td>4 (13.7)</td>
<td>9 (25)</td>
<td>0.35</td>
</tr>
<tr>
<td>Others anti-epileptic drugs</td>
<td>7 (24.1)</td>
<td>6 (16)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

more than one type of headache, like inter-ictal/preictal which was present in 12 patients (18.4%), and one patient (1.5%) had interictal/post-ictal, another one also (1.5%) had interictal/ictal/post-ictal, and one patient (1.5%) had ictal/pre-ictal headache.

There was no significant difference in age, gender, type of epilepsy syndrome, and the antiepileptic used in patients who had headaches compared to patients without headaches (Table 2).

In a subgroup analysis of patients with migraine compared with non-migraine headaches, there was no significant difference in age, gender, type of epilepsy syndrome, and antiepileptic drug used except for the valproic acid, which showed fewer migraine patients compared with non-migraine patients (Table 3).

Discussion. Our study shows that about 46% of patients with epilepsy had headache as a comorbidity compared to 2% in the control group. The link between headache and seizures is controversial, and the literature review on this topic for the pediatric age group is limited.

In a study by Kanemura et al⁴ that enrolled 98 pediatric epilepsy patients, 35% of them had headache. Another study conducted by Yamane et al⁵ enrolled 50 pediatric epilepsy patients, and headache was reported by 46% of them, while Papavasiliou et al⁶ found that 11.4% among 70 pediatric epilepsy patients reported headache. Published studies in adult epileptic patients up to 2015 showed that the prevalence of migraine headache ranged from 6.6% to 32.9%, and the minimum age included in those studies was 10 years.⁷,12,18-32 The most recent studies were published by Wang et al³² who interviewed 1109 adult patients aged 18 years or older, and they found that headache occurred in 12.5% of the patients. In 2015, Mainieri³³ reported that 53.9% of epilepsy patients had headache.

In cohorts of migraine patients, epilepsy was reported infrequently. In a cohort of 172 headache patients, 1.7% had unprovoked seizures and 3 of 84 (2.3%) had coexisting migraine and epilepsy.⁶ In another study that was conducted at a pediatric headache center and that enrolled 1,795 patients, 56 (3.1%) patients also had epilepsy. Among these epileptic patients, 46/56 (82%) had migraine headache.³⁴

The pathophysiology behind the relationship between headache and epilepsy was reviewed in 2008, particularly the migraine type.³⁴ It is postulated that migraine attacks, similar to epileptic seizures, may be triggered by excessive neocortical cellular excitability. In migraine, this leads to cortical spreading depression and aura followed by additional recruitment of the trigeminal nucleus, resulting in central sensitization and pain. However, in epilepsy, neuronal overactivity can cause further neuronal recruitment and lead to firing in a rhythmic manner that constitutes an epileptic seizure. Migraine aura and headache may act as a trigger for epilepsy.³⁵ Additionally, some forms of
epilepsy and migraine are known to be channelopathies, which result from mutations in the same genes that can cause migraine, epilepsy, or both. This is similar to familial hemiplegic migraine syndromes where different mutations are found and can produce epilepsy, migraine, or both, and this can explain why some antiepileptic drugs, including valproate and topiramate, are effective in both conditions.  

For the timing of headache related to seizures, Yamane et al\(^5\) showed that about 60% of headaches were inter-ictal and the rest were pre- or post-ictal. In another group of pediatric and adult patients, 71% had inter-ictal headaches.\(^6\) These findings are similar to our study, where most headaches occurred in the inter-ictal period and affected 84% of our patients. However, Kanemura et al\(^4\) indicated that there was a higher prevalence in the post-ictal period in 28/34 (82%) of their patients, which is not consistent with our, and others’, results. In a group of adult patients, post-ictal headache was the most common type, especially in patients taking polytherapy; these patients have a higher seizure frequency, suggesting that a severe epilepsy phenotype and seizures can act as a trigger for headache attacks.\(^28,32,30\)

The migraine type was also the most frequent type of headache seen in 44.6% of our patients, while tension-type headache was present in 18.4% and unclassified headache was present in 36.9% of patients. Similar findings were reported in other studies such as Ottman et al\(^7\) who enrolled 1948 adult patients with epilepsy and demonstrated a two-fold higher risk for migraine in patients with epilepsy compared to their first-degree relatives without epilepsy. They also showed a two-fold higher risk of migraine compared to controls (24% vs. 12%). In Yamane et al\(^5\) migraine was present in 43.5% of the patients and 17.4% had tension-type headache, while in 39.1% of the patients, the type of headache could not be established. Others reported migraine in more specific epileptic syndromes, such as benign Rolandic epilepsy and benign occipital epilepsy of childhood,\(^1,8,9\) others found it more common in benign epilepsy with centrotemporal spikes and juvenile myoclonic epilepsy.\(^11\)

In our study, migraine was observed less frequently in patients who took valproate compared to patients who received other treatments, indicating a potential preventative effect for migraine in epilepsy patients who are treated with this drug compared to other drugs. However, further studies are required to confirm this hypothesis. Although valproic acid was shown to be effective in adults,\(^37\) there are few controlled trials in children. A previous placebo-controlled trial showed the efficacy of topiramate for prevention of migraine in children,\(^38\) but a recent study comparing topiramate, amitriptyline, and placebo found no difference compared to placebo.\(^39\) In our study, topiramate was administered in epileptic patients with or without headache, and there was no statistically significant difference between the groups, which is in agreement with the findings of Powers et al.\(^49\)

We also found that headache and epilepsy started in the same year in 28 patients (43%), but headache preceded epilepsy in 19 patients (29%) and epilepsy started before headache in 17 patients (26%). This indicates that in most patients, the headache started in the same year with epilepsy. Our findings are comparable to the findings of Toldo et al\(^34\) where in 44% of patients, epilepsy started earlier than headache with 28.6% starting in the same year, while headache started before seizures in 27.4% of the patients. Yamane et al. showed that the headache usually starts in the same year or after an epilepsy diagnosis.\(^5\)

The main limitation of our study is the recall bias of our patients and the cross-sectional nature. However, it has a relatively large sample size compared to other, similar studies and it is the only study in Saudi patients. A larger sample size with a prospective cohort study is required to better address the questions related to comorbidity of headache in pediatric epilepsy patients.

In conclusion, headache, predominantly migraine, is a common problem in pediatric epileptic patients, that can be secondary to similarity in their pathophysiology. A careful history related to headaches is recommended in those patients to improve their care and quality of life. Choosing valproic acid when possible can also be of importance in preventing migraine in these patients.

Acknowledgment. We would like to thanks American manuscript editing for English language editing. Also, we would like to thanks the radiologists in King Abdullah Children Specialist Hospital, King Abdul-Aziz Medical City, Riyadh, Saudi Arabia, for reviewing the images of the patients.

References

The association between anxiety and depression with 25(OH)D and thyroid stimulating hormone levels

Habib Erensoy, MD.

ABSTRACT

Objectives: To evaluate the relationships between the serum levels of these parameters and mood disorders, including depression and anxiety.

Methods: One hundred and fifty patients (77 with anxiety and 73 with depression), aged 18 to 79 years old, who were referred to the Neuropsychiatry Clinic of Uskudar University in Istanbul, Turkey were included in this study from June 2018 to December 2018. According to the Beck Anxiety Inventory and Beck Depression Inventory II results, the anxiety patients met the mild and moderate anxiety criteria and the depression patients met the moderate and severe depression criteria, respectively. Venous blood samples were collected after overnight fasting, and the 25(OH)D and thyroid stimulating hormone (TSH) levels were measured.

Results: The data showed a significantly higher TSH level in the females when compared to their male counterparts in the severe depression subgroup (p=0.011).

Conclusion: A serum TSH evaluation may be considered as a useful biochemical marker for more efficient depression management.

doi: 10.17712/nsj.2019.4.20190028

Depression and anxiety are considered to be the most prevalent mental diseases, causing decreased productivity and function of individuals in their daily activities and the loss of economic resources as well. Therefore, a comprehensive program of chronic disease management should be considered for the effective treatment of these disorders. In their meta-analysis, Lim et al. evaluated the depression prevalences in 30 different countries between 1994 and 2014. Their data showed prevalences of 12.9%, 7.2%, and 10.8% for the aggregate point, one-year, and lifetime depression levels, respectively. Additionally, the current prevalence of anxiety disorders has been reported as 7.3% worldwide.

During the past decade, various epidemiological studies have indicated that dietary patterns are an underlying cause of the onset of psychiatric symptoms. In this regard, “nutritional psychiatry” mainly discusses the nutritional effects of a single nutrient on mood disorders, including depression and anxiety.
discovery of the systemic role of 25(OH)D opened up a novel area of study for the effects of this vitamin on the regulation of different physiological and pathological processes and on the prevention or treatment of diseases. 25(OH)D is supplied through both dietary sources and the photochemical synthesis of epithelial cells. The classical roles of this vitamin have been described as calcium homeostasis modulation and bone metabolism. However, the effect of this molecule on the central nervous system has recently been studied. This vitamin has neuroprotective properties, such as in the synthesis of neuromediators, the production and release of neurotrophins, the homeostasis of intracellular calcium, and nervous tissue protection against oxidative damage. The correlation between a 25(OH)D deficiency and depressive disorders and symptoms has been well-described in recent studies. Hoogendijk et al. in a cohort study of 1,200 individuals older than 65 years, observed significantly lower 25(OH)D levels of 14% and 14% in patients with minor and major depression, respectively, when compared to the healthy controls, even after adjusting for the age, sex, body mass index, smoking status, and number of chronic conditions. Moreover, the effects of 25(OH)D supplementation on the depressive symptoms of overweight and obese patients have also indicated a significant improvement in depression in the patients receiving 20,000 IU of cholecalciferol one or twice per week when compared to a placebo group. However, limited studies have been published about the associations between this agent and anxiety disorders. Furthermore, some studies have denied this kind of association. In addition to 25(OH)D, thyroid hormones also play critical roles in adult brain functions, and varying degrees of psychiatric symptoms have been reported in patients with hypothyroidism or hyperthyroidism. Moreover, thyroid dysfunction has been recognized to be implicated in emotional and cognitive disturbances. It has been reported that anxiety disorders were observed in approximately 60% of hyperthyroid patients, while depression symptoms were reported in 31–69% of these patients. In contrast, depression features, cognitive dysfunction, apathy, and psychomotor slowing have been associated with hypothyroidism. In their study, Berthla et al. reported a high prevalence of psychiatric symptoms/disorders in patients with thyroid dysfunctions.

Recent studies have also reported an association between a vitamin D deficiency and thyroid dysfunction. Low 25(OH)D levels have been reported in patients suffering from hypothyroidism and Grave’s disease. Two mechanisms have been proposed for this phenomenon: poor vitamin D absorption from the intestine and the improper activation of the body of vitamin D in these patients.

Based on the above information, the aim of this study was to evaluate the correlations between the 25(OH)D and thyroid stimulating hormone (TSH) levels and depression and anxiety disorders.

Methods. Patients. One hundred and fifty patients (77 with anxiety and 73 with depression), aged 18 to 79 years old, who were referred to the Neuro Psychiatry Clinic of Uskudar University in Istanbul, Turkey were enrolled in this experimental study. When considering a study power of 80% and a confidence interval of 95%, the study population was calculated according to the following formula: sample size=Z1-α/2/2^P(1-P)/d2. This study was performed according to the tenets of the Helsinki Declaration, and it was approved by the research ethics committee of Uskudar University (Code: 61351342-/2019-80). Written informed consent was obtained from all of the patients prior any clinical examinations.

All of the patients diagnosed with depression and anxiety were included in this study. A history of serum 25(OH)D and TSH altering diseases, such as hepatic dysfunction, renal and thyroid diseases, and diabetes mellitus, or the current use of the aforementioned vitamin supplements were considered to be exclusionary criteria.

Clinical assessments. The patients’ moods were evaluated for the presence of depression and anxiety via the Beck Depression Inventory II (BDI-II) and the Beck Anxiety Inventory (BAI), respectively. Twenty-nine multiple choice questions were included in each test, and the maximum score for each question was 3. The BDI-II scores lower than 9 were designated as the absence of depression. Depression was classified into 3 subgroups: mild (BDI-II=10–15), moderate (BDI-II=16–23), and severe (BDI-II≥24). The BAI scores of less than 15 were considered to be negative for anxiety. Accordingly, the anxiety status was also categorized as mild (BAI=16–22), moderate (BAI=23–42), and severe (BAI≥43). Those patients with BDI-II scores of ≤9 and BAI scores of ≤15 were excluded from the study.

Sampling and laboratory analysis. Venous blood samples were collected after overnight fasting, and the
Table 1 - General characteristics of individuals.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Anxiety n=77</th>
<th>Depression n=73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters</td>
<td>Male n=43</td>
<td>Female n=34</td>
</tr>
<tr>
<td>Age (year)</td>
<td>36.9±14.42</td>
<td>37.38±11.89</td>
</tr>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>20.4±11.05</td>
<td>19.54±10.84</td>
</tr>
<tr>
<td>TSH (µIU/ml)</td>
<td>2.54±1.63</td>
<td>2.43±1.47</td>
</tr>
<tr>
<td>Beck Depression</td>
<td>19.0±2.03</td>
<td>19.85±9.87</td>
</tr>
<tr>
<td>Beck Anxiety</td>
<td>29.18±9.16</td>
<td>27.38±7.76</td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD, TSH - thyroid stimulating hormone*

Table 2 - Comparison of biochemical parameters between anxiety and depression groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Anxiety n=77</th>
<th>Depression n=73</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>20.02±10.9</td>
<td>17.63±11.1</td>
<td>0.145</td>
</tr>
<tr>
<td>TSH (µIU/ml)</td>
<td>2.49±1.55</td>
<td>2.63±1.62</td>
<td>0.621</td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD, TSH - thyroid stimulating hormone*

Table 3 - Comparison of biochemical parameters between anxiety subgroups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mild anxiety n=18</th>
<th>Moderate Anxiety n=59</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>21.79±15.5</td>
<td>19.48±9.16</td>
<td>0.938</td>
</tr>
<tr>
<td>TSH (µIU/ml)</td>
<td>2.56±1.44</td>
<td>2.47±1.6</td>
<td>0.678</td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD, P<0.05 was considered as statistically significant, TSH - thyroid stimulating hormone*

Table 4 - Comparison of biochemical parameters between depression subgroups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Moderate depression n=12</th>
<th>Severe depression n=61</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>15.92±11.09</td>
<td>18.09±11.19</td>
<td>0.641</td>
</tr>
<tr>
<td>TSH (µIU/ml)</td>
<td>1.68±0.79</td>
<td>2.81±1.69</td>
<td>0.118</td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD, P<0.05 was considered as statistically significant, TSH - thyroid stimulating hormone*

25(OH)D and TSH levels were measured in all of the subjects using a cobas e 411 immunoassay analyzer (Roche Diagnostics GmbH, Mannheim, Germany). 25(OH)D levels of <10, 11–29, and ≥30 ng/ml were categorized as deficiency, insufficiency, and normal, respectively. A 0.3–4.5 µIU/ml interval was considered to be a normal serum TSH level.

Statistical analysis. The data were presented as the mean±standard deviation, and they were analyzed using IBM SPSS Statistics for Windows version 23 (IBM Corp., Armonk, NY, USA). A non-parametric Kruskal-Wallis test was used to compare the means between the groups. A bivariate correlation analysis was also conducted to assess the associations between the clinical variables and the 25(OH)D or TSH levels. A p-value of <0.05 was considered to be statistically significant.

Results. General characteristics of the individuals. Table 1 shows the general information about the participants. There were 77 participants in the anxiety group (43 males and 34 females) and 73 participants in the depression group (25 males and 48 females). The average ages of the males and females in the anxiety group were 36.9±14.42 and 37.38±11.89 years old, respectively. In the depression group, the average ages of the males and females were 30.52±7.85 and 38.16±11.88 years old, respectively. The 25(OH)D and TSH level comparisons showed no significant differences between the anxiety and depression groups (p=0.145 and p=0.621, respectively) (Table 2). 25(OH)D and TSH level comparisons between the anxiety and depression subgroups (Table 3 & Table 4) show the 25(OH)D and TSH level differences between the anxiety and depression subgroups. As reported, no statistical differences were observed in the 25(OH)D and TSH levels between the two subgroups. In addition, the 25(OH)D and TSH levels among the males and females in the anxiety subgroup showed no significant differences. However, a significantly higher TSH level was observed in the females when compared to the males in the severe depression subgroup (3.0±1.49 µIU/ml versus 2.38±0.02 µIU/ml, respectively, p=0.011) (Table 5 and Table 6).

Correlations between the 25(OH)D and TSH levels and the BDI-II and BAI scores. The correlations between the 25(OH)D and TSH levels and the BDI-II and BAI scores were presented in Table 7 and Table 8. No statistically significant correlations were found between the biochemical parameters and the BDI-II and BAI scores in the studied groups.
Table 5 - Comparison of biochemical parameters between male and female individuals through anxiety sub-groups.

<table>
<thead>
<tr>
<th>Anxiety sub-groups n=77</th>
<th>Male n=10</th>
<th>Female n=8</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Anxiety n=18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>22.64±16.91</td>
<td>20.73±14.6</td>
<td>0.859</td>
</tr>
<tr>
<td>TSH (µIU/ml)</td>
<td>2.79±1.6</td>
<td>2.28±1.24</td>
<td>0.534</td>
</tr>
<tr>
<td>Moderate anxiety n=59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>n=33</td>
<td>n=26</td>
<td></td>
</tr>
<tr>
<td>TSH (µIU/ml)</td>
<td>19.72±8.83</td>
<td>19.17±9.74</td>
<td>0.939</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD, TSH - thyroid stimulating hormone.

Table 6 - Comparison of biochemical parameters between male and female individuals through depression sub-groups.

<table>
<thead>
<tr>
<th>Depression sub-groups n=73</th>
<th>Male n=5</th>
<th>Female n=7</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate depression (n=12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>19.77±13.1</td>
<td>13.72±10.17</td>
<td>0.345</td>
</tr>
<tr>
<td>TSH (µIU/ml)</td>
<td>1.83±0.96</td>
<td>1.6±0.74</td>
<td>0.705</td>
</tr>
<tr>
<td>Severe depression (n=61)</td>
<td>n=20</td>
<td>n=41</td>
<td></td>
</tr>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>21.34±12.84</td>
<td>16.5±10.08</td>
<td>0.199</td>
</tr>
<tr>
<td>TSH (µIU/ml)</td>
<td>2.38±2.02</td>
<td>3.01±1.49</td>
<td>0.011*</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD, TSH - thyroid stimulating hormone.

Table 7 - Correlation of biochemical parameters with anxiety beck degree.

<table>
<thead>
<tr>
<th>Anxiety sub-groups (n=77)</th>
<th>Beck.Ansiety</th>
<th>r</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild Anxiety (n=18)</td>
<td>-0.175</td>
<td>0.486</td>
<td></td>
</tr>
<tr>
<td>TSH (µIU/ml)</td>
<td>0.232</td>
<td>0.077</td>
<td></td>
</tr>
<tr>
<td>Moderate Anxiety (n=59)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild Anxiety (n=18)</td>
<td>0.003</td>
<td>0.991</td>
<td></td>
</tr>
<tr>
<td>Moderate Anxiety (n=59)</td>
<td>-0.163</td>
<td>0.218</td>
<td></td>
</tr>
</tbody>
</table>

r - Correlation coefficient, TSH - thyroid stimulating hormone.

Table 8 - Correlation of biochemical parameters with depression beck degree.

<table>
<thead>
<tr>
<th>Depression sub-groups n=73</th>
<th>Beck.Depression</th>
<th>r</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate depression (n=12)</td>
<td>0.525</td>
<td>0.097</td>
<td></td>
</tr>
<tr>
<td>Severe depression (n=61)</td>
<td>0.007</td>
<td>0.959</td>
<td></td>
</tr>
<tr>
<td>TSH (µIU/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate depression (n=12)</td>
<td>-0.386</td>
<td>0.241</td>
<td></td>
</tr>
<tr>
<td>Severe depression (n=61)</td>
<td>-0.145</td>
<td>0.265</td>
<td></td>
</tr>
</tbody>
</table>

r - Correlation coefficient, TSH - thyroid stimulating hormone.

Discussion. The present study was conducted to evaluate the associations between anxiety and depression and the levels of 25(OH)D and TSH. One hundred and fifty patients were divided into depression (77 participants) and anxiety (73 participants) groups according to their BDI-II and BAI scores.

Vitamin D exhibits neuroprotective properties in the brain through the crucial neurotrophic signaling regulations required for neuronal development and health, the modulation of inflammation by inflammatory cytokine inhibition, and reactive oxygen species lowering protein activation. This vitamin also increases the biosynthesis of brain-derived neurotrophic factors (implicated in the schizophrenia pathogenesis) and glial-derived factors (essential for dopaminergic survival and function). Recent studies have suggested that the regional expression of the vitamin D receptor in different parts of the brain is one of the crucial factors in the pathogenesis of psychiatric illnesses. Many of these regions express 1α-hydroxylase, which converts 25(OH)D to 1,25(OH)2D3, and this explains the autocrine and paracrine properties of this vitamin.

Recently, it has been reported that low vitamin D levels are associated with schizophrenia, depression, and anxiety in the general population. In a cohort study conducted between 2015 and 2017, Fond et al. reported hypovitaminosis D in 21.4% of the subjects with no vitamin D supplementation during the previous 12 months. Additionally, this hypovitaminosis D was severely associated with depressive and anxiety symptoms; however, vitamin D supplementation significantly improved these symptoms. In contrast, Choukri et al. in a double blind randomized controlled clinical trial including 152 healthy women, reported the non-beneficial effects of vitamin D supplementation on depressive symptoms and psychological outcomes. Our data also showed lower levels of 25(OH)D in the depression group when compared to the anxiety group. However, this difference was not found to be statistically significant. Moreover, no other significant differences were observed between the 25(OH)D levels and the depression or anxiety subgroups. This may be due to this fact that the average levels of this vitamin were in the insufficiency or sufficient range among the individuals.

Vitamin D has been mainly implicated in bone metabolism and calcium/phosphorous homeostasis. However, the roles of this vitamin in thyroid functions and diseases, including Hashimoto’s thyroiditis and Graves’ disease, have been studied recently. Moreover, the associations between thyroid malfunctions and psychiatric symptoms, including depression and anxiety, have also been reported previously. Primary thyroid disorders, such as hyperthyroidism and hypothyroidism, may be the underlying causes of various neuropsychiatric symptoms ranging from mild depression and anxiety to...
overt psychosis. Furthermore, anxiety and depression disorders have been found to occur in approximately 60% and 31–61% of hyperthyroidism cases, respectively.

In our study, the mean serum TSH level was within the normal range, but a significantly higher TSH level was observed in the females in the severe subgroup when compared to the males. Lee et al., in a study of 7,270 healthy subjects, also reported higher TSH levels in the females when compared to their male counterparts (2.0±1.01 mU/l versus 1.67±0.87 mU/l, respectively, p<0.01). Some scientists have proposed the “brain hypothyroidism” theory for the pathogenesis of depression. In this regard, the occurrence of depression is due to local brain hypothyroidism along with normal serum thyroid hormone levels due to deiodinase type II inhibition and the impairment of T4 transport across the blood brain barrier.

Although several studies have pointed to a significant association between mood disorders and a vitamin D deficiency, the different perspectives are not fully understood, and they remain controversial. Several studies have also shown a correlation between a vitamin D deficiency and depression symptoms. However, it remains unclear whether low vitamin D levels are the cause or the effect of depression. In the United States, more than 50% of psychiatric inpatients have vitamin D deficiencies of less than 10 ng/ml. We measured the vitamin D levels in psychiatric outpatients, and we did not find any relationships between the vitamin D level and the mood disorder severity. However, the lack of statistical significance in the measured parameters among the studied population may have been due to the small population size, which was one of the limitations of our study. Therefore, a larger population should be considered in future studies. Additionally, the presence of a healthy control group could help provide a better interpretation of the data.

In conclusion, patients with depression or anxiety may exhibit low vitamin D levels due to lower outdoor activity levels or reduced nutrient intakes. However, an evaluation of vitamin D receptor genetic mutations is recommended for future studies in order to better understand the possible mechanisms between the vitamin D biology and mood disorders with regard to thyroid functions.

References


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Translation and validation of the Arabic version of the Boston carpal tunnel syndrome questionnaire

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ABSTRACT

The BCTQ-A, SSS, and FSS scores were significantly lower post-CTR.

Conclusions: The BCTQ-A is reliable, valid, reproducible, and responsive to interventions. The Arabic version can be now used with Arabic-speaking patients with CTS.

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Carpal tunnel syndrome (CTS) is a common entrapment neuropathy affecting the median nerve at the wrist. The diagnosis of CTS is made clinically and supported by the finding of median neuropathy at the wrist on electrodiagnostic studies (EDX). Atroshi et al\(^1\) reported a prevalence of clinically certain CTS of 3.8%, and a prevalence of clinically and EDX confirmed CTS of 2.7%.\(^1\) Both carpal tunnel release (CTR) and conservative interventions are used for the treatment of CTS; the former may be more effective in relieving symptoms and improving hand function.\(^2\) A recent study has estimated a lifetime prevalence of CTR of 3.1%.\(^3\) The use of a validated outcome measure is imperative to monitor the response to CTS therapy.

The Boston carpal tunnel questionnaire (BCTQ) is a patient-reported outcome measure of proven reliability, validity, and responsiveness to surgical and non-surgical treatment.\(^4\) The BCTQ is composed of 2 scales, the symptom severity scale (SSS) and the functional status scale (FSS).
scale (FSS). The SSS consists of 11 items, incorporating 6 domains (pain, numbness, paresthesia, nocturnal symptoms, weakness, and overall functional status) scored on a 5-point scale ranging from 1 (never/none) to 5 (most severe). The FSS consists of 8 functional activities commonly affected by CTS scored on a 5-point scale ranging from 1 (no difficulty) to 5 (cannot perform the activity at all). The BCTQ score reflects CTS severity in a typical 24-hour period within the last 2 weeks before completing the questionnaire. The BCTQ has been translated and validated in many languages, but not yet in Arabic. Validation of an Arabic version of the BCTQ would be useful to help physicians assess the impact of CTS from the patients’ perspective and objectively assess post-intervention improvement. This study sought to translate and culturally adapt the BCTQ into Arabic and to assess its psychometric properties, including reliability, reproducibility, validity, and responsiveness to CTR.

Methods. Participants and data collection. This is a cross-sectional study. The study was conducted at King Saud University Medical City (KSUMC), Riyadh, Kingdom of Saudi Arabia. Patients were consecutively recruited from the Neurophysiology Clinic between January 2016 and May 2018. We enrolled patients 18 years of age or older who had clinical CTS confirmed by EDX. The diagnosis of CTS was confirmed by a neurologist, and was based on all of the following: (1) hand/wrist paresthesia (with or without pain), often awakening the patient from sleep, triggered by manual activities, and relieved by shaking the hands or placing them under running water, and (2) an EDX showing features of median neuropathy at the wrist as described previously.

Patients were asked to complete the Arabic version of the BCTQ (BCTQ-A) after being interviewed by a neurologist who confirmed the diagnosis of clinical CTS. Illiterate patients were assisted by a family member in completing the questionnaire. After EDX was completed, only patients whose clinical CTS was confirmed by EDX were included in the study.

To test for reproducibility (test-retest reliability), 36 consecutive patients with CTS were asked to complete again the BCTQ-A after 1 week and return it by e-mail. To test for responsiveness, we subsequently contacted those patients who had carpal tunnel release (CTR) 2 months after the procedure and asked them to complete an electronic version of the questionnaire.

The study was approved, as a part of a larger project (E-15-1581), by the Institutional Review Board of King Saud University. All participants signed an informed consent.

Translation and cultural adaptation. A multistep forward-backward translation method, according to the cross-cultural adaptation guidelines, was adapted to produce an Arabic version of the BCTQ. The translation process was conducted by a committee of 3 neurologists and 1 translator. Forward translation into Arabic was independently performed by 2 neurologists (both bilingual, with Arabic as their first language). After reaching an agreement on the forward translation, the provisional Arabic version was independently back-translated into English by a neurologist and a translator (both bilingual, with English as their first language). Any inconsistencies in translation were discussed by the committee members and resolved by consensus before producing the provisional Arabic version (BCTQ-A). For cognitive debriefing, 5 patients with CTS were asked to review the BCTQ-A and report any unclear items. Finally, production of the final version, BCTQ-A, was completed (Appendix).

Statistical analysis. Descriptive statistics was applied to demographic variables. For each individual, the SSS and FSS scores were obtained by summing the scores of the items on each scale. Reliability (internal consistency) of each scale of the BCTQ-A was assessed by Cronbach’s α coefficients. A Cronbach α >0.7 was considered satisfactory.

Reproducibility of the BCTQ-A was assessed on 36 stable patients with CTS with a 1-week test–retest, by computing the intraclass correlation coefficient (ICC) separately for each of the 2 scale scores. An ICC >0.7 was considered satisfactory. A Bland–Altman plot was used to assess the absolute agreement of the test–retest scores, and the 95% limits of agreement were calculated by using the formula Mdd +1.96 * Sdd, where Mdd is the mean difference between paired test-retest scores, and Sdd is the standard deviation of these differences. The minimum detectable change (MDC) was defined as the minimal change in the scores of each scale required to differentiate a true change from a change due to variability in scoring or measurement error. The MDC was calculated using the formula 1.96*√2*SEM, where SEM is the standard error of measurement. The SEM was calculated using the formula Sdb √(1-ICC), where Sdb is the standard deviation of the baseline scores for each scale.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.
Factor analysis was used to explore the latent variables (hypothetical constructs) of the BCTQ-A. Validity was assessed by comparing the latent variables and factor loadings of the BCTQ-A with those of the English version. The Cronbach $\alpha$ was calculated for each factor.

To assess for responsiveness, a Wilcoxon signed-rank test was performed to evaluate the differences in the total BCTQ-A, SSS, and FSS scores at baseline and at follow-up post CTR. The effect size (ES) was computed by dividing the test statistic by the square root of the number of observations (2 observations per patient, pre- and post-CTR). An ES of $> 0.5$ was considered large, and an ES of $0.3 - 0.49$ was considered moderate. Statistical analysis was performed using the statistical software SPSS version 23 (IBM, Armonk, N.Y, USA). A 2-tailed $p<0.05$ was considered statistically significant.

**Results.** In total, 134 consecutive patients with clinically and EDX confirmed CTS (114 women, 20 men) participated. Of those, 109 (81.3%) patients returned a completed questionnaire. The most frequently missing item was FSS item 1 (writing, $n=17$), followed by FSS item 3 (holding a book while reading, $n=14$). The mean age of our cohort was $49.2 \pm 11.3$ years. CTS of the right or left hand was diagnosed in 41 (30.6%) and 8 (6%) patients, respectively, and of both hands in 85 (63.4%) patients. No problems were encountered in the translation process, nor with the cognitive debriefing, as all the BCTQ items were readily translatable into Arabic language and consistent with the local culture.

Only data from completed questionnaires were included in the analysis. The mean SSS score was $32.0 \pm 8.4$, and the mean FSS score was $18.5 \pm 7.6$. 

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**Figure 1** - Test-retest reliability of the symptom severity scale (SSS). A) Retest SSS score as a function of the baseline SSS score, B) Bland-Altman blot with 95% limits of agreement (dotted line).

**Figure 2** - Test-retest reliability of the functional status scale (FSS). A) Retest FSS score as a function of the baseline FSS score. B) Bland-Altman blot with 95% limits of agreement (dotted line).
The Cronbach α was 0.91 for the total BCTQ-A score, 0.88 for the SSS and 0.87 for the FSS. The ICCs for the SSS and FSS were 0.88 (95% confidence interval [CI] 0.77–0.94) and 0.89 (95% confidence interval [CI] 0.79–0.95), respectively (Figures 1A and 2A). The Bland–Altman plot showed good agreement between the 2 measurements for each scale, with no proportional bias. The Md for the SSS was 2.88 (95% CI: -7.69 to 13.48), (Figure 1B). The Md for the FSS was – 0.86 (95% CI: -10.56 to 8.84), (Figure 2B). The SEM for the SSS and FSS were 2.9 and 2.6, respectively. The MDC for the SSS and FSS were 4.7 and 4.5, respectively, indicating that a score difference ≥5.0 on either scale represents a true change.

Factor analysis of the combined 19 items from both scales was conducted. Principal axis factoring was used as an extraction method, followed by determination of factor loading using an oblique rotation method. The Kaiser-Meyer-Olkin (KMO) measure was 0.85, suggesting sampling adequacy for each item, and that our data were suitable for factor analysis.

There was a discrepancy in the retention rules regarding the number of factors that could be extracted; using the criterion of eigenvalue (amount of variance in the total sample accounted for by a factor) greater than 1.0 indicated 4 factors, but parallel analysis indicated 2 factors. However, after examining the scree plot, and to validate our data in comparison to previous studies,20,21 we decided to extract three factors. The first factor of the BCTQ-A had an eigenvalue of 7.29, and explained 38.4% of the total variance of the BCTQ-A scores. The second and third factors had eigenvalues of 2.20 and 1.33, respectively, indicating that the 3 factors together explained 56.9% of the cumulative variance of the BCTQ-A scores. To analyze factor loadings, and

### Table 1 - Factor loadings for the BCTQ-A scale items.

<table>
<thead>
<tr>
<th>Items</th>
<th>Factors 1</th>
<th>Factors 2</th>
<th>Factors 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSS-1 Hand/wrist pain at night – severity</td>
<td>0.642</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSS-2 Hand/wrist pain at night – wakening frequency</td>
<td></td>
<td>0.565</td>
<td></td>
</tr>
<tr>
<td>SSS-3 Hand/wrist pain – daytime</td>
<td></td>
<td></td>
<td>0.808</td>
</tr>
<tr>
<td>SSS-4 Hand/wrist pain – daytime, frequency</td>
<td></td>
<td></td>
<td>0.800</td>
</tr>
<tr>
<td>SSS-5 Hand/wrist pain – daytime, duration</td>
<td></td>
<td></td>
<td>0.525</td>
</tr>
<tr>
<td>SSS-6 Hand numbness – severity</td>
<td></td>
<td></td>
<td>0.397</td>
</tr>
<tr>
<td>SSS-7 Hand weakness – severity</td>
<td></td>
<td></td>
<td>0.415</td>
</tr>
<tr>
<td>SSS-8 Hand tingling – severity</td>
<td></td>
<td></td>
<td>0.647</td>
</tr>
<tr>
<td>SSS-9 Hand numbness/tingling – night, severity</td>
<td></td>
<td></td>
<td>0.920</td>
</tr>
<tr>
<td>SSS-10 Hand numbness/tingling – wakening, frequency</td>
<td></td>
<td></td>
<td>0.635</td>
</tr>
<tr>
<td>SSS-11 Grasping small objects</td>
<td></td>
<td></td>
<td>0.638</td>
</tr>
<tr>
<td>FSS-1 Writing</td>
<td></td>
<td></td>
<td>0.698</td>
</tr>
<tr>
<td>FSS-2 Buttoning clothes</td>
<td></td>
<td></td>
<td>0.579</td>
</tr>
<tr>
<td>FSS-3 Holding a book while reading</td>
<td></td>
<td></td>
<td>0.785</td>
</tr>
<tr>
<td>FSS-4 Gripping a telephone handle</td>
<td></td>
<td></td>
<td>0.596</td>
</tr>
<tr>
<td>FSS-5 Opening jars</td>
<td></td>
<td></td>
<td>0.581</td>
</tr>
<tr>
<td>FSS-6 Household chores</td>
<td></td>
<td></td>
<td>0.664</td>
</tr>
<tr>
<td>FSS-7 Carrying of grocery bags</td>
<td></td>
<td></td>
<td>0.781</td>
</tr>
<tr>
<td>FSS-8 Bathing and dressing</td>
<td></td>
<td></td>
<td>0.628</td>
</tr>
</tbody>
</table>

Only factor loadings >0.3 were included in the table. *FSS - functional status scale, SSS - symptom severity scale

### Table 2 - Sensitivity to change of the total BCTQ-A, SSS, and FSS scales after carpal tunnel release surgery.

<table>
<thead>
<tr>
<th>Scales</th>
<th>Baseline M±SD</th>
<th>Follow-up M±SD</th>
<th>P-value*</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSS (n=36)</td>
<td>33.1±9.4</td>
<td>20.8±9.5</td>
<td>&lt;0.001</td>
<td>0.55</td>
</tr>
<tr>
<td>FSS (n=36)</td>
<td>22.0±7.9</td>
<td>17.8±9.1</td>
<td>0.004</td>
<td>0.34</td>
</tr>
<tr>
<td>BCTQ-A (n=36)</td>
<td>55.1±16.1</td>
<td>38.5±17.6</td>
<td>&lt;0.001</td>
<td>0.51</td>
</tr>
</tbody>
</table>

*p-values were obtained using a Wilcoxon signed-rank test. BCTQ-A - Arabic version of the Boston carpal tunnel syndrome questionnaire, FSS - functional status scale, SSS - symptom severity scale, M - mean, SD - standard deviation, ES - effect size.
due to the presence of correlation between the 3 factors (range 0.46–0.59), the “promax” oblique rotation method was employed. Using a cutoff of 0.3 to define significant loading, all the items of the FSS, and items 7 (hand weakness) and 11 (difficulty grasping small objects) of the SSS had significant loadings on factor 1 (functional status factor, Table 1). The SSS items 1, 2, 6, 8, 9, and 10 had significant loadings on factor 2 (sensory symptoms factor). The SSS items 3, 4, and 5 had significant loadings on factor 3 (pain factor). No cross-loading or unloading were observed. The Cronbach α coefficients for factors 1, 2, and 3 were 0.89, 0.85, and 0.78, respectively.

The responsiveness of the BCTQ-A, SSS, FSS was assessed in 36 patients at 2 months post-CTR. The total BCTQ-A, SSS, and FSS scores significantly decreased (indicating an improvement) post-CTR, with an average change of 16.6, 12.3, and 4.2 points, respectively (Table 2).

**Discussion.** This study described the successful translation and validation of the BCTQ into Arabic. No difficulties were encountered during the translation and cross-cultural adaptation, supporting the conceptual equivalence of the original and Arabic (BCTQ-A) versions. The BCTQ-A demonstrated excellent reliability, reproducibility, and validity, and is sensitive to changes, as shown by its responsiveness to CTR.

The internal consistency of the SSS and FSS of the Arabic version is similar to that of the original English version of the BCTQ. It is also similar to the internal consistency reported by other validation studies of the BCTQ. We decided to maintain a one-week interval to assess test-retest reliability; such interval would be long enough to allow patients to forget their initial responses but not long enough to allow for a true change in their CTS status. When calculating the scores for each scale on an individual level, we decided to use the sum of the scores rather than the mean score of all items, which was used in the original study. It is more practical for a busy clinician monitoring the response during a follow-up visit to add-up item scores than to calculate the mean. As we have demonstrated, a change of ≥ 5.0 points on either scale represents a true change. Reproducibility of the BCTQ-A is confirmed by a satisfactory ICC for each scale, and is further supported by the good agreement of the successive measurements on the Bland–Altman plot. The ICCs for the SSS and FSS in this study are comparable to those measured in previous studies.

Contrary to other studies, we did not use the correlation between the BCTQ-A and other quality-of-life outcome measures, but we chose exploratory factor analysis to test the hypothetical constructs of the BCTQ-A. The 3-factor structure (function, sensory symptoms, and pain) in our study provides the best account for the data, and explains 56.9% of the total variance. Factor loadings for all the 19 BCTQ-A items are satisfactory (Table 1). Moreover, the BCTQ-A does not have any complex items with cross-loading of > 0.3. It is unclear why SSS item 6 has the lowest factor loading (0.397) of all the 19 items in our study. A previous study also showed low factor loadings for this item, and attributed it to the lack of specification of the exact time when numbness occurs, whereas its factor loadings in other studies were higher (ranged from 0.508 to 0.754) than in our study.

The responsiveness of the Arabic version was supported by the ability of the BCTQ-A and its subscales to detect improvements post-CTR, with a significant p-value and an acceptable ES. Notwithstanding the differences in the methodology used to calculate the ES between our study and the original BCTQ, both studies showed a lower responsiveness of the FSS compared with the SSS. This has also been shown in other BCTQ validation studies. A time-lag in the post-CTR improvements in functional activities with respect to the improvements in symptoms severity is a possible explanation. However, the FSS is mostly a generic scale, and the activities included are affected by many musculoskeletal conditions of the upper extremities. An association between CTS and musculoskeletal injuries (rotator cuff syndrome and epicondylitis) has been reported, but was not examined in our study. Therefore, we cannot exclude a role of such conditions in hampering a more robust responsiveness of the FSS.

This study has a few limitations. Our sample size was relatively small for factor analysis when using only completed surveys. However, it met the minimum requirements (more than 5 participants per item, and more than 100 participants in total), and the values...
of factor loadings and KMO indicated the adequacy of the sample. The most frequently missed item in the BCTQ-A was FSS item 1, which concerns writing, followed by FSS item 3, which concerns the ability to hold a book while reading. Possible explanations for missing data could be that these activities were infrequently performed by patients who returned incomplete surveys, or illiteracy. Because there is no recommended methodology for handling missing data in the original BCTQ, the statistical analysis was only performed on complete questionnaires.

In conclusion, we have translated and culturally adapted the Arabic version of the BCTQ, and demonstrated its rigorous psychometric properties including reliability, reproducibility, validity, and responsiveness to CTR. The Arabic version can be now used for clinical and research purposes in Arab patients with CTS.

References

**استبيان بوسطن لمتلازمة النفق الرسغي**

ماهي شدة ألم اليد او الرسغ أثناء الليل؟
- لا أعاني من ألم اليد او الرسغ خلال الليل (1)
- ألم خفيف (2)
- ألم متوسط (3)
- ألم شديد (4)
- ألم شديد جدا (5)

ما هو معدل استيقاظك من النوم بسبب ألم اليد أو الرسغ خلال آخر أسبوعين ( مرة/يوم)؟
- أبدا (1)
- مرة واحدة (2)
- مترين الى ثلاث مرات (3)
- أربع الى خمس مرات (4)
- أكثر من خمس مرات (5)

هل تعاني من ألم باليد أو الرسغ خلال النهار؟
- لا أعاني من ألم خلال النهار (1)
- ألم خفيف خلال النهار (2)
- ألم متوسط خلال النهار (3)
- ألم شديد خلال النهار (4)
- ألم شديد جدا خلال النهار (5)

كم مرة تشعر بألم باليد أو الرسغ خلال النهار ( مرة/يوم)؟
- أبدا (1)
- مرة أو مرتين باليوم (2)
- ثلاث إلى خمس مرات باليوم (3)
- أكثر من خمس مرات باليوم (4)
- الألم مستمر (5)

إذا شعرت بالألم خلال النهار، تقريبا كم تستغرق مدة الألم (بالدقائق)؟
- أقل من 10 دقائق (1)
- من 10 إلى 60 دقيقة (2)
- أكثر من 60 دقيقة (3)
- الألم مستمر خلال النهار (5)

هل تعاني من خدر باليد أو الرسغ؟
- لا يوجد (1)
- أعاني من خدر خفيف (2)
- أعاني من خدر متوسط (3)
- أعاني من خدر شديد (4)
- أعاني من خدر شديد جدا (5)

هل تعاني من ضعف باليد أو بالرسغ؟
- لا يوجد ضعف (1)
- ضعف خفيف (2)
- ضعف متوسط (3)
- ضعف شديد (4)
استبيان بوسطن لمتلازمة النفق الرسغي

هل تعاني من احساس بالتنمیل في يدك؟
- لا يوجد تنمیل
- تنمیل خفیف
- تنمیل متوسط
- تنمیل شدید (أداة)
- تنمیل شدید جدا

ما هي شدة الخدر (فقد الاحساس) أو التنمیل في اللیل؟
- لا يوجد خدر أو تنمیل
- خفیف
- متوسط
- شدید (أداة)
- شدید جدا

ما هو معدل استيقاظك من النوم لیلا بسبب خدر أو تنمیل اليد خلال آخر أسبوعين؟
- أبدا
- مرة واحدة
- مرتين إلى ثلاث مرات
- أربع إلى خمس مرات
- أكثر من خمس مرات

هل تعاني من صعوبة بالإمساك أو استعمال الأشياء الصغیرة كالقلم أو المفتاح؟
- لا يوجد صعوبة
- صعوبة خفیفة
- صعوبة متوسطة
- صعوبة شدیدة

مستوى الحالة الوظیفیة

خلال أي يوم من الأسبوعین الماضیة، هل سببت لك أعراض الید أو الرسغ أي صعوبة في الأنشطة التالیة؟ (يرجى وضع دائرة أمام الاختیار الأنسب)

<table>
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<tr>
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<th>صعوبة خفیفة</th>
<th>صعوبة متوسطة</th>
<th>صعوبة شدیدة</th>
<th>لا أستطیع ممارسة النشاط أبدا</th>
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<td>1</td>
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<td>امساك الكتاب</td>
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<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
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<tr>
<td>أثناء القراءة</td>
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<td>3</td>
<td>2</td>
<td>1</td>
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<td>1</td>
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<td>1</td>
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<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>الحمل أكياس التسوق</td>
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<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
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<tr>
<td>الاستحمام واللبس</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Reliability and validity of the turkish translation of pedsq™ multidimensional Fatigue scale in Duchenne Muscular Dystrophy

Ipek Alemdaroğlu-Gürbüz, PT, PhD, Numan Bulut, PT, MSc, Sibel Bozgeyik, PT, MSc, Naima Ulug, PT, PhD, Selen S. Arslan, PT, PhD, Öznu Yılmaz, PT, PhD, Ayşe Karaduman, PT, PhD.

ABSTRACT

The objectives: To perform the Turkish translation, reliability, and validity study of the PedsQ™ Multidimensional Fatigue Scale (PedsQ-MFS) in patients with Duchenne Muscular Dystrophy (DMD).

Methods: This prospective, cross-sectional, observational study was held in Hacettepe University, Faculty of Physical Therapy and Rehabilitation between January 2016-August 2018. Turkish translation of the PedsQ-MFS was conducted based on the steps addressed in the translation manual of the original research. The psychometric features of the Turkish version of PedsQ-MFS including feasibility, internal consistency, and test-retest reliability, construct, and criterion-related validity as well as parent/child agreement were investigated on a total of 71 children and their parents.

Results: The mean age of boys with DMD included in the study was 102.94±23.23 months with a mean 17.15±2.98 BMI. Internal consistencies of Child Self Report General Fatigue, Sleep/rest Fatigue, and Cognitive Fatigue items were 0.74, 0.65, and 0.83 while 0.89, 0.84, and 0.91 in Parent Proxy Report. The ICC values of Child Self Report and Parent Proxy Report were 0.87 and 0.91, respectively. Parent Proxy Report succeeded more acceptable fit indices than Child Self Report. A statistically significant correlation was found between PedsQ-MFS and PedsQ-Neuromuscular Module (p<0.05). Moderate agreement was detected between parent and child.

Conclusion: The Turkish version of PedsQ-MFS was determined to be a reliable and valid tool to evaluate fatigue in 5-12 years old, ambulant children with DMD.
Duchenne Muscular Dystrophy (DMD) is the most common childhood neuromuscular disease which affects 1/3500–6000 male births.\textsuperscript{1, 2} The disease is caused by a mutation in the dystrophin gene, which is localized at Xp21, and progressive muscle degeneration occurs over time.\textsuperscript{3, 4} As seen in other neuromuscular diseases, the most prevalent symptoms are irreversible muscle weakness and fatigue, which quickly show themselves during daily activities.\textsuperscript{5} Fatigue is an important pathophysiological factor that hinders the realization of both physical and cognitive functions in individuals and causes limitations in exercise and activities. The levels of fatigue in daily living activities and functional skills are strongly correlated with the disorder.\textsuperscript{5, 6} Fatigue decreases the physical capabilities and quality of life of individuals while increasing their dependency levels.\textsuperscript{7} It also creates a pathophysiological situation that affects the motivation of the individual to maintain their physical and cognitive functions, as seen in many different types of neuromuscular diseases.\textsuperscript{8}

Fatigue is also an issue that may limit social participation. Patients with DMD who showed severe fatigue were found to have more problems with regard to physical functions, social functioning, mental health, physical pain status, and general health.\textsuperscript{9} Fatigue can be assessed using questionnaires that evaluate the loss of strength after exercise, changes in electromyographic activity recorded during an exercise period, and questionnaires that address fatigue directly and/or evaluate psychological aspects of fatigue.\textsuperscript{5} Special assessment scales for individuals with pediatric neuromuscular diseases—whose population mostly consists of DMD patients—are limited. However, experts need methods to determine the specific outcomes of promising drugs that have been developed in recent years. Also, considering the lack of a self-report assessment tool to assess fatigue in Turkish children with neuromuscular diseases; this study aimed to determine the psychometric features of the PedsQLTM-3.0 Multidimensional Fatigue Scale (PedsQL-MFS)-Turkish version in children with DMD.

**Methods.** This prospective, cross-sectional, observational study was performed in Hacettepe University, Faculty of Physical Therapy and Rehabilitation, Pediatric Neuromuscular Diseases Unit between January 2016-August 2018.

**Subjects.** A total of 71 patients with DMD, whose functional levels were between 1–3 (Level 1: The child is able to walk and climb the stairs, independently; Level 2: The child is able to walk and climb the stairs by using handrails, taking less than 12 seconds; Level 3: The child climbs the stairs slowly, taking more than 12 seconds) according to the Brooke Lower Extremity Functional Classification (BLEFC),\textsuperscript{10} aged between 5–12 years, who were on corticosteroids for more than 6 months, and who were still ambulant were included in the study with their parents. The children with severe physical and cognitive impairments that block performance and communication during the implementation of questionnaire and functional assessments, and the children with less cooperation were excluded from the study.

Hacettepe University’s Non-invasive Clinical Research Ethics Committee (No: GO 16/331) provided the ethical approval. Children (and their parents) who were directed to the Hacettepe University, Faculty of Physical Therapy and Rehabilitation, Pediatric Neuromuscular Diseases Unit for a routine physical examination after the diagnosis of DMD, signed a written consent form to be included in the study. This study followed the principles of Helsinki Declaration. All of the following assessments performed in this study were implemented approximately at the same time of the day for each child; frequently in the morning, rarely in the midday.

**Method. PedsQL\textsuperscript{TM}-3.0 Multidimensional Fatigue Scale.** The PedsQL-MFS allows to evaluate 2-18 years old pediatric patient population in terms of general symptomatic fatigue, and consists of 18 items. Test items are collected under three subgroups: general fatigue (six items, such as ‘feeling tired’, and ‘feeling too tired to do things that you like to do’), fatigue in sleep/rest (six items, such as ‘feeling tired at morning wake up’, and ‘needing lots of rest’), and cognitive fatigue (six items, such as ‘difficulty paying attention to something’ and ‘difficulty remembering what people tell you’). Clinical

**Table 1 - Demographic characteristics of the patients (n=71).**

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Min</th>
<th>Max</th>
<th>X±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (month)</td>
<td>55.0</td>
<td>161.0</td>
<td>102.94±23.23</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>95.0</td>
<td>152.0</td>
<td>123.41±11.31</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>14.0</td>
<td>46.0</td>
<td>26.42±7.23</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>10.90</td>
<td>24.79</td>
<td>17.15±2.98</td>
</tr>
</tbody>
</table>
experience and studies on chronic pediatric diseases were considered to develop PedsQL-MFS.\textsuperscript{11,12} It contains questionnaires for the child to evaluate their own fatigue and for parents to evaluate their child's fatigue. The child and adolescent questionnaires cover the ages 5–7, 8–12, and 13–18, while the young adult questionnaire covers the ages 18–25. For all child, adolescent, young adult, and parental questionnaires, scoring is done on a five-point Likert scale (0 = Never; 1 = Virtually Never; 2 = Sometimes; 3 = Frequently; 4 = Almost Always). The items are scored by linearly reversing the item scores (0 = 100; 1 = 75; 2 = 50; 3 = 25; 4 = 0) so that the higher the score, the better the quality of life, which indicates fewer symptoms of fatigue. Thus, a score of 0 indicates great fatigue, and a score of 100 points indicates less fatigue in PedsQL-MFS item scoring.\textsuperscript{11,13}

The permission to perform the Turkish translation of the questionnaire was obtained from the developer of the source scale. The translation steps were as follows:

I. The English version of the questionnaire was translated into Turkish by 2 persons, independent of each other, that one of them with sufficient knowledge in the field of physiotherapy and rehabilitation.

II. Then the translations were compared and the differences were evaluated. A common opinion was reached and a single joint translation was created from 2 independent translations.

III. In the next stage, the Turkish questionnaire was translated back into English independently by 2 native speakers of English who also knew Turkish well, and did not know about the questionnaire.

IV. The new back-translated questionnaire was compared with the original questionnaire and the differences were evaluated.

V. After the translation process was over, all translations and reports were evaluated by a committee of experts consisting of methodologists, health experts, language experts and translators involved in the translation. Created questionnaires were corrected by this committee in terms of semantic, idiomatic, experiential, and conceptual equivalence.

VI. The final version of the questionnaire prepared by the committee was applied to 10 people and it was determined how the questionnaire worked during the application and the unidentified questions were corrected. Thus, the cultural adaptation of the

<table>
<thead>
<tr>
<th>Items</th>
<th>Child Self Report Mean (SD)</th>
<th>ICC</th>
<th>Parent Proxy Report Mean (SD)</th>
<th>ICC</th>
</tr>
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<tbody>
<tr>
<td>Q1</td>
<td>65.66 (31.17)</td>
<td>0.60</td>
<td>Q1</td>
<td>54.04 (24.48)</td>
</tr>
<tr>
<td>Q2</td>
<td>72.88 (32.95)</td>
<td>0.53</td>
<td>Q2</td>
<td>55.45 (27.79)</td>
</tr>
<tr>
<td>Q3</td>
<td>76.58 (31.68)</td>
<td>0.39</td>
<td>Q3</td>
<td>70.24 (29.61)</td>
</tr>
<tr>
<td>Q4</td>
<td>82.04 (29.97)</td>
<td>0.51</td>
<td>Q4</td>
<td>72.18 (28.57)</td>
</tr>
<tr>
<td>Q5</td>
<td>76.05 (31.35)</td>
<td>0.57</td>
<td>Q5</td>
<td>63.20 (28.82)</td>
</tr>
<tr>
<td>Q6</td>
<td>78.34 (32.37)</td>
<td>0.37</td>
<td>Q6</td>
<td>65.84 (27.52)</td>
</tr>
<tr>
<td>General</td>
<td>75.26 (20.04)</td>
<td>0.80</td>
<td>General</td>
<td>63.49 (22.51)</td>
</tr>
<tr>
<td>Q7</td>
<td>65.49 (36.79)</td>
<td>0.68</td>
<td>Q7</td>
<td>72.88 (26.37)</td>
</tr>
<tr>
<td>Q8</td>
<td>79.40 (31.12)</td>
<td>0.64</td>
<td>Q8</td>
<td>79.92 (22.91)</td>
</tr>
<tr>
<td>Q9</td>
<td>73.94 (34.06)</td>
<td>0.80</td>
<td>Q9</td>
<td>70.77 (25.95)</td>
</tr>
<tr>
<td>Q10</td>
<td>63.90 (35.29)</td>
<td>0.71</td>
<td>Q10</td>
<td>68.83 (27.80)</td>
</tr>
<tr>
<td>Q11</td>
<td>80.63 (33.07)</td>
<td>0.53</td>
<td>Q11</td>
<td>81.86 (24.39)</td>
</tr>
<tr>
<td>Q12</td>
<td>78.16 (32.46)</td>
<td>0.63</td>
<td>Q12</td>
<td>80.80 (24.31)</td>
</tr>
<tr>
<td>Sleep/rest</td>
<td>73.59 (20.86)</td>
<td>0.86</td>
<td>Sleep/rest</td>
<td>75.85 (18.86)</td>
</tr>
<tr>
<td>Q13</td>
<td>74.47 (31.57)</td>
<td>0.57</td>
<td>Q13</td>
<td>65.85 (29.99)</td>
</tr>
<tr>
<td>Q14</td>
<td>72.35 (32.02)</td>
<td>0.42</td>
<td>Q14</td>
<td>75.52 (24.63)</td>
</tr>
<tr>
<td>Q15</td>
<td>71.30 (34.71)</td>
<td>0.76</td>
<td>Q15</td>
<td>77.64 (23.38)</td>
</tr>
<tr>
<td>Q16</td>
<td>68.13 (34.48)</td>
<td>0.60</td>
<td>Q16</td>
<td>75.00 (26.12)</td>
</tr>
<tr>
<td>Q17</td>
<td>71.65 (33.97)</td>
<td>0.73</td>
<td>Q17</td>
<td>75.00 (25.78)</td>
</tr>
<tr>
<td>Q18</td>
<td>66.73 (33.89)</td>
<td>0.40</td>
<td>Q18</td>
<td>75.88 (25.33)</td>
</tr>
<tr>
<td>Cognitive</td>
<td>70.69 (24.03)</td>
<td>0.83</td>
<td>Cognitive</td>
<td>74.14 (21.90)</td>
</tr>
<tr>
<td>Total</td>
<td>73.33 (17.92)</td>
<td>0.87</td>
<td>Total</td>
<td>70.61 (19.23)</td>
</tr>
</tbody>
</table>

Q - Question
Table 3 - 3-factor model results of confirmatory factor analysis.

<table>
<thead>
<tr>
<th>Scales</th>
<th>χ²</th>
<th>df</th>
<th>χ²/df</th>
<th>RMSEA</th>
<th>CFI</th>
<th>NFI</th>
<th>GFI</th>
<th>AGFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child Self Report</td>
<td>209.11</td>
<td>132</td>
<td>1.58</td>
<td>0.092</td>
<td>0.81</td>
<td>0.62</td>
<td>0.76</td>
<td>0.69</td>
</tr>
<tr>
<td>Parent Proxy Report</td>
<td>233.15</td>
<td>132</td>
<td>1.76</td>
<td>0.105</td>
<td>0.88</td>
<td>0.77</td>
<td>0.74</td>
<td>0.67</td>
</tr>
</tbody>
</table>

RMSEA - root mean squared error of approximation, CFI - comparative fit index, NFI - normative fit index, GFI - goodness-of-fit index, AGFI - adjusted GFI

Table 4 - The Turkish Version of PedsQL Multidimensional Fatigue Scale Factor Loadings.

<table>
<thead>
<tr>
<th>Scale/items</th>
<th>Factor 1</th>
<th>Factor 2</th>
<th>Factor 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>General fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. I feel tired</td>
<td>.417</td>
<td>.223</td>
<td>.138</td>
</tr>
<tr>
<td>2. I feel physically weak (not strong)</td>
<td>.087</td>
<td>.086</td>
<td>.453</td>
</tr>
<tr>
<td>3. I feel too tired to do things that I like to do</td>
<td>.504</td>
<td>.126</td>
<td>.538</td>
</tr>
<tr>
<td>4. I feel too tired to spend time with my friends</td>
<td>.522</td>
<td>.269</td>
<td>.216</td>
</tr>
<tr>
<td>5. I have trouble finishing things</td>
<td>.527</td>
<td>.498</td>
<td>.440</td>
</tr>
<tr>
<td>6. I have trouble starting things</td>
<td>.585</td>
<td>.425</td>
<td>.408</td>
</tr>
<tr>
<td>Sleep/rest fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. I sleep a lot</td>
<td>-.043</td>
<td>.399</td>
<td>.246</td>
</tr>
<tr>
<td>8. It is hard for me to sleep through the night</td>
<td>.160</td>
<td>.335</td>
<td>-.112</td>
</tr>
<tr>
<td>9. I feel tired when I wake up in the morning</td>
<td>.361</td>
<td>.509</td>
<td>.075</td>
</tr>
<tr>
<td>10. I rest a lot</td>
<td>.079</td>
<td>.318</td>
<td>.168</td>
</tr>
<tr>
<td>11. I take a lot of naps</td>
<td>.049</td>
<td>.091</td>
<td>.758</td>
</tr>
<tr>
<td>12. I spend a lot of time in bed</td>
<td>.079</td>
<td>.257</td>
<td>.527</td>
</tr>
<tr>
<td>Cognitive fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. It is hard for me to keep my attention on things</td>
<td>.451</td>
<td>.710</td>
<td>.738</td>
</tr>
<tr>
<td>14. It is hard to for me to remember what people tell me</td>
<td>.733</td>
<td>.759</td>
<td>.135</td>
</tr>
<tr>
<td>15. It is hard for me to remember what I just heard</td>
<td>.695</td>
<td>.779</td>
<td>.125</td>
</tr>
<tr>
<td>16. It is hard for me to think quickly</td>
<td>.820</td>
<td>.696</td>
<td>.139</td>
</tr>
<tr>
<td>17. I have trouble remembering what I was just thinking</td>
<td>.762</td>
<td>.849</td>
<td>.045</td>
</tr>
<tr>
<td>18. I have trouble remembering more than one thing at a time</td>
<td>.676</td>
<td>.915</td>
<td>.038</td>
</tr>
</tbody>
</table>

Table 5 - Correlation between the Turkish version of PedsQL-Multidimensional Fatigue Scale and other outcome measures.

<table>
<thead>
<tr>
<th>Scales</th>
<th>Child Self Report</th>
<th>Parent Proxy Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>PedsQL-Neuromuscular Module-Child</td>
<td>0.62**</td>
<td>0.36**</td>
</tr>
<tr>
<td>PedsQL-Neuromuscular Module-Parent</td>
<td>0.31**</td>
<td>0.74**</td>
</tr>
<tr>
<td>10 Minute Walk Test</td>
<td>-0.15</td>
<td>-0.15</td>
</tr>
<tr>
<td>Standing from supine</td>
<td>-0.70</td>
<td>-0.08</td>
</tr>
<tr>
<td>Ascending 4 steps</td>
<td>-0.38</td>
<td>-0.03</td>
</tr>
<tr>
<td>Descending 4 steps</td>
<td>-0.20</td>
<td>-0.12</td>
</tr>
<tr>
<td>6 Minute Walk Test</td>
<td>0.13</td>
<td>0.22</td>
</tr>
<tr>
<td>North Star Ambulatory Assessment</td>
<td>-0.14</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01
The Turkish version of the PedsQL-MFS questionnaire was completed.

Demographic properties including age (years), height (cm), weight (kg), and body mass indexes (BMI; kg/m²), as well as communication information, steroid use, and diagnostic information were recorded. The following functional evaluations were carried out.

**The Evaluation of Functional Performance and Ambulation.** Individuals participating in the study were subjected to timed performance tests, such as standing from supine position, 10 m walk, and ascending/descending four steps, which were considered to be a significant outcome measure to show functional performance in DMD. Another functional performance test—the six-minute walk test (6MWT), which has been used as a gold standard measurement for many clinical studies and which was found valid and reliable for patients with DMD—was also used. The distance walked in six minutes was recorded in meters.

Individuals with DMD—depending on their progressive muscle weakness—tend to modify their movements in order to perform their daily living activities. The North Star Ambulatory Assessment (NSAA) grades daily activities that require ambulation as normal (2 points), modified (1 points), and dependent (0 points). The NSAA is a measure of 17 items that can be completed within 15 minutes, evaluating the skills necessary to maintain ambulatory function, from standing (item 1) to running (item 17). Each item in the NSAA is scored using a three-point scale. The total score is determined by summing the scores of all items, and ranges from 0 (no activity can be achieved) to 34 (all activities are achieved without help).

**Assessment of Quality of Life.** The Turkish version of The Pediatric Quality of Life Inventory (PedsQL) Neuromuscular Module was used in the evaluation of the health-related quality of life of the patients. This scale was found to be valid and reliable in assessing the health-related quality of life of children with neuromuscular diseases between 2 and 18 years of age. The PedsQL-3.0 Neuromuscular Module was developed in the form of a parent report for children between the ages of 2 and 4, and in the form of both the child’s personal report and a parent report for children between

---

**Table 6** - Inter-correlations between the child-self and parent proxy reports of Turkish version of PedsQL Multidimensional Fatigue Scale.

<table>
<thead>
<tr>
<th>Child-Self Report</th>
<th>Parent Proxy Report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Total</td>
<td>0.46’</td>
</tr>
<tr>
<td>General</td>
<td>0.29’</td>
</tr>
<tr>
<td>Sleep/Rest</td>
<td>0.45’</td>
</tr>
<tr>
<td>Cognitive</td>
<td>0.43’</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01

---

**Figure 1** - Bland-Altman Plot for test-retest reliability of child self-report.

**Figure 2** - Bland-Altman Plot for test-retest reliability of parent proxy report.
5 and 18 years of age. The scale consists of 25 items in 3 categories. Higher scores from the PedsQL-3.0 Neuromuscular Module indicate better health-related quality of life.\(^1\)

**Psychometric and Statistical Analysis.** The IBM SPSS Statistics for Windows, Version 21 (Statistical Package for the Social Sciences, IBM Corp., Armonk, N.Y., USA) statistical analysis program was used to assess data obtained from the patients. Descriptive characteristics were identified as minimum, maximum, and mean± standard deviation (X±SD) for the quantitative data, while number (n) and percent (%) values were used for qualitative data. Data was analyzed in terms of normal distribution by using a histogram, the variation coefficient rate, the Skewness-Kurtosis, and Kolmogorov-Smirnov tests. It was determined that the data was not distributing, normally.

**Feasibility.** Each item's missing values percentage was examined to determine the feasibility of the PedsQL-MFS Turkish version.\(^1\)

**Internal Consistency Reliability.** The standardized Cronbach alpha coefficient was used to detect the internal consistency of the scale. For the Turkish version of PedsQL-MFS, the acceptable internal consistency was decided according to the criteria as Chronbach alpha coefficient >0.7.\(^2\)

**Test-Retest Reliability.** The same physiotherapist applied the questionnaire twice to 71 children and their parents with a 2-week interval to test the test-retest reliability of the PedsQL-MFS. The test-retest reliability of the instrument was examined by calculating the intraclass correlation coefficient (ICC), and the ICC values between 0.1-0.3 were accepted as weak, 0.3-0.5 as moderate, and >0.5 as strong.\(^2\)

**Construct Validity.** The factor structure of the Turkish version of PedsQL-MFS was investigated by confirmatory factor analysis (CFA). CFA determines if the new instrument presents similar factor solution with the original questionnaire. Thus, to perform analysis; root mean squared error of approximation (RMSEA), goodness-of-fit index (GFI), the chi-squared test (x2), comparative fit index (CFI), adjusted goodness-of-fit index (AGFI), and normed-fit index (NFI) were used. If the degrees of freedom (x2df) is found <3.0, the GFI, CFI, NFI, and AGFI values are found more than 0.9, and RMSEA is determined <0.1; the instrument is accepted to behave similar with the original instrument.\(^2\) Also, a further analysis was performed to evaluate factor structure by using the exploratory factor analysis (EFA). Varimax rotation of the 18 items of the Turkish version of PedsQL-MFS was performed for principal component analysis.

**Criterion-Related Validity.** Correlations were examined between the scores (total and sub-scores) of the translated questionnaire and functional performance, ambulatory assessment, and quality of life assessment scores using Spearman’s correlation coefficient (rho) to test the validity of the questionnaire in Turkish patients with DMD.

**Parent/Child Agreement.** The Spearman’s correlation coefficient and ICCs were used for interpretation of agreement between the child’s self-report and parent's proxy report. The significance levels according to the Spearman’s correlation coefficient were accepted as strong if \(r=0.7–1.00\), moderate if \(r=0.30–0.70\); and weak or insignificant if \(r=0.05–0.30\). Levels were determined to be statistically significant at \(p<0.05\).

**Results.** Seventy-one boys with DMD aged 55 to 161 months, and 69 mothers (97.18%) and 2 fathers (2.82%) whose mean age was 37.05±3.75, and who were all graduated from high-school were included in this study. Demographic features of the children were given in Table 1. Sixty-two percent of the children were in level I, 31% in level II, and the others were in level III according to the BLEFC. The children were all on steroids and going to primary school.

**Feasibility.** Missing data from children’s self-reports and parents’ proxy reports were calculated in order to determine the feasibility of the Turkish version of the PedsQL-MFS. Missing data from the self-reports and parent proxy reports were 0.007% and 0%, respectively.

**Internal Consistency Reliability.** The internal consistencies of child self-report and parent proxy report determined by Cronbach's alpha coefficient were 0.74 for general fatigue, 0.65 for sleep/rest fatigue, and 0.83 for cognitive fatigue, while 0.89, 0.84, and 0.91 for the parent proxy report, respectively.

**Test-Retest Reliability.** The ICC values of the PedsQL-MFS Turkish Version was shown in Table 2, and the Bland-Altman plots were given for the test-retest reliability of the questionnaire in Figure 1 and 2.

**Construct Validity.** Table 3 presented the confirmatory factor analysis results of the 3-factor model of the child self-report and parent proxy report. The assessment tool had an acceptable RMSEA for the child self-report and an acceptable x2df for child self and parent proxy reports. However, the RMSEA for parent proxy report and the CFI, GFI, and AGFI of the child self-report and parent proxy report were slightly below the cut-off value.

The factor loadings of the items of the child self-report ranged within 0.34–0.75, 0.21–0.79, and 0.61–0.81 for the GF, SRF, and CF, while the factor
loadings of the items of the parent proxy report ranged within 0.70–0.80, 0.74–0.87, and 0.58–0.83 for the GF, SRF, and CF, respectively. Therefore, parent proxy report of the PedsQL-MFS Turkish version was found to have more acceptable fit indices than the child-self report. However, the result of the estimated ranged correlation between the GF, SRF, and CF was 0.66–0.85. Three factors such as Factor 1 (cognitive fatigue), Factor 2 (general fatigue), and Factor 3 (sleep/rest fatigue) for both the child self and the parent proxy reports were extracted by factor analysis with varimax rotation (EFA). The eigen values’ cut off was 1.0, with total variances of 51.7% and 68.1% for the self-report and proxy report, respectively (Table 4). Items one, four, five, and six split into the cognitive factor (Factor I), and items 11, 12, and 13 split into the general factor (Factor 2) in self-report which demonstrated highest load on a factor other than a priori hypothesized factor structure. All items from the parent proxy report agreed with the a priori hypothesized factor structure.

**Criterion-related Validity.** Table 5 demonstrated correlations between the PedsQL-Neuromuscular Module, the 10 m walk test, standing from supine position, ascending and descending 4 steps, the 6MWT, the NSAA, and the PedsQL-MFS total score and sub-scores. A statistically significant correlation was detected between the PedsQL-MFS and PedsQL-Neuromuscular Module scales (p<0.05).

**Parent/Child Agreement.** The ICCs between patients with DMD and their parents for PedsQL-MFS were as follows: total fatigue 0.62, general fatigue 0.42, sleep/rest fatigue 0.56, and cognitive fatigue 0.49. The ICCs were ranged in the moderate agreement. Correlations between DMD patients and their parents across the PedsQL-MFS were given in Table 6.

**Discussion.** This study provided the psychometric properties of the PedsQL-MFS Turkish version. It showed that the Turkish version of the PedsQL-MFS is a feasible, reliable, and valid instrument for evaluating fatigue in children with DMD between 5-12 years old. Furthermore, this study is the first study to evaluate multidimensional fatigue in DMD.

In 2013, Hu et al. found minimal missing data in their validity and reliability study of the Chinese version of the PedsQL Neuromuscular Module in 56 Chinese DMD children.23 Similarly, missing data was also minimal in our study. In addition, this study showed that both DMD children and their parents have good quality data on fatigue.

The intra-rater reliability was high in both the total and sub-scores of the PedsQL-MFS (Turkish version) parent proxy and child self-reports. This result supported the PedsQL-MFS as a reliable measure for children with DMD.

According to the CFA examination of the goodness of fit, the PedsQL-MFS (Turkish version) is structurally compatible with the original form. Moreover, the scale was found to be compatible with the fatigue of the population we studied. These results are similar to the CFA results for PedsQL-MFS translations into other languages.24,25 When EFA, which was used to examine the further construct validity of the PedsQL-MFS, was considered, the total variances were found to be higher in both children and caregivers than in previous studies, indicating that it gives more accurate results than other studies evaluating fatigue. However, the EFA results confirmed the exceptions regarding seven items in the child self-report. It is thought that this is caused by the limited number of children or the difficulty in understanding a subjective symptom such as fatigue.

PedsQL was determined to have a moderate-to-strong relationship between the PedsQL-MFS total and sub-scores and the PedsQL-Neuromuscular Module (excluding the PedsQL-Neuromuscular Module parent form and the PedsQL-Multidimensional Fatigue Scale child form general fatigue subscale). These results are similar to those of a study by Varni et al. performed in 200936 regarding the relationship between the Fatigue Scale and the PedsQL Generic Scale.

One of the most common problems that occurs secondary to muscle weakness is fatigue. It is known that this symptom starts with complaints such as lagging slightly behind peers in functional activities in early life, but it will also affect functions such as walking and climbing the stairs in the future, significantly affecting the child’s quality of life. Significant relationships between quality of life and fatigue overlap with studies in the literature related to the effects of fatigue on the quality of life of children with DMD. The reason for not having any relationship between PedsQL-MFS and ambulatory and performance tests that are frequently used in clinical practice may origin from the multidimensional aspect of the questionnaire which evaluates not only general fatigue caused by daily routine, but also sleep/resting fatigue and cognitive fatigue that are not directly related to the physical performance in daily activities. Thus, the result was considered to be acceptable when the structural characteristic of the questionnaire was regarded.

The moderate agreement between children with DMD and parent reports was found to be better than both adult and child studies of the PedsQL-MFS scale in literature.27,28 However, these results also
showed that the data obtained from the children were not exactly same with the data obtained from the parents. Since the PedsQL-MFS has the ability to detect also the psychological aspect of fatigue with cognitive subheading, the perception of fatigue might be understood differently by children and parents, which prevented a “complete” or “exact” agreement between them. Thus, collection of data regarding fatigue from both parents and children is important in terms of accurate assessment of fatigue from different perspectives in clinical practice.

The limited number of patients with DMD and the inclusion of only physically active, ambulant children in current study can be considered as a limitation. Also, the missing information on the daily doses of steroids for each child is another limitation of the study.

In conclusion, the Turkish version of the PedsQL-MFS is a reliable and valid instrument to evaluate general, sleep/rest, and cognitive fatigue in 5-12 years old, ambulant children with DMD. The scale can be considered as a promising tool to be used as an outcome measure that evaluates fatigue and quality of life from the perspectives of parents and children with DMD in clinical trials in the future. Further studies are needed to be performed on a large number of patients with wide range of functionality to investigate broader use of the Turkish version of PedsQL-MFS.

Acknowledgement. We would like to thank to the SCRIBENDI professional editing company (https://www.scribendi.com/) for English language editing.

References

ARE PHYSICIANS HELPING CANCER SURVIVORS LIVE HEALTHY LIVES?

AUGUST 26, 2019 - A recent study indicates that certain physicians who care for patients with cancer do not often promote healthy lifestyle changes to cancer survivors, and they may fear that providing such advice would distress or overwhelm patients. Published early online in CANCER, a peer-reviewed journal of the American Cancer Society, the findings are noteworthy because maintaining a healthy lifestyle is especially important to the long-term well-being of cancer survivors.

Cancer survivors face increased risks of cardiovascular disease and other conditions, and guidelines advise physicians—including oncologists—to encourage cancer survivors to adopt healthy lifestyles to help protect their long-term health.

To investigate the extent to which physicians follow these recommendations, a team led by Tammy Stump, PhD, and Bonnie Spring, PhD, faculty at the Northwestern University Feinberg School of Medicine in Chicago, surveyed 91 physicians: 30 primary care physicians; 30 oncologists; and 31 specialists (urologists, gynecologists, and dermatologists) who treat survivors of prostate cancer, breast cancer, and melanoma, respectively. Interviews also were conducted with 12 of the oncologists who were sent the survey.

Among primary care physicians, 90 percent reported recommending health promotion such as weight loss and smoking cessation to at least some cancer survivors. However, only 26.7 percent of oncologists and 9.7 percent of specialists said they ever did so.

In interviews, oncologists expressed fear that promoting healthy lifestyle changes would distress or overwhelm patients. They also noted that they often lack the time and training to make such recommendations to patients. Most physicians believed that at least half of cancer survivors would take their medications properly to prevent cancer recurrence, but they believed that patients would not do so if they were also trying to lose weight.

“Even though oncologists clearly believe that cancer survivors should adopt a healthy lifestyle, they don't have the time to address more than cancer care—that’s their expertise,” said Dr. Stump. “Ultimately, we believe that healthy lifestyle support can be provided to cancer survivors most effectively as part of
integrated survivorship care delivered by health promotionists trained in nutrition, physical activity, and behavioral coaching in a program designed with the input of oncologists to meet the specific needs of cancer survivors,” added Dr. Spring.


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ASPIRIN MAY INTERACT WITH CELLS’ DNA MODIFICATIONS TO ALTER BREAST CANCER OUTCOMES

AUGUST 12, 2019 - A New findings suggest that women with specific DNA characteristics in certain areas of the genome may live longer if they take aspirin before they are diagnosed with breast cancer. Published early online in CANCER, a peer-reviewed journal of the American Cancer Society, the findings point to the need for studies on the potential of aspirin to prevent or treat breast cancer in some individuals.

It is often unclear why some patients benefit from a particular therapy while others do not. In some cases, gene sequences play a role, but in other cases, chemical modifications to DNA may be important. The latter are termed epigenetic changes, and they include a process called DNA methylation.

Tengteng Wang, PhD, MSPH, and her mentor Marilie Gammon, PhD, of the University of North Carolina at Chapel Hill, wondered whether DNA methylation may influence the effects of aspirin in patients with breast cancer. The team examined DNA methylation in breast tumor tissues—including at DNA sites that control the expression of 13 breast cancer–related genes—and also in cells circulating in patients’ blood. The study is the first to examine the effect of DNA methylation on the association between aspirin use and mortality in women with breast cancer.

In the study of 1266 women who were diagnosed with breast cancer during the 1996–1997 period, 476 died from any cause and 202 died specifically from breast cancer by the end of 2014. In women who used aspirin, the risk of dying from any cause and the risk of dying from breast cancer was lower among those whose DNA was not methylated in the region that controlled expression of the breast cancer–related BRCA1 gene. Other methylation patterns related to aspirin use and mortality were also observed.

The authors noted that the findings could help identify individuals who may benefit from aspirin after a breast cancer diagnosis due to their cells’ DNA methylation profile. Future research should consider a more comprehensive DNA methylation profile in order to better characterize women who are at risk.
“Consideration of DNA methylation profiles as potential modifiers of the aspirin-mortality association may provide new insights on the underlying biological mechanisms on aspirin use in relation to mortality after breast cancer diagnosis,” said Dr. Wang. “Our findings, if confirmed, may also impact clinical decision-making by identifying a subgroup of patients, using epigenetic markers, for whom pre-diagnosis aspirin use impacts subsequent mortality, and may help refine risk reduction strategies to improve survival among women with breast cancer,” added Dr. Gammon.

In an accompanying editorial, Kristen Malecki, PhD, MPH, of the University of Wisconsin-Madison, noted that the findings support the importance of research examining interactions between epigenetics and low-cost therapies such as aspirin. According to Dr. Malecki, “The study by Wang et al. shows that beyond gene-environment interactions, epigenetic and environment interactions also exist, and suggest that DNA methylation could in the future help to support the identification of individuals for whom treatment may or may not be successful.

**Full citation:** “Pre-diagnosis aspirin use, DNA methylation, and mortality after breast cancer: a population-based study.” Tengteng Wang, Lauren E. McCullough, Alexandra J. White, Patrick T. Bradshaw, Xinran Xu, Yoon Hee Cho, Mary Beth Terry, Susan L. Teitelbaum, Alfred I. Neugut, Regina M. Santella, Jia Chen, and Marilie D. Gammon. CANCER; Published Online: August 12, 2019 (DOI: 10.1002/cncr.32364).


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Clinical Image

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Notice: Authors are encouraged to submit clinical images for possible publication in the Journal. These may be in any field of Clinical Neurosciences, and should approximately follow the format used here. Please address any submissions to the Assistant Editor, Neurosciences Journal, Prince Sultan Military Medical City, PO Box 7897, Riyadh 11159, Kingdom of Saudi Arabia.
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Tuberous sclerosis

Clinical Presentation

An 11-year-old boy presented to the pediatric neurology clinic for evaluation of seizures. On examination, he has multiple hypopigmented lesions. His brain MRI is shown in Figure 1.

Questions:

1. What is the name of this lesion?
   A. Subependymal nodules.
   B. Subependymal giant cell astrocytoma.
   C. Periventricular heterotopia
   D. Choroid plexus papilloma

2. What is the most likely diagnosis?
   A. Tuberous sclerosis complex.
   B. Neurofibromatosis type 1.
   C. Hypomelanosis of Ito.
   D. Sturge-Weber syndrome.

Figure 1 - Brain MRI of 11-year-old boy presented to the Pediatric Neurology Clinic for evaluation of seizures.

doi: 10.17712/nsj.2019.4.20190107
3. Which of the following statements is correct regarding the genetics of this disease?

A. It is autosomal dominant with variable penetrance
B. It is autosomal dominant with complete penetrance
C. It can be caused by a mutation in TSC1 gene that encodes for the protein tuberin
D. It can be caused by a mutation in TSC2 gene that encodes for the protein hamartin

4. What is the best management of lesion shown in Figure 1?

A. Anti epileptic drugs
B. Radiotherapy
C. No treatment
D. mTOR inhibitors

5. Which of following is a major criterion for diagnosis of TSC?

A. Meningioma
B. Vestibular schwannoma
C. Subependymal nodules
D. Optic glioma
E. Neurofibroma

**Answers & Discussion**

1. B
   It is a low-grade brain tumor (WHO grade 1) that arise within the ventricles of brain (Foramen of Monro). It is commonly associated with tuberous sclerosis complex (TSC). One of major criteria of diagnosis TSC.¹

2. A
   Tuberous sclerosis complex is a genetic disorder affecting cellular differentiation, proliferation and migration resulting in variety of hamartomatous lesions that may affect every organ system of body.¹

3. A
   Tuberous sclerosis complex is an autosomal dominant disorder with variable penetrance. Tuberous sclerosis complex is caused either by a mutation in TSC1 gene on chromosome 9 that encodes for protein hamartin or by a mutation in TSC2 gene on chromosome 16 that encodes for protein tuberin.²

4. D
   Rapamycin and everolimus, an mTOR inhibitors, has been shown to reduce the size of subependymal giant cell tumors in TSC.³

5. C
   Major criteria:
   - Angiofibromas (3 or more) or forehead plaque
   - Hypomelanotic macules (3 or more)
• Ungual fibromas (2 or more)
• Shagreen patch
• Multiple retinal hamartomas
• Cortical dysplasias (more than 3). This includes tubers and cerebral white matter radial migration lines.
• Subependymal nodule(s)
• Subependymal giant cell astrocytoma(s)
• Cardiac rhabdomyoma
• Lymphangioleiomyomatosis (LAM)
• Angiomyolipomas (2 or more) e common.¹

References
WHO URGES COUNTRIES TO INVEST IN ELIMINATING HEPATITIS

26 July 2019, Geneva - Ahead of World Hepatitis Day (28 July), WHO calls on countries to take advantage of recent reductions in the costs of diagnosing and treating viral hepatitis and scale up investments in disease elimination.

A new study by WHO, published today in Lancet Global Health, has found that investing US$6bn per year in eliminating hepatitis in 67 low- and middle-income countries would avert 4.5 million premature deaths by 2030, and more than 26 million deaths beyond that target date.

A total of US$58.7 billion is needed to eliminate viral hepatitis as a public health threat in these 67 countries by 2030. This means reducing new hepatitis infections by 90% and deaths by 65%.

“Today 80% of people living with hepatitis can’t get the services they need to prevent, test for and treat the disease,” said WHO Director-General Dr Tedros Adhanom Ghebreyesus. “On World Hepatitis Day, we’re calling for bold political leadership, with investments to match. We call on all countries to integrate services for hepatitis into benefit packages as part of their journey towards universal health coverage.”

By investing in diagnostic tests and medicines for treating hepatitis B and C now, countries can save lives and reduce costs related to long-term care of cirrhosis and liver cancer that result from untreated hepatitis.

Some countries are already taking action. The Government of India, for example, has announced that it will offer free testing and treatment for both hepatitis B and C, as part of its universal health coverage plan. This has been facilitated through the reduction in prices of medicines. In India, a hepatitis C cure costs less than US$40 and a year of hepatitis B treatment costs less than US$30. At these prices, hepatitis C cure will result in healthcare cost savings within three years.

The Government of Pakistan has also been able to procure hepatitis C curative treatment at similarly low prices. Providing curative treatment to all those currently diagnosed with hepatitis C could also reduce healthcare costs in Pakistan within three years. Meanwhile, Pakistan is faced with one of the highest new annual infection rates of hepatitis C virus and is launching a new infection control and injection safety plan on the occasion of World Hepatitis Day to stop transmission.

No access to prevention, testing and treatment for most

For the vast majority of the 325 million people living with hepatitis B and/or C, accessing testing and treatment remains beyond reach.
Of the estimated 257 million living with hepatitis B infection:
• 10.5% (27 million) knew their infection status in 2016.
• Of those people diagnosed, only 17% (4.5 million) received treatment in 2016.
• In 2016, 1.1 million people newly developed chronic hepatitis B infection—a primary cause of liver cancer.

Of the estimated 71 million people living with chronic hepatitis C infection in 2015:
• 19% (13.1 million) knew their infection status in 2017.
• Of those people diagnosed, 15% (2 million) received curative treatment in that same year. Overall, between 2014 and 2017, 5 million people have received hepatitis C curative treatment.
• In 2017, 1.75 million people newly developed chronic hepatitis C infection.

**World Hepatitis Day**
WHO’s global hepatitis strategy, endorsed by all WHO Member States, aims to reduce new hepatitis infections by 90% and deaths by 65% between 2016 and 2030.

On World Hepatitis Day 2019, WHO calls on all countries to “Invest in eliminating hepatitis” through costing, budgeting and financing of elimination services within their universal health coverage plans. While there has been broad support among WHO Member States in adopting the WHO hepatitis elimination strategy, with 124 out of 194 countries developing hepatitis plans, over 40% of country plans lack dedicated budget lines to support elimination efforts.

WHO has also released online calculators (www.hepccalculator.org and www.hepbcalculator.org) designed to help decision makers to evaluate the cost-effectiveness of their hepatitis treatment programmes.

There are five types of viral hepatitis infections – A, B, C, D and E. Over 95% of deaths are caused by chronic hepatitis B and C infections, while hepatitis A and E rarely cause life-threatening illnesses. Hepatitis D is an additional infection occurring in people living with hepatitis B.

**Editor’s note**
For World Hepatitis Day 2019 “Invest in eliminating hepatitis”, WHO will be joining the Government of Pakistan in inaugurating the Prime Minister’s Initiative for hepatitis in Islamabad, Pakistan. This is a country with one of the fastest growing hepatitis C epidemics in the world, but also in the process of adopting progressive policies to reverse the tide.

**SDG Health Price Tag**
In 2017, the SDG Health Price Tag study estimated the investments needed to reach 16 health-related targets of the Sustainable Development Goals in 67 low- and middle-income countries that account for 75% of the world’s population. This study did not include the costing for hepatitis.

The new study published today is based on the same modelling scenarios and methods to estimate the costs of reaching global hepatitis elimination targets.

WORLD HUNGER IS STILL NOT GOING DOWN AFTER THREE YEARS AND OBESITY IS STILL GROWING – UN REPORT

15 July 2019 - An estimated 820 million people did not have enough to eat in 2018, up from 811 million in the previous year, which is the third year of increase in a row. This underscores the immense challenge of achieving the Sustainable Development Goal of Zero Hunger by 2030, says a new edition of the annual The State of Food Security and Nutrition in the World report released today.

The pace of progress in halving the number of children who are stunted and in reducing the number of babies born with low birth weight is too slow, which also puts the SDG 2 nutrition targets further out of reach, according to the report.

At the same time, adding to these challenges, overweight and obesity continue to increase in all regions, particularly among school-age children and adults.

The chances of being food insecure are higher for women than men in every continent, with the largest gap in Latin America.

“Our actions to tackle these troubling trends will have to be bolder, not only in scale but also in terms of multisectoral collaboration,” the heads of the United Nations’ Food and Agriculture Organization (FAO), the International Fund for Agricultural Development (IFAD), the UN Children’s Fund (UNICEF), the World Food Programme (WFP) and the World Health Organization (WHO) urged in their joint foreword to the report.

Hunger is increasing in many countries where economic growth is lagging, particularly in middle-income countries and those that rely heavily on international primary commodity trade. The annual UN report also found that income inequality is rising in many of the countries where hunger is on the rise, making it even more difficult for the poor, vulnerable or marginalized to cope with economic slowdowns and downturns.

“We must foster pro-poor and inclusive structural transformation focusing on people and placing communities at the centre to reduce economic vulnerabilities and set ourselves on track to ending hunger, food insecurity and all forms of malnutrition,” the UN leaders said.

Slow progress in Africa and Asia
The situation is most alarming in Africa, as the region has the highest rates of hunger in the world and which are continuing to slowly but steadily rise in almost all subregions. In Eastern Africa in particular, close to a third of the population (30.8 percent) is undernourished. In addition to climate and conflict, economic slowdowns and downturns are driving the rise. Since 2011, almost half the countries where rising hunger occurred due to economic slowdowns or stagnation were in Africa.

The largest number of undernourished people (more than 500 million) live in Asia, mostly in southern Asian countries. Together, Africa and Asia bear the greatest share of all forms of malnutrition, accounting for more than nine out of ten of all stunted children and over nine out of ten of all wasted children worldwide. In southern Asia and sub-Saharan Africa, one child in three is stunted.

In addition to the challenges of stunting and wasting, Asia and Africa are also home to nearly three-quarters of all overweight children worldwide, largely driven by consumption of unhealthy diets.

Going beyond hunger
This year’s report introduces a new indicator for measuring food insecurity at different levels of severity and monitoring progress towards SDG 2: the prevalence of moderate or severe food insecurity. This indicator is based
on data obtained directly from people in surveys about their access to food in the last 12 months, using the Food Insecurity Experience Scale (FIES). People experiencing moderate food insecurity face uncertainties about their ability to obtain food and have had to reduce the quality and/or quantity of food they eat to get by.

The report estimates that over 2 billion people, mostly in low- and middle-income countries, do not have regular access to safe, nutritious and sufficient food. But irregular access is also a challenge for high-income countries, including 8 percent of the population in Northern America and Europe. This calls for a profound transformation of food systems to provide sustainably-produced healthy diets for a growing world population.

Key facts and figures
Number of hungry people in the world in 2018: 821.6 million (or 1 in 9 people)
in Asia: 513.9 million
in Africa: 256.1 million
in Latin America and the Caribbean: 42.5 million
Number of moderately or severely food insecure: 2 billion (26.4%)
Babies born with low birth weight: 20.5 million (one in seven)
Children under 5 affected by stunting (low height-for-age): 148.9 million (21.9%)
Children under 5 affected by wasting (low weight-for-height): 49.5 million (7.3%)
Children under 5 who are overweight (high weight-for-height): 40 million (5.9%)
School-age children and adolescents who are overweight: 338 million
Adults who are obese: 672 million (13% or 1 in 8 adults)

Note to editors
The heads of agencies issuing today’s report are: José Graziano da Silva, Director-General of FAO; Gilbert F. Houngbo, President of IFAD; Henrietta H. Fore, Executive Director of UNICEF; David Beasley, Executive Director of WFP; and Tedros Adhanom Ghebreyesus, Director-General of WHO.

The report is part of tracking progress towards Sustainable Development Goal 2 Zero Hunger, which aims to end hunger, promote food security and end all forms of malnutrition by 2030.

The 2017 report identified three factors behind the recent rise in hunger: conflict, climate and economic slowdowns. This year’s report focuses on the role of economic slowdowns and downturns in food security and nutrition.

Readers should avoid comparing Prevalence of Undernourishment numbers across different editions of the report because the entire data set is reviewed and revised, including possible backward revisions, before each publication. This ensures that the latest report takes into account any new information received since the release of the previous edition.