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CONTENTS

ORIGINAL ARTICLES

CASE REPORTS

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ORIGINAL ARTICLE

Can neuropathy be predicted by halp score in diabetic patients?

Özge Özen Gökmuharremoğlu[1], Aysel Çoban Taşkın[2]

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ABSTRACT

Objective: In the pathogenesis of diabetes mellitus, insufficient insulin secretion, improper glucose utilization, and insulin resistance in tissues lead to oxidative stress and inflammation and cause neuropathy in peripheral nerves. Hemoglobin, albumin, lymphocyte, and platelet (HALP) scores give an idea of nutritional and inflammatory status. In this report, we aimed to evaluate the relationship between HALP score and diabetic polyneuropathy.

Materials and Methods: Patients admitted to our electrophysiology laboratory between 2022 and 2024 with a prediagnosis of polyneuropathy due to type 2 diabetes were included in the study. Demographic data (age, gender), hemogram (hemoglobin, lymphocyte, monocyte, platelet), biochemical values (fasting blood glucose, HbA1c, urea, creatinine, albumin, cholesterol, triglyceride), and electromyography results were retrospectively reviewed from the hospital information system.

Results: The study included 155 type 2 diabetic patients with a prediagnosis of distal symmetric polyneuropathy; 79 had sensorimotor polyneuropathy, while 76 did not. Mean age was similar between groups, but males were more prevalent in the neuropathy group ($p = 0.002$). Cholesterol ($p = 0.001$) and platelet levels ($p < 0.001$) were higher in the group without neuropathy, whereas HbA1c was higher in the neuropathy group ($p = 0.03$). No significant difference was observed in HALP scores between the two groups according to the presence of neuropathy ($p = 0.327$).

Conclusion: The HALP score is known as a prognostic indicator, especially in patients with malignancy and ischemic stroke. This study found no statistically significant difference between the patient groups with diabetic polyneuropathy and those without diabetic polyneuropathy in terms of HALP scores. Comprehensive and more detailed studies are needed to investigate the potential of the HALP score to predict the development of diabetic neuropathy.

Keywords: HALP Score, Diabetic Neuropathy, Inflammation, Nutritional Status.

INTRODUCTION

The most common subtype (approximately 90%) of Diabetes Mellitus, a metabolic disease characterized by chronic hyperglycemia exposure, is type 2 diabetes mellitus (T2DM) [1]. Diabetic peripheral neuropathy (DPNP) is one of the prominent and common microvascular complications of DM [1].

It has been reported that the prevalence of DPNP, which is the most common type of neuropathy universally, varies between 6% and 51% in recent studies in Europe and the United States [1]. Several risk factors contribute to the development of neuropathy, including age, diabetes duration, glycemic control, and comorbid conditions such as hypercholesterolemia, hypertension, obesity, and smoking [1]. The pathogenesis of neuropathy is complex and multifactorial. It is well-established that hyperglycemia and prolonged diabetes are linked to microvascular complications, and the diabetic microenvironment is thought to involve ongoing low-grade inflammation activated by the immune system [2]. Immune cells, cytokines, chemokines, soluble adhesion molecules, and other inflammatory markers are elevated in peripheral nerve or cerebrospinal fluid samples from patients with diabetic neuropathy [3]. Inflammation,

driven by reactive oxygen species produced due to elevated glucose levels and impaired energy production, contributes to oxidative stress [4]. Additionally, hyperglycemia and free radicals can lead to changes in albumin concentration and structural modifications in albumin, impairing its antioxidant function and exacerbating oxidative stress [5].

The HALP score (hemoglobin [g/L] × albumin [g/L] × lymphocyte count [cells/L] / platelet count [cells/L]) has recently been used to predict prognosis, particularly in cancer [6]. In studies involving diabetic retinopathy and nephropathy, higher HALP scores were associated with a lower incidence of these microvascular complications [7,8].

Our study aimed to evaluate the relationship between HALP score and diabetic polyneuropathy.

METHODS

This study was designed retrospectively, and the Declaration of Helsinki conducted it; ethics committee approval was obtained from the Kastamonu Training and Research Hospital Clinical Research Ethics Committee (date: 10/12/2024 and endorsement number: 2024-KAEK-123). Between 01.Jan.2022 and 01.Sep.2024, adults who applied to Kastamonu Training and Research Hospital and Tepecik Training and Research Hospital Electrophysiology laboratory, diagnosed with T2DM according to WHO / ADA diagnostic criteria and referred to us with a preliminary diagnosis of polyneuropathy were included. Patients were included in the study retrospectively. Patients with type-1 diabetes mellitus, neoplastic and hematological diseases, active or chronic immunosuppressive drugs, severe hepatic and renal dysfunction, acute infection findings, or rheumatological diseases were excluded. Demographic data (age, gender), complete blood count (hemoglobin, lymphocyte, neutrophil, neutrophil, monocyte, platelet), biochemical parameters (fasting blood glucose, HbA1c, urea, creatinine, albumin, cholesterol, triglyceride), and electromyography results were recorded retrospectively. Patients diagnosed with sensorimotor polyneuropathy, characterized by nerve conduction abnormalities in at least three limbs and predominantly axonal involvement in the lower and distal extremities, were assigned to the polyneuropathy group. In contrast, patients whose nerve conduction studies showed normal results on electromyography were placed in the non-polyneuropathy (non-PNP) group. The HALP Score was calculated using the formula [(hemoglobin x serum albumin x lymphocyte count) / Platelet count] [9]. The data from both the polyneuropathy and non-polyneuropathy groups were compared.

The data were analyzed using SPSS version 26.0 (IBM Statistics for Windows, Chicago, IL, USA). Descriptive statistics were employed to assess the clinical characteristics of the participants. The chi-square test was used to compare data between the two groups for categorical variables. Differences in mean and median values were analyzed using the Mann-Whitney U test and independent samples t-test. Results were considered significant at a 95% confidence interval and a p-value of less than 0.05.

RESULTS

The study included 155 adults, 76 patients without polyneuropathy, and 79 patients with polyneuropathy. Demographic data revealed that women comprised 58.9% of the non-polyneuropathy group, while men represented 66.7% of the polyneuropathy group (Table 1).

The cruel age was 63 ± 9.6 within the polyneuropathy gather and 60.5 ± 12.2 within the non-PNP gather, with no factually noteworthy distinction between the bunches (p = 0.106) (Table 2).

Table 1. The gender distribution of neuropathy

	Gender			
	Male (n:60)	**Famele (n:95)**	**Total (n:155)**	**P value**
Non-PNP*	20 (%33,3)	56 (%58,9)	76 (%49)	0.002
PNP	40 (%66,7)	39 (%41,1)	79 (%51)	

Chi-Spuare test

*PNP: Polyneuropathy

Table 2. The age distribution by neuropathy

	PNP median/mean ± SD	**Non-PNP median/mean ± SD**	**Test statistic**	**p value**
Age	64/ 63 ± 9,6	59,5/ 60,5 ± 12,2	1,627	0.106

Independent samples t test – median / mean ± SD

Table 3. Comparison of laboratory values based on the presence of neuropathy

	PNP	Non-PNP	p
Hemoglo-bin	13 ± 2	13.1 ± 1.7	0.593[3]
Hematocrit	39.5 ± 5.8	39.5 ± 4.6	0.996[3]
Neutrophil	4.7 (1.7- 174) / 78.43	4.8 (2.5- 10.4) / 75.47	0.680[4]
Lympho-cyte	2.2 (0.5- 4.2) / 70.41	2.4 (0.8- 5,2) / 84.03	0.057[4]
Monocyte	0.6 (0.2- 1.2) / 79.20	0.6 (0.3- 1.2) / 74.66	0.526[4]
Glucose	163 (65- 792) / 82.22	140.5 (81- 393) / 71.43	0.132[4]
Cholesterol	174.5 (100- 301) / 62.07	209.5 (124- 316) / 85.25	0.001[4]
Ttriglycer-ide	155.5 (57- 667) / 70.53	179 (51- 915) / 82.79	0.086[4]
Hba1c	7.5 (5.7- 13.5) / 81.83	7.2 (5.2- 15) / 66.55	0.030[4]
BUN	33 (16- 164) / 83.65	29 (11- 112) / 69.91	0.055[4]
Creatinine	0.8 (0.2- 4.2) / 76.90	0.9 (0.3- 1.7) / 77.11	0.977[4]
Albumine	4.2 (2.4- 4.9) / 71.65	4.2 (2.4- 4.9) / 83.66	0.093[4]
Platelet	237 (10- 403) / 63.75	**280.5 (133- 739) / 91.15**	**<0.001[4]**

[3] Independent samples t test – median (min-max) / mean ± SD

[4] Mann-Whitney U test- median (min-max) / mean ± SD

Table 4. The relationship between the presence of neuropathy and the HALP score

	PNP	Non-PNP	p value
HALP score	49.2 (7.3 - 268.3)	45.9 (21.3 - 151.4)	0.327

Mann-Whitney U test- median (min-max) / mean ± SD

Cholesterol and platelet levels were higher within the non-polyneuropathy bunch, whereas HbA1c levels were raised within the polyneuropathy gather. The difference between laboratory values according to the presence of neuropathy is shown in Table 3.

No measurably critical distinction was found when comparing the two bunches concerning the HALP score (p = 0.327). The relationship between the presence of neuropathy and the HALP score is shown in Table 4.

DISCUSSION

The most common microvascular complication of T2DM, which continues to climb with the aging population, is DPNP [2]. It is length-dependent damage to peripheral nerves. In the complex pathogenesis of DPN, impaired metabolism and inflammatory processes in peripheral nerve axons constitute the main elements [2]. In our study, the predictive role of the HALP score, which is used to estimate cancer prognosis and is thought to play a role in the mechanisms involved in pathogenesis, in diagnosing diabetic PNP was investigated, and no significant predictive value was determined in the presence of neuropathy.

Diabetic polyneuropathy (DPN), characterized by peripheral nerve dysfunction, is explained by three pathophysiological mechanisms [10]. First, inflammation activates signaling pathways such as nuclear factor kappa B, activator protein 1, and mitogen-activated protein kinases [10]. Second, hyperglycemia induces oxidative stress, triggering the activation of pathways including polyol, hexosamine, protein kinase C, advanced glycosylation end products, and glycolysis [10]. Third, mitochondrial dysfunction leads to increased production of reactive oxygen and nitrogen species, resulting in lipid peroxidation, protein modifications, nucleic acid damage, and, ultimately, axonal degeneration and segmental demyelination [10].

It is suggested that chronic inflammation plays a role in the pathogenesis of diabetic neuropathy. This has led to a focus on immune system-associated cells, such as neutrophils, lymphocytes, and platelets [11]. Parameters such as neutrophil-lymphocyte (NLR) ratio and platelet-lymphocyte (PLR) ratio have been examined. The systemic immune-inflammation index (SII), which combines these three cells, has also been studied in diabetic neuropathy and other microvascular complications of diabetes [11,12].

Albumin, a protein synthesized in the liver, is essential for binding and transporting various substances , including fatty acids, hormones, bilirubin, metal ions, and drugs [13]. Additionally, albumin has well-documented physiological functions, including antioxidant, anti-inflammatory, antiplatelet, and anticoagulant activities, as well as roles in immune regulation, endothelial cell protection, and neuronal defense against ischemia and reperfusion injury [14].

A study has shown a significant inverse relationship between serum albumin level and the risk of DPN, with this association being more substantial in patients with a higher body mass index (BMI ≥ 24 kg/m^2) [15]. In our study, the two groups detected no significant difference in albumin levels.

HALP score has recently been reported as a prognostic indicator, especially in patients with malignancy and ischemic stroke [16]. This score reflects the patient's nutritional status and systemic inflammation [17]. In oncology, a high HALP score is linked to better long-term survival. In contrast, a study of patients with myelodysplastic syndrome found that a high HALP score was associated with poor prognosis, especially in cases of severe thrombocytopenia [18]. A study of 1,337 ischemic stroke patients found that high HALP scores were strongly associated with a reduced risk of recurrent stroke and death within 90 days and one year [19].

In relation to diabetic microvascular complications, research related to diabetic retinopathy (DR) has shown that patients who have a high HALP score (≥49.2) tend to have a lower rate of retinopathy compared to those with lower HALP scores [20].

Another study involving 674 patients found a negative relationship between HALP score and DR incidence, suggesting that the HALP score may be more sensitive in men [21]. In research focused on diabetic nephropathy, a HALP score below 45.9 demonstrated a sensitivity of 73% and a specificity of 52% in detecting diabetic nephropathy [7].

Comorbidities, prior treatments, and demographic factors can influence the HALP score. Additionally, the sample size in our study was smaller than in many published studies, and factors such as the duration of diabetes, blood glucose control, and medication effects were not recorded. One of the limitations of our study was the lack of a classification of the type and severity of diabetic neuropathy and data on the duration of diabetic neuropathy symptoms.

HALP score is known as a prognostic indicator especially in patients with malignancy and ischemic stroke. In this study, no statistically significant difference was found between the patient groups with diabetic polyneuropathy and those without diabetic polyneuropathy in terms of HALP scores. Comprehensive and more detailed studies are needed to investigate the potential of the HALP score to predict the development of diabetic neuropathy.

Ethical approval

The study was approved by the Kastamonu Training and Research Hospital Clinical Research Ethics Committee (date: 10/12/2024 and approval number: 2024-KAEK-123).

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Clinical and electrophysiological features of Guillain-Barré syndrome: A 7-year experience of Hacettepe University Department of Neurology

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ABSTRACT

Objective: Guillain-Barré Syndrome (GBS) is the most common cause of severe acute paralytic neuropathy. In this retrospective study, we present the GBS experience of the Hacettepe University Department of Neurology and discuss the clinical and electrophysiological features.

Material and Methods: Demographic data, presenting complaints, cerebrospinal fluid (CSF) findings, EMG results, and treatments of patients with electrophysiological findings compatible with GBS between August 2017 and August 2024 were retrospectively reviewed.

Results: Fifty-nine patients diagnosed with GBS (41 males, mean [min-max] age 49 [3–92] years) were recorded. Among them, 66% (n=39) were classified as AIDP, 22% (n=13) as AMAN, 3% (n=2) as AMSAN, and 9% (n=5) as MFS. It was noted that EMG was performed within an average of 11 days after the onset of the first symptom. Sensory complaints were the initial symptoms in half of the patients. Six patients (10%) required mechanical ventilation during follow-up. Prolonged or absent F-waves in one or more nerves were recorded in 64% (n=38) of upper limbs and %90 (n=53) of lower limbs. Reduced distal compound muscle action potentials (CMAP) in two or more nerves were observed in 51 patients (86%), prolonged distal motor latency (DML) in two or more nerves in 40 patients (68%) and slowed motor nerve conduction velocities (NCV) in two or more nerves in 26 patients (44%). Sural SNAP amplitudes were normal in 33 patients (56%), decreased in 14 (24%), and absent in 12 (20%). The conduction block was recorded in 10 patients (17%), and temporal dispersion was noted in 19 patients (32%). Treatment included IVIg in 40 patients (68%) and plasmapheresis in 2 (3%), and due to insufficient treatment response, the number of patients requiring plasmapheresis after IVIg or vice versa was 13 (22%).

Conclusion: This study showed that AIDP is the most common electrophysiological subtype of GBS in our population. Our study found that AIDP was GBS's most common electrophysiological subtype. Prolonged or absent F-waves reduced distal CMAP amplitudes, prolonged DML, slowed NCV, decreased upper limb SNAP amplitudes, and partially preserved sural sensory responses observed in our study were consistent with the findings of other studies.

Keywords: Guillain-Barré Syndrome, electromyography, neuromuscular disease, immunoglobulins, intravenous, plasmapheresis.

INTRODUCTION

Guillain-Barré Syndrome (GBS) is an immune-mediated disease characterized by acute peripheral neuropathy and is a significant cause of neurological morbidity worldwide [1]. Its pathogenesis involves cellular and humoral immunity. The clinical spectrum of GBS includes subtypes such as acute inflammatory demyelinating polyneuropathy (AIDP), acute motor-sensory axonal neuropathy (AMSAN), acute motor axonal neuropathy (AMAN), and Miller-Fisher Syndrome (MFS) [2]. AIDP is the most common form in Western countries, while axonal forms such as

AMAN and AMSAN are more prevalent in Asia and South America.

Although the exact etiology of GBS remains unclear, preceding viral or bacterial infections are believed to trigger antigenic responses in the peripheral nerves [3]. The diagnosis of GBS is based on clinical history, neurological examination, and electrophysiological studies. Key features include the absence of F-waves, prolonged distal motor latency, and sensory nerve action potential (SNAP) abnormalities, which are crucial for early diagnosis [4]. While SNAP amplitudes in the upper extremities were reduced, the preserved sural SNAP pattern has been reported in the literature to increase diagnostic sensitivity. Intravenous immunoglobulin (IVIg) and plasma exchange are effective treatment modalities that prevent mortality and morbidity in GBS [5].

This study retrospectively reviews the clinical and electrophysiological features of patients diagnosed with GBS in the Hacettepe University Department of Neurology.

METHODS

We searched the medical history of the patients in our EMG laboratory's database, which are available between August 2017 and August 2024, using the keywords "demyelinating,""Guillan Barrè Syndrome," "acute motor axonal neuropathy," "AMAN," "acute motor-sensory axonal neuropathy," "AMSAN," "Miller-Fisher Syndrome" and "MFS". The inclusion criteria were, a confirmed diagnosis of GBS based on clinical, neurological, and electrophysiological evaluations and the availability of complete electrophysiological records. All clinical and electrophysiological data were retrospectively collected from 59 patients diagnosed with GBS.

Demographic characteristics (age, sex), presenting symptoms, the time interval between symptom onset and hospital admission, history of predisposing factors such as surgery or infection (upper respiratory tract infection [URTI], acute gastroenteritis, vaccination, treatments administered, ventilator requirements, cerebrospinal fluid (CSF) analysis, and EMG findings were recorded.

Electrophysiological examinations included distal motor latency (DML), compound muscle action potential (CMAP) amplitude, sensory nerve action potential (SNAP) amplitude, motor and sensory nerve conduction velocities, F-wave latency, and H-reflex response.

This study was designed retrospectively, and permission and consent were obtained to review patient files. Ethical approval was granted by the Ethics Committee of Hacettepe University Faculty of Medicine (Decision No: 2024/10-64).

RESULTS

Between August 2017 and August 2024 were retrospectively reviewed, 59 patients (41 males, mean [range] age 49 [3–92] years) diagnosed with GBS were recorded in our unit. The demographic and clinical features of all patients are summarized in Table 1. Among these patients, 66% (n=39) were

Table 1. Demographic, Clinical, and Electrophysiological Features of Patients Diagnosed with GBS

Parameter	Findings
Age (Median, years)	49 [3–92]
Gender, n (%)	
Female	18 (31%)
Male	41 (69%)
Male/Female ratio	2.2
History of infection, n (%):	
URTI	17 (29%)
Acute gastroenteritis	12 (20%)
Vaccination	1 (2%)
Surgery	1 (2%)
Unknown	28 (47%)
GBS Subtypes, n (%):	
AIDP	39 (66%)
AMAN	13 (22%)
AMSAN	2 (3%)
MFS	5 (9%)
Treatment, n (%):	
IVIg	40 (69%)
Plasmapheresis	2 (3%)
IVIg + Plasmapheresis (or vice versa)	
(Due to insufficient treatment)	13 (22%)
No treatment	2 (3%)

URTI: Upper respiratory tract infection, **AGE**: Acute gastroenteritis, **AIDP**: Acute inflammatory demyelinating polyneuropathy, **AMSAN**: Acute motor-sensory axonal neuropathy, **AMAN**: Acute motor axonal neuropathy, **MFS**: Miller-Fisher Syndrome, **IVIg**: Intravenous immunoglobulin

classified as AIDP, 22% (n=13) as AMAN, 3% (n=2) as AMSAN, and 9% (n=5) as MFS.

Sensory complaints were the initial symptoms in 50% (n=30) of the patients, followed by motor complaints in 47% (n=28) and cranial neuropathy in 5% (n=3). Some patients had multiple symptoms simultaneously. A history of infection was noted in 49% (n=29) of the patients within the preceding 30 days. Among these, 17 (59%) had URTI, 12 (41%) had acute gastroenteritis, and one patient had undergone lumbar spinal stenosis surgery two weeks before symptom onset. In 47% (n=28) of the patients, no predisposing factors were identified before GBS symptoms.

CSF sampling was performed within an average of 12 (range:2-45) days after symptom onset, revealing elevated protein levels with a mean of 125 mg/dL (range: 25-354 mg/dL). CSF protein levels of 20 patients could not be obtained for various reasons, such as the absence of CSF sampling or the patient being referred to our center from an external hospital. Among the 39 patients who underwent CSF sampling, 29 (74%) had elevated CSF protein levels (N:15-40 mg/dL).

Regarding treatment, 69% (n=40) of the patients received IVIg, while 3% (n=2) underwent plasmapheresis. Due to insufficient treatment response, 22% (n=13) required plasmapheresis after IVIg or vice versa. Additionally, 3% (n=2) underwent physical therapy and rehabilitation. Two patients were transferred due to hospital bed availability issues, and no data on their treatment course was available. During follow-up, mechanical ventilation was required in 10% (n=6) of the patients.

EMG was conducted within an average of 11 days after the onset of the first symptom. On average, each patient underwent EMG twice (1–5 times). Prolonged or absent F-wave latencies in one or more nerves were recorded in 64% (n=38) of upper limbs and 90% (n=53) of lower limbs. Reduced distal CMAP amplitudes in two or more nerves were observed in 51 patients (86%), prolonged DML in two or more nerves in 40 patients (68%), and slowed motor nerve conduction velocities in two or more nerves in 26 patients (44%).

In the upper limbs, sensory nerve action potential (SNAP) amplitude reductions in one or more nerves were detected in 26 patients (44%). Sural SNAP amplitudes were normal in 33 patients (56%), decreased in 14 (24%), and absent in 12 (20%). Preservation of sural SNAP in the presence of upper limb SNAP abnormalities was observed in 16 patients (27%).

Table 2. Electrophysiological Findings

Parameter	Findings	Count (n)	Percentage (%)
NCS and Needle EMG	NCS + Needle EMG	45	76.3
	NCS only	14	23.7
F-Wave (Upper Limb)	Prolonged/absent in ≥1 nerve	38	64.4
F-Wave (Lower Limb)	Prolonged/absent in ≥1 nerve	53	89.8
Distal CMAP Amplitude	Reduced in ≥2 nerves	51	86.4
	Reduced in 1 nerve	2	3.3
	Normal	6	10.3
DML	Prolonged in ≥2 nerves	40	67.7
Conduction Block		10	16.9
Temporal Dispersion		19	32.2
Preserved Sural SNAP		16	27.1
Nerve Conduction Velocity	Slowed in 1 nerve	14	23.7
	Slowed in ≥2 nerves	26	44.1
	Normal	19	32.2
H reflex	Number of patients studied	8	13.5
	Absent H reflex*	7	87.5
	Sural DSAP is normal*	6	75

NCS: Nerve Conduction Studies, **CMAP:** Compound Muscle Action Potential, **DML:** Distal Motor Latency, **SNAP:** Sensory Nerve Action Potential

* This value is proportional to the number of patients in whom the H reflex was studied.

Conduction block was detected in 10 patients (17%), and temporal dispersion was noted in 19 patients (32%). H-reflexes were evaluated in eight patients and were absent in seven (88%). Among these seven patients, six had normal sural SNAP amplitudes. All electrophysiological findings are summarized in Table 2.

DISCUSSION

We reviewed the data of 59 patients diagnosed with GBS in our center over 7 years. We compared the clinical and electrophysiological data we obtained with the features reported in the literature.

Guillain-Barré Syndrome has an annual incidence of approximately 1.3 cases per 100,000 population globally and is more commonly observed in males than females [6]. Although GBS can occur at any age, its frequency increases in young adults and individuals over 55. Our study similarly demonstrated a male predominance (n=41, 70%) and a median age of 49 years [3–92], consistent with the literature.

Classical GBS symptoms often begin with weakness, occasionally accompanied by paresthesia. The weakness is relatively symmetrical, affecting both distal and proximal muscles of the lower extremities, and frequently progresses to the upper extremities within days or even hours. Weakness progresses rapidly, with 50% of patients reaching maximum disability within two weeks and 90% within four weeks [7]. Reflex loss is a common early finding. The facial nerve is most involved among cranial nerves, with facial diplegia occurring in approximately half of the patients. Ocular motor dysfunction is observed in 15% of cases, with complete ophthalmoplegia in 3–5%. In our study, the most common presenting symptoms were sensory complaints (30 patients, 50%), followed by motor symptoms (28 patients, 47%), cranial nerve involvement in three patients (5%), and autonomic symptoms in one patient (2%). Some patients had multiple presenting symptoms simultaneously.

Between 50% and 70% of GBS cases are associated with infections such as gastroenteritis, respiratory tract infections, or vaccinations within 2–4 weeks before symptom onset [7]. Campylobacter jejuni is most frequently linked with the axonal form of GBS, while cytomegalovirus infections are more often associated with sensory symptoms and cranial nerve involvement [8]. Rarely, GBS may occur following surgery or as part of other diseases [9]. In our study, 49% of patients (n=29) reported a history of infection within the 30 days preceding symptom onset, including 17 cases of upper respiratory tract infections (59%) and 12 cases of acute gastroenteritis (41%).

GBS progresses rapidly, with half of the patients reaching maximum disability within two weeks and 90% within four weeks. More than half of affected individuals lose the ability to walk, and approximately one-third of hospitalized patients require respiratory support and intensive care unit monitoring [10]. In our study, 10% of patients (n=6) required mechanical ventilation during follow-up.

Diagnostic support for GBS includes CSF examination and electrophysiological studies. In CSF, protein levels are elevated, and the cell count is typically $<10/mm^3$. In our study, EMG was performed within an average of 11 days after the onset of symptoms, and CSF sampling was conducted at a mean of 12 days. The mean CSF protein level was 125 mg/dL.

Electrophysiological studies, particularly nerve conduction studies (NCS) and needle EMG, play a vital role in confirming the clinical diagnosis of GBS. Accurately identifying the electrophysiological subtypes of GBS is essential for understanding the disease's dynamic nature. Sequential electrophysiological evaluations are key in achieving this and ensuring precise subtype classification.

Uncini's criteria aim to minimize diagnostic errors by providing detailed definitions of these dynamic processes and the specific features of different subtypes [12]. In most of our patients (n=36,61%), EMG was performed at least twice. The most well-known form, AIDP, is observed in 80–95% of cases, particularly in Europe and North America [11]. While GBS is often used interchangeably with AIDP, other forms exist, such as AMAN and AMSAN. In

our study, AIDP was the most frequently observed subtype (66%, n=39), consistent with the literature.

Diagnosis of AIDP is based on findings such as motor nerve conduction velocities <70%, distal motor latencies >130% of normal values, distal CMAP durations >120%, and F-wave latency >120% in at least two nerves. If only one of these findings is present, the absence of F-waves in two nerves and decreased ulnar SNAP amplitudes with preserved sural SNAP amplitudes should be noted. Axonal subtypes (AMAN and AMSAN) are characterized by the absence of AIDP-specific findings, with features such as distal CMAP amplitudes reduced to <80% and conduction block in at least two nerves [12]. AMSAN is characterized by significant damage to sensory nerves, with at least a 50% reduction in SNAP amplitudes in at least two nerves, persisting in subsequent examinations. Additionally, acute denervation signs, such as fibrillation potentials and positive sharp waves, typically appear 7–10 days after symptom onset [13]. In our study, patients underwent an average of two EMG studies (range: 1–5). Findings such as prolonged or absent F-waves, reduced distal CMAP amplitudes, prolonged distal motor latencies, and preserved sural SNAP amplitudes observed in our study were consistent with previous literature.

The treatment of GBS relies on a multidisciplinary approach, with immunotherapy and comprehensive supportive care serving as the foundation of effective management. Effective treatment modalities include IVIg and plasma exchange. In our clinic, IVIg was the most frequently administered treatment.

CONCLUSION

Our study findings demonstrate that the clinical and electrophysiological features of GBS observed in our cohort align with existing literature. The acute phase of GBS, characterized by rapid progression, underscores the importance of early diagnosis and close monitoring. Electrophysiological evaluations and serial follow-up studies play a critical role in guiding treatment and providing valuable insights.

Ethical approval

This study was designed retrospectively, and permission and consent were obtained to review patient files. Ethical approval was granted by the Ethics Committee of Hacettepe University Faculty of Medicine (Decision No: 2024/10-64).

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Assessment of glycemic control and duration of diabetes in distal symmetric diabetic polyneuropathy

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ABSTRACT

Diabetes is widespread disease that lead many complications. One of most common complication is neuropathy. However precise pathophysiological mechanism is still not understanding clearly. With this study we hope that we can understand either duration or severity of diabetes causes more trouble.

Keywords: diabetes, polyneuropathy, distal symmetric diabetic polyneuropathy.

INTRODUCTION

Peripheral neuropathy is the general name given to all diseases that cause damage to the peripheral nervous system in some way. And best way to classify it, is according localization [1]. And one of the most common localizations is distal symmetric polyneuropathy. In distal symmetric polyneuropathy, patients usually complain of numbness, tingling and pain [2].

Diabetes is a common disease that can cause many types of neuropathy. Many factors may be effective in the development of neuropathy in diabetic patients [3]. This study aims to determine whether duration or glycemic control is more effective in diabetic polyneuropathy patients by comparing the duration of diabetes and hemoglobin A1c levels of patients diagnosed with distal symmetric diabetic polyneuropathy.

METHODS

For this study, diabetes duration, hemoglobin A1c levels and electrophysiological characteristics of patients who were admitted to Gaziantep University Hospital between 01.08.2024 and 01.10.2024 and diagnosed with distal symmetric diabetic polyneuropathy were evaluated retrospectively.

RESULTS

Total of 47 patients, 23 male and 24 female patients, were included in the study. Spearman correlation coefficient was used to analyze the relationship between diabetes duration and parameters in nerve conduction studies. Pearson correlation coefficient was used and linear regression model was applied to analyze the relationship between HBA1c and parameters in nerve conduction studies. Situations in which lower extremity peripheral nerves could not be stimulated at all were considered as severe polyneuropathy. A negative correlation was observed between the duration of diabetes and the sensory amplitudes and nerve conduction velocities of the sural nerves. No significant correlation or linear regression relationship was detected between HBA1c and

the parameters in nerve conduction studies. No significant relationship was found between the development of severe polyneuropathy and duration of diabetes and HBA1c. No significant correlation or linear regression relationship was detected between HBA1c and the parameters in nerve conduction studies. No significant relationship was found between the development of severe polyneuropathy and the duration of diabetes and HBA1c.

CONCLUSIONS

In this study, although the duration of diabetes was associated with a decrease in both amplitude and speed of conductions, no significant difference was observed between duration and Hemoglobin A1c levels in the development of severe neuropathy. The retrospective design and the fact that other factors known to be effective in the development of diabetic polyneuropathy were not taken into account in this study are aspects of the study that are open to criticism.

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CASE REPORT

A vasculitic neuropathy case related to cryoglobulinaemic vasculitis

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ABSTRACT

Vasculitis are a group of autoimmune disease which cause inflammation on vessel wall and vessel damage that leads to ischemia and necrotic damage in affected organs [1]. Vasculitic and autoimmune connective tissue disease can be a reason of peripheric neuropathy which will be hard to diagnose but also can be treatable [1]. Acute or sub-acute, painful, multifocal sensorial or sensorimotor polyneuropathy or asymmetric distal polyneuropathy may be the first sign of vasculitic disorder [1,2].

Acute motor sensorial axonal neuropathy (AMSAN) is a rare form of Guillain-Barre Syndrome which peripheral neurons has axonal damage and presenting with both motor and sensorial symptoms [3].

In this case report we will discuss the diagnostic period of a 76 years old patient who first evaluated as AMSAN in his polyclinic examination, tests and imaging's than hospitalized for further investigation and detailed evaluation which ends up with diagnosed as Cryoglobulinemic Vasculitis.

Keywords: acute motor sensorial axonal neuropathy, cryoglobulinemia, cryoglobulinemic vasculitis, neuropathy, vasculitis, vasculitic neuropathy.

INTRODUCTION

Cryoglobulinemic Neuropathy is a type of vasculitic neuropathy caused by increased cryoglobulins in blood and damage to the vessel walls ends up with ischemic and necrotic tissue damage [4,5]. Cryoglobulins are immunoglobulins that can be precipitated under 37 degrees [5]. Also, cryoglobulinemia can be asymptomatic it can affect small vessels and cause immuno-complex-related vasculitis [4]. Most cases are related to hepatitis C. Most hepatitis C patients will develop cryoglobulin but only %15 of patients can be shown clinical presentations of vasculitic disease [5]. Most cases presented with mononeuritis multiplex or symmetrical sensory-motor neuropathy [2]. In rare cases, it can be seen as ganglionopathy-like sensorial involvement [3].

The symptoms typically begin with distal paresthesias resembling sensory neuropathy. Distal symmetric muscle weakness follows paresthesias. Usually, the weakness starts mild and affects the extensor muscles of the foot. In rare severe cases supported ambulation will be needed. Deep tendon reflexes are often diminished or absent. Nerve conduction studies mostly show sensorial and motor fibers affected by axonal neuropathy [4].

CASE PRESENTATION

A 76-year-old male patient applied to the clinic with progressing symptoms which are numbness, pain, and weakness in his hands this complaint

was shown in his legs and caused difficulties in walking. The patient defined his symptoms started 2,5 months ago with numbness, pain, and weakness in his right hand, and after 20 days spread to his left hand, arm, and legs. There was no significant history of infectious diseases before his complaints. The patient stated that he had applied to outpatient clinics and had no results before. Thus the patient came to the neuromuscular clinic of our hospital and for further investigation, diagnosis, and treatment he was hospitalized.

In the patient's history, he had benign prostate hyperplasia and chronic kidney disease with an unknown etiology. Thus he had been using 0,4 mg tamsulosin, 500 mg anti-acidosis, and 5 mg prednisolone daily. When asked for the patient's family history it was learned that two of his brothers passed away because of malignant diseases.

In the patient's neurological examination, there was no significant loss of consciousness or orientation. No pathological exam findings in the cerebellar system and cranial nerve had been determined. The patient was right-hand dominated. In muscle force examination both upper limb's proximal muscle force was 4/5, 3/5 in distal; both low limbs proximal was 4/5, right ankle dorsiflexion 3/5, plantar flexion 4+/5, left ankle dorsiflexion 2+/5, plantar flexion 4+/5. There was atrophy in the patient's thenar and hypothenar muscles. There was glove-sock-type hypoesthesia. Both brachioradialis and Achill reflexes are absent bilaterally.

The laboratory tests of the hospitalized patient resulted in a creatine level of 3,04 mg/dL (high), parathyroid hormone level of 25,7 ng/L (normal); thyroid stimulating hormone level of 3,03 mIU/L (normal); vitamin B12 level of 954 ng/L (high). The first nerve conduction study performed by the patient hospitalized first in motor nerves compound muscle action potentials (CMAP) was achieved low or could not be achieved symmetrically. In sensorial conduction study, sensorial nerve action potentials (SNAP) could not be achieved. When studies were performed with a concentric needle there were denervation potentials in both the tibialis anterior muscle, right gastrocnemius medialis muscle, right extensor digitorum muscle, and right first dorsal interosseos muscle. This study's results are shown in Tables 1 and 2.

Table 1. Nerve Conduction Study performed in first hospitalized

Motor CV				
Stimulation size	Lat. ms	Ampl. mV	Dur. ms	Vel. m/s
R, Abductor digiti minimi, Ulnaris, C8 T1				
Wrist	4,6	**0,08**	2,68	
L, Abductor digiti minimi, Ulnaris, C8 T1				
Wrist		**0**		
R, Abductor pollicis brevis, Medianus, C8 T1				
Wrist	3,8	**0,16**	3,44	
L, Abductor pollicis brevis, Medianus, C8 T1				
Wrist	3,2	**0,7**	6,04	
Elbow	7,2	**0,5**	6,64	53,0
R, Tibialis anterior, Peroneus, L4 L5 S1				
Head of fibula	3,0	0,7	9,96	
Popliteal fossa	4,1	0,7	8,25	56,1
R, Abductor hallucis, Tibialis, L4 L5 S1				
Medial malleolus	4,1	**0,21**	5,0	
L, Abductor hallucis, Tibialis, L4 L5 S1				
Medial malleolus	4,7	**0,35**	5,14	
R, Extensor digitorum brevis, Peroneus, L5-S1				
Sole of the foot		**0**		
L, Extensor digitorum brevis, Peroneus, L5-S1				
Sole of the foot		**0**		

* Sensorial Nerve Action Potentials (SNAP) could not be achieved

Table 2. Needle EMG

Site	Fibrill.	PSW	Fascicul.	MUP ampl	MUP dur	MUP polyphasicity	Interf. Pattern type	Comment
R, Deltoideus, Axillaris, C5 C6	No	No	No	Normal	Normal	No	Not examined	Normal
R, Biceps brachii, Musculocutaneus, C5 C6	No	No	No	Normal	Normal	No	Not examined	Normal
R, Interosseus I, Ulnaris, C8 T1	+++	+++	No				No contraction	
R, Rectus femoris, Femoralis, L2-L4	No	No	No	Normal	Normal	No	Not examined	Normal
R, Tibialis anterior, Peroneus, L4-L5-S1	+++	+++	No	Normal	Normal	+	Not examined	
R, Gastrocnemius, Tibialis, S1-S2	+	+	No	Normal	Normal	No	Not examined	
R, Ekstansor digitorum	++	++	No	Normal	Normal	+	Not examined	
L, Tibialis anterior, Peroneus, L4-L5-S1	++	++	No				No contraction	

With the lights of this electrophysiological study, the outcomes are coherent with significant symmetric sensory-motor axonal polyneuropathy in an acute period which is defined as AMSAN at first sight.

With these findings, we performed cerebrospinal fluid (CSF) testing. CSF protein was 217 mg/L (N: 150-450 mg/L) and there were no leukocytes.

Since the patient had chronic kidney disease, it was decided to perform plasmapheresis as the primary treatment option.

After 5 cycles of plasmapheresis, there was no significant clinical progression or improvement in neurological examination.

For the maintenance treatment, 48 mg of methyl-prednisolone daily was started. Because the patient had a chronicle kidney disease in which aetiology was unknown we performed further laboratory investigations. The levels of C-reactive protein (CRP), rheumatoid factor, Anti Hbc total were high and the level of C4 Complement was found low. Moreover, Myeloperoxidase (MPO)-Elisa (p-ANCA), Anti Hbs, and cryoglobulin were found positive. In the Immune fixation electrophoresis investigation, the kappa band was found dense.

These outcomes returned with a doubt of vasculitis thus we referred the patient to rheumatology and nephrology. After these consultations, new investigations were requested. These investigations were thorax Computed Tomography (CT) and abdominal ultrasonography (USG), immunofixation electrophoresis, blood cryoglobulin level, hepatitis markers, and beta 2 microglobulins.

In abdominal USG investigation, both renal parenchyma's EKO was increased as Grade 0-1.

In thorax CT there were millimetric densities in the right lung middle lobe, left lung lingular segment, and bilateral inferior lobes peribronchovascular zones were attracted attention and these lesions suggested clinical tracing as infectious progress.

In renal biopsy, the rate of global sclerosis was very high (%85) so it was not helpful for differential diagnosis.

For vasculitic assessment, the other systems were also investigated but there were no significant findings.

We performed a second EMG study 3 months after the first one and as well as the first study CMAP was symmetrically low or absent. Like the first investigation, SNAP's could not be achieved. There was no denervation potential in the concentric needle study. This study's results are shown in Tables 3 and 4.

These electrophysiological findings defined a chronicle severe axonal mainly distal polyneuropathy which affected both sensorial and motor fibres. Sural nerve biopsy had no help for diagnosis.

Table 3. Second Nerve Conduction Study Results (performed 3 months later after the first one)

Motor CV				
Stimulation size	Lat. ms	Ampl. mV	Dur. ms	Vel. m/s
R, Extensor indicis, Radialis, C6 C7 C8				
Upper third of the forearm	3,0	0,9	7,32	
Middle third of the shoulder	6,1	0,46	7,6	56,8
R, Abductor digiti minimi, Ulnaris, C8 T1				
Wrist	4,1	**0,14**	4,0	
Elbow	7,5	**0,13**	4,84	50,0
Arm	10,3	**0,14**	5,09	50,0
L, Abductor digiti minimi, Ulnaris C8 T1				
Wrist		**0**		
R, Abductor pollicis brevis, Medianus C8 T1				
Wrist		**0**		
L, Abductor pollicis brevis, Medianus C8 T1				
Wrist	3,4	**0,7**	5,64	
Elbow	7,8	**0,8**	6,6	50,0
R, Tibialis anterior, Peroneus, L4 L5 S1				
Head of fibula	3,8	1,0	9,8	
Popliteal fossa	6,4	1,2	10,5	40,0
L, Tibialis anterior, Peroneus, L4 L5 S1				
Head of fibula	4,0	0,42	7,9	
Popliteal fossa	5,9	0,23	8,15	40,0
R, Abductor hallucis, Tibialis, L4 L5 S1				
Medial malleolus		**0**		
L, Abductor hallucis, Tibialis, L4 L5 S1				
Medial malleolus		**0**		
R, Extensor digitorum brevis, Peroneus, L4 L5 S1				
Sole of the foot		**0**		
L, Extensor digitorum brevis, Peroneus, L4 L5 S1				
Sole of the foot		**0**		

*Sensorial Nerve Action Potentials (SNAP) could not be achieved

Table 4. Needle EMG

Interpretation								
Site	Fibril.	PSW	Fascicul.	MUP ampl.	MUP dur.	MUP polyphasicity	Interf. Pattern type	Muscle pattern
R. Biceps brachii, Musculocutaneus, C5 C6	No	No	No	Normal	Normal	+	Not examined	Normal
R Interosseus I, Ulnaris, C8 T1	No	No	No				NO CONTRACTION	
R, Rectus femoris, Femoralis, L2-L4	No	No	No	Normal	Normal	No	Not examined	Normal
R, Tibialis anterior, Peroneus, L4 L5 S1	No	No	No	N-	+	+		

After new studies, the patient was evaluated multi-disciplinary and defined as having "cryoglobulinemia related vasculitic neuropathy". While the patient's follow-up was continuing the patient passed away because of sepsis after a lung infection.

DISCUSSION

Even though Vasculitic and connective tissue-related neuropathies are clinical cases that stay in the background during diagnosis, they are important to bring to mind because of their treatability [1]. Sometimes, peripheral neuropathies are the first symptom of vasculitic disease [2]. Underlying physiopathology is end-organ damage caused by vasculitis-related vessel wall damage, which leads to ischemia and necrosis [1].

Primary, secondary vasculitis or non-systemically localized vasculitis can cause neuropathy [2]. Neuropathies in systemic vasculitis are most common in Charge Strauss syndrome (%50-70), Poly Arthritis Nodosa (PAN), and Microscopic Poly Angitis. In secondary vasculitic causes, we can see clinical cases like Hepatitis B-related PAN (%80), Hepatitis C-related mixt cryoglobulinemia (~%60), and rheumatoid vasculitis (%45-50). No neuropathy is noticed in Kawasaki disease, Takayasu Arteritis, and anti-glomerular basal membrane disease, and very rare in Giant Cell Arteritis and Behchet disease [1,2].

Neuropathy can start in vasculitic cases as distal neuropathy or acute, sub-acute painful sensorial and sensorimotor neuropathy. Systemical symptoms may be together. Stepwise progression is typical. In some cases the symmetrical and slow progress will cause to be misidentified as idiopathic distal polyneuropathy. Rarely fulminant progression can mimic Gullian-Barre Syndrome [2-4].

Electrophysiological studies must be performed bilaterally on the suspect of vasculitis to show asymmetry [2,4]. Sometimes, symmetrical involvement can be seen in chronic cases. Nerve conduct studies are important for finding the nerve that will be chosen for biopsy [2,4].

In cryoglobulinaemic vasculitis, the cryoglobulins in the blood must be cleaned fast with plasmapheresis for good results [4]. Additionally, there are open studies that show rituximab may be helpful for poly-neuropathy symptoms [4]. Since it develops under the condition of hepatitis, antiretroviral drugs may be helpful for treatment [4]. At the same time, glucocorticoids and intravenous immunoglobulins can be useful [4].

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE REPORT

Rapid response to botulinum antitoxin in hyperhidrosis patient

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ABSTRACT

Botox injections are shots that use a toxin to prevent a muscle from moving for a limited time. These shots are often used to smooth wrinkles on the face. They're also used to treat neck spasms, sweating, overactive bladder, lazy eye and other conditions.

Keywords: botilinum toxin, systemic complications of botilinum.

INTRODUCTION

Botulinum toxin is a neuro-toxin secreted by Clostridium botulinum that has many medical uses.

The most potent form of the toxin, which has eight different types, is botulinum toxin A. Only types A and B are used for medical and aesthetic purposes. It was first used in the treatment of strabismus in 1973. Botulinum toxin acts by decreasing acetylcholine release in the presynaptic terminal and causing neuromuscular blockade. Although ptosis may have complications such as facial asymmetry and diplopia, it also has rare systemic effects. In this case report, we wanted to present a patient who had botulinum toxin injection due to hyperhidrosis and complained of dyspnea, dysphagia and fatigue.

CASE-REPORT

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COMPLAINT: The patient who had Botulinum toxin injection due to hyperhidrosis complained of dyspnea, dysphagia and fatigue after the application.

Patient anamnesis : Due to hyperhidrosis, botulinum injection was applied to the foot plantar face and armpit axillary region in the first session, and 10 days later, a control additional dose injection was applied to the hand palmar face and armpit axillary region. The patient applied to us with complaints of dysphagia, dyspnea and weakness in the arms, which developed 2 weeks after the control.

Patient medical record was remarkable otherwise.

Neurological exam: Conscious, speech corneal light reflexes and eye movements was normal. Facial asymmetry not observed. Absent gag reflex. Patient can count til 14 in one breath. Head anteflexion power was -5/5. Right and left upper extremity proximal muscle strength 2/5. Right and left upper extremity distal muscle strength 3/5. Right and left lower extremity muscle strength 4/5. Deep tendon reflexes was normal. Plantar reflexes was normal.

Clinical follow-up: The patient, who applied to the outpatient clinic because she experienced shortness of breath and difficulty swallowing after botulinum toxin injection, was admitted to the Neurology service for further examination and treatment with the diagnosis of Generalized botulismus. No acute pathology was observed in the non-contrast brain MRI and DWI. In the upper extremity general screening EMG performed on the patient, motor nerve CMAP values were found to be low in the upper extremities. In the repetitive nerve stimulation test performed on the patient, no significant decremental response was observed in low frequency stimulations (2-3-5 Hz). No postexercise facilitation was detected.

The examination could not be completed because the patient could not tolerate the high-frequency stimulation. Routine blood tests were taken from the patient. The patient's results were HbA1c: 4.8, LDL: 100, HDL: 49, RFT: N, TFT: N, Vit D: 16.46, Hepatitis Markers: N, Ferritin: 44, Sedimentation: 6. Botulism anti-toxin was administered to the patient. At the 6th hour of treatment, the patient's swallowing dysfunction and upper extremity muscle deficits resolved.

The patient was started on mestinon 60 mg tablets in 3x1 dosage.

The patient, who had no additional complaints, was discharged with recommendations and neurological emergencies explained.

DISCUSSION

Botulinum antitoxin is a treatment that targets toxins that are in circulation and have not yet caused blockage in the neuromuscular junction and prevents the worsening of the clinic. So it is assumed that it will not correct the current neuromuscular blockade. However, it can cause dramatic clinical improvements in generalized botulismus.

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Conflict of interest

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CASE REPORT

Guillain Barre syndrome with peripheral facial paralysis: case report

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ABSTRACT

Facial nerve paralysis is a common clinical condition. It is mostly located unilaterally. A 51 year old patient who presented with unilateral peripheral facial nerve paralysis due to the Guillain-Barré Syndrome is presented.

Keywords: Unilateral peripheral facial nerve paralysis, Guillain-Barre Sendrome.

INTRODUCTION

Facial nerve paralysis is one of the clinical manifestations that is accepted to develop due to unilateral ischemic, infectious or inflammatory causes of the facial nerve or as a result of compression of the facial nerve in the fallopian canal. Etiology of facial nerve paralysis can often be determined and it is a symptom of a serious underlying disease and therefore requires detailed examination and immediate treatment [1]. In this case report, we present a patient who applied to us with symptoms of peripheral facial paralysis (PFP) and was subsequently diagnosed with Guillain Barre syndrome (GBS) with EMG and CSF protein elevation.

CASE PRESENTATION

A 51-year-old female patient complained of common body pains. The patient's body pains started 3 weeks ago and she had antibiotic treatment considering an infection. but the patient did not show clinical improvement. Then 5 days later PFP occurred in the patient. Prednisolone treatment was started at an external center. After ten days of prednisolone, minimal improvement in complaints was observed. It has been referred to us for further examination. When we examined the patient, no pathology was observed except for the right PFP in the neurological examination and the patient's electromyelography (EMG) was found to be compatible with sensorimotor mixed type polyneuropathic involvement. CSF protein resulted as 74. At the next control examination, the patient had difficulty walking, paresthesia in the hands and feet, and the Achilles reflex could not be obtained bilaterally. The patient was admitted to the neurology service ward with a preliminary diagnosis of GBS. A positive response was obtained with early initiation of intravenous immunoglobulin infusion (IVIG) treatment.

DISCUSSION

Peripheral facial nerve paralysis is one of the most common neuropathies. Guillain-Barre Syndrome is an autoimmune, acute and often severe and fulminant polyradiculopathy triggered by a previous bacterial or viral infection. The most common and earliest symptom of GBS is paresthesia. But the main finding is the symmetrical weakness that occurs in

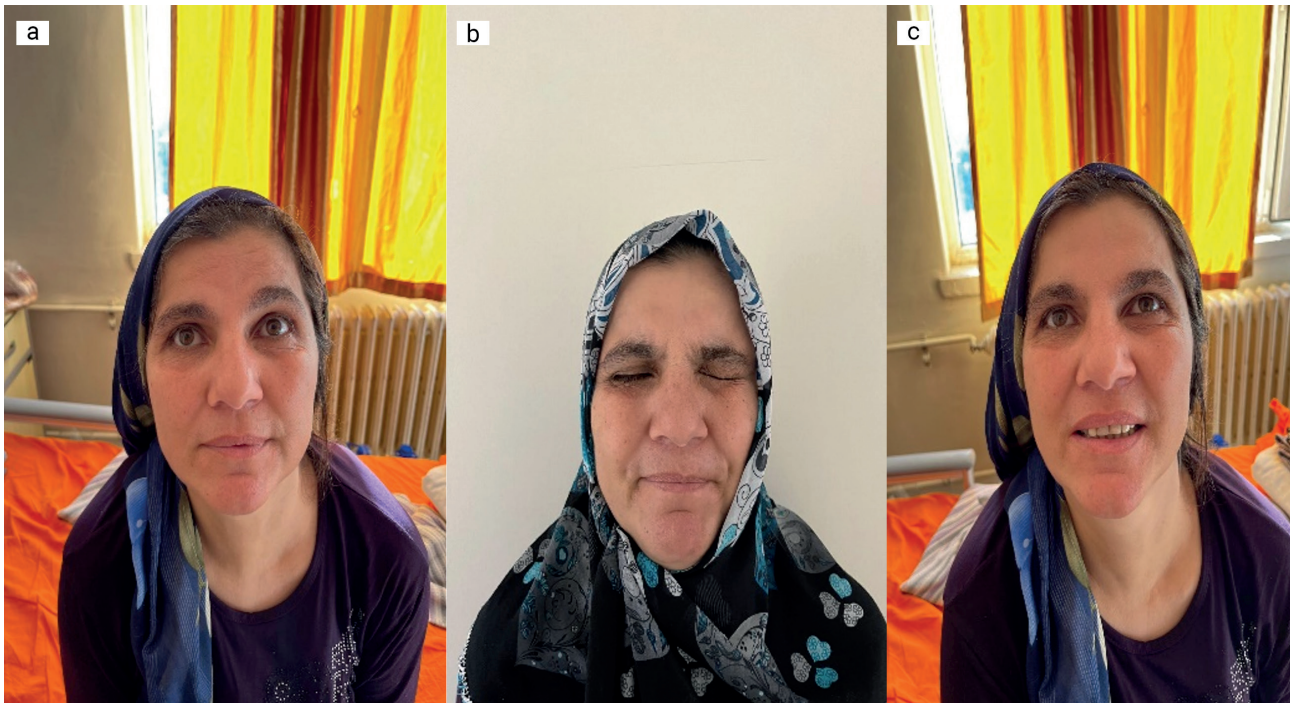

Figure 1. a) The patient cannot raise his right eyebrow. b) In this photo, the patient cannot close his right eye completely. c) The right nasolabial groove is faintly observed.

the early stages of the syndrome. Both distal and proximal muscles may be involved, usually distal. After involvement of the distal muscles in the lower extremity, the involvement may progress to the intercostal muscles, leading to respiratory failure and the need for mechanical ventilation. Although cranial nerve involvement is less common in the syndrome, the majority are bilateral. The frequency of facial nerve paralysis varies between 25-55% and the frequency of oculomotor paresis varies between 5-13% [1]. Other cranial nerve involvements may be seen, although rare, and may also be accompanied by dysarthria and dysphagia. Some patients have distinct and persistent clinical variants of GBS that do not progress to the classic pattern of sensory loss and weakness [2]. These variants include:

- Weakness without sensory symptoms (pure motor variant)
- Weakness limited to cranial nerves (bilateral facial paralysis with paresthesia)
- Upper extremities (pharyngeal-cervical-brachial weakness)
- Lower extremities (paraparetic variant)
- Miller Fisher syndrome with ophthalmoplegia, areflexia, and ataxia [3].

In general, GBS variants are rarely isolated, often partially overlapping with the classical syndrome or showing features characteristic of other variant forms. Symptoms usually begin 3-4 weeks after the viral infection. As in our patient, in addition to electrophysiological tests, CSF analysis shows protein increase without specific cell increase for GBS. It is usually treated with IVIG and plasmapheresis. The prognosis is generally good. Our patient was considered to have GBS, which is a weakness group limited to cranial nerves. The diagnosis of our patient was confirmed with the positive response to the treatment that was started early and the patient healed clinically [2].

CONCLUSION

In patients with spontaneous peripheral facial nerve paralysis taking acurate anamnesis and performing physical examination with wide range of laboratory and radiological imaging are necessary to explained the etiology, and it is necessary to keep the diagnosis of GBS in mind in patients presenting with peripheral facial nerve paralysis.

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The authors declare that there is no conflict of interest.

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CASE REPORT

Phenotypical reflection of a patient with a possible pathological variation of the vcp gene and difficulties in neuromuscular differential diagnosis

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ABSTRACT

The differential diagnosis of muscle weakness includes a wide spectrum of diseases, from cerebrovascular diseases to motor neuron diseases, peripheral neuropathies, neuromuscular junction diseases and myopathies. Although many methods are used to make a diagnosis, including anamnesis, examination, laboratory, electrophysiological examinations, radiological examinations, biopsy and genetic analysis, there are still many patients who cannot be diagnosed. In this article, we present a case in which it was not possible to differentiate between inclusion body myopathy, amyotrophic lateral sclerosis and hereditary motor neuropathy. A 59-year-old male patient presented with chronic progressive muscle weakness and myalgias. The patient, who had complaints for approximately 8-9 years, had a family history supporting an autosomal dominant inheritance pattern. In the patient's neurological examination, muscle weakness affecting the distal and proximal parts of the bilateral lower and upper extremities, atrophy in the thenar and hypothenar regions of the upper extremity, and hypoactive deep tendon reflexes were detected. Other neurological examinations were normal. Laboratory tests revealed no pathology other than moderate CK elevation. Electrophysiological findings supporting the association of motor neuropathy and myopathy were detected in electromyography. No pathology was detected in muscle biopsy other than mild inflammatory changes. Genetic examination of the patient revealed a heterozygous mutation (c.365C>G protein Thr122Arg) in the T122R variant of the Valosin-containing protein (VCP) gene. When the literature is reviewed, although there are some variants of VCP gene mutations associated with familial inclusion body myopathy, amyotrophic lateral sclerosis accompanied by frontotemporal dementia, and Charcot-Marie-Tooth (CMT) 2Y, this variant in our patient has not been described before. The patient's family history of autosomal dominant trait and the presence of both IBM and CMT clinics suggest that these two clinics are phenotypically reflected together as a secondary to the current mutation. In this period when genetic treatments are rapidly developing, it is of great importance to identify genetic muscle diseases and new variants, so such cases should be reported. In patients whom differential diagnosis cannot be made, advanced genetic examinations should be performed even if genetic examinations such as NGS are found negative.

Keywords: VCP mutation, motor neuron disease, inclusion body myositis, hereditary polyneuropathy.

INTRODUCTION

The etiology of muscle weakness may not be determined even if many methods are used. When genetic studies such as next-generation sequencing are also inadequate, whole exon sequencing should be used as the last step for diagnosis. With this method, we detected a new possible pathogenic variation in the valosin-containing protein (VCP) gene in a patient with muscle weakness. Among the 241 VCP variants identified to date, 102 have been classified as likely pathogenic or pathogenic [1]. The clinical manifestations of these defined variations are in three main forms: inclusion body myositis (IBM) and Paget disease, Charcot-Marie-Tooth (CMT) 2Y and amyotrophic lateral sclerosis

(ALS) and frontotemporal dementia (FTD) complex [2-5]. In the patient we described, all these clinics are observed together with the new variation.

CASE REPORT

A 59-year-old male patient presented to our neurology clinic with quadriparesis. His first complaints were back pain and widespread muscle pain that started 5-6 years ago. Over time, numbness and tingling in the fingers and quadriplegic weakness, more severe in the lower extremities, developed in all extremities. He had difficulty climbing stairs and began to fall frequently. There was no known disease in his medical history. He had been using gabapentin for 2 years due to neuropathic pain. There was a 35 pack/year smoking history. When his family history was examined, it was learned that his mother, brother and sister also had a similar history of weakness.

In his neurological examination, bilateral thigh flexion and extension were 3-4/5, left knee flexion and extension were 3/5, right knee extension was 2/5 flexion was 3/5, right foot dorsiflexion was 1/5 plantar flexion was 3/5, left foot dorsiflexion and plantar flexion was 3-4/5, bilateral handgrip was 2-3/5, bilateral elbow flexion was 3/5, elbow extension was 4/5, bilateral shoulder abduction and adduction was 4/5. There was bilateral, asymmetric, and distally dominant muscle weakness. There was muscle atrophy in all four extremities. There were no pathological reflexes or clonus. Deep tendon reflexes could be obtained in the upper extremities, but not in the lower extremities. There were no autonomic symptoms. Pes cavus and hammertoe deformities were present. He could walk with only one support. There were fasciculations in the arms. There was difficulty swallowing solid foods.

In his examinations, hemogram, routine biochemistry, rheumatological markers, HbA1c, brucella, syphilis, thyroid functions, vitamin B12, folic acid, sedimentation, peripheral blood smear, serum protein electrophoresis were found to be normal. Creatine kinase (CK) level was detected as 323 U/L. No significant pathology was detected in complete urine analysis.

Sensory nerves were found to be normal in electromyography (EMG). Motor responses in the median and ulnar nerves could not be obtained

RIGHT	LEFT	Muscle	Maximal Contraction	Submaximal contraction		Spontaneous activity		
				Duration	Polyphasia	Fb	PSW	
	*	M.INTER OSSE DORS 1	severe reduce	↑	N	-	-	
	*	M.ABD.POLL.BREVIS	no voluntary activity			3+	3+	
	*	M.ABD.DIG.MINIMI		N,myogenic	↑	-	-	
*		M.INTER OSSE DORS 1	mild reduce	N,↑	N	3+	3+	pseudomyotonia
	*	M.TIB.ANT.	submaximal	N	N	1+	1+	
	*	M.RECTUS FEMORIS	severe reduce	N,myogenic	↑	-	-	
	*	M.TRAPEZIUS		N	N	-	-	

RIGHT	LEFT	Examined Nerve	Conduction velocity m/sec	Distal conduction latency miliseconds	Distance mm	Amplitude
	*	**N.MEDIANUS (S)**	45	2,4		32µV
	*	**N.ULNARIS (S)**	44	3,2		32µV
	*	**N.SURALIS (S)**	42	3,2		8µV
	*	**N.MEDIANUS (Mt)**	NO RESPONSE			mV
	*	**N.ULNARIS (Mt)**	NO RESPONSE			mV
	*	**N.FIBULARIS (Mt)**	43	4,4		6-5mV

Figure 1. EMG findings. N: nervus, M: musculus, Fb: fibrillation, PSW: positive sharp waves, S: sensorial, Mt: motor, m/sec: meters/second, mV: milivolts, µV: microvolts, mm: milimeters, ↑: increased

on the left. Fibular nerve motor compound muscle action potential (CMAP) conduction velocity and amplitude were normal. Denervation potentials, more neurogenic motor unit potentials (MUP) in the distal and more myogenic motor unit potentials (MUP) in the proximal, and loss of MUP were observed in needle EMG (Figure 1).

Cranial and cervical magnetic resonance imaging showed no findings other than mild cerebral atrophy.

Muscle biopsy was performed for differential diagnosis of myopathy (Figure 2). Histopathological findings were interpreted as not supporting the presence of myopathy.

The pedigree was established by the medical genetics polyclinic and was evaluated as autosomal dominant (OD) inheritance pattern (Figure 3).

In order to make a genetic diagnosis for the patient, "whole exome sequencing" (WES) was performed. As a result of the analysis, the c.365C>G change in the 4th exon of the VCP gene was detected as heterozygous. This change was not reported in the Clinvar database (1) and was classified as a likely pathogenic change according to the American College of Medical Genetics and Genomics (ACMG) criteria [6].

Pathogenic alterations in the VCP gene have been associated with autosomal dominant inheritance of early-onset Paget disease and inclusion body myopathy with frontotemporal dementia 1 (IBMPFD-1) (Multisystem proteinopathy) (OMIM#167320), autosomal dominant inheritance of frontotemporal dementia and/or amyotrophic lateral sclerosis 6 (OMIM#613954), and autosomal dominant inheritance of Charcot Marie Tooth disease type 2Y (OMIM#616687) [7].

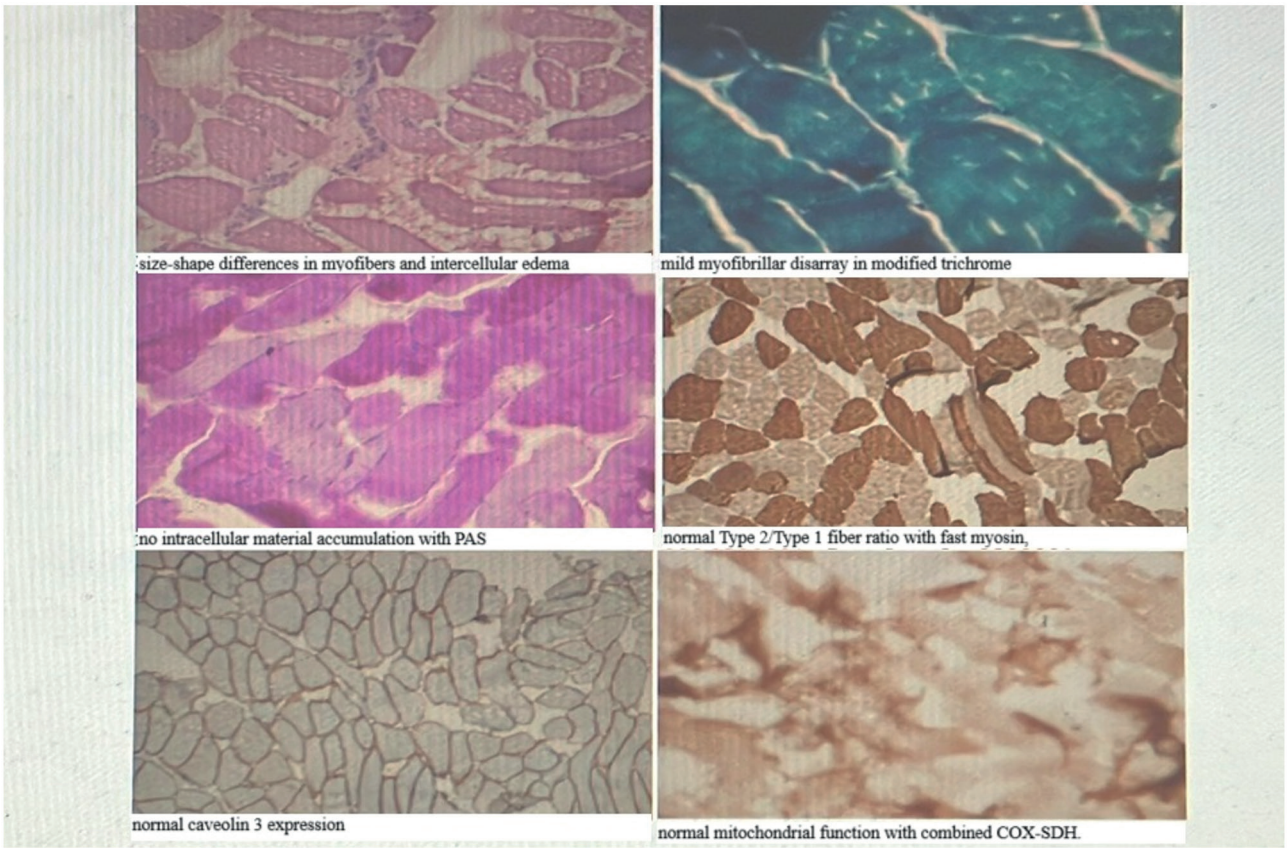

Figure 2. Muscle biopsy images: Microscopic findings showed no signs of muscle injury other than size-shape differences in myofibers and intercellular edema. There was no increase in interstitial tissue in Masson trichrome. There was no obvious pathology except mild myofibrillar disarray in modified trichrome and NADH-TR. There was no Myophosphorylase enzyme was normal in controlled repeat stainings (McArdle disease was excluded). There was no intracellular material accumulation with Oil red O and PAS, and no amyloidosis with crystal violet.. In immunohistochemical staining, sarcolemmal dystrophin, sarcoglycans (A, B, D, G), dysferlin, caveolin 3, cytoplasmic calpain 3 and collagen 6 expression were normal. With fast myosin, Type 2/Type 1 fiber ratio and distribution were normal. There were no pathological immature fibers with neonatal myosin. No inflammatory cells were detected with LCA, CD3, CD20, CD68. Pathological diagnosis resulted as striated muscle tissue showing nonspecific changes.

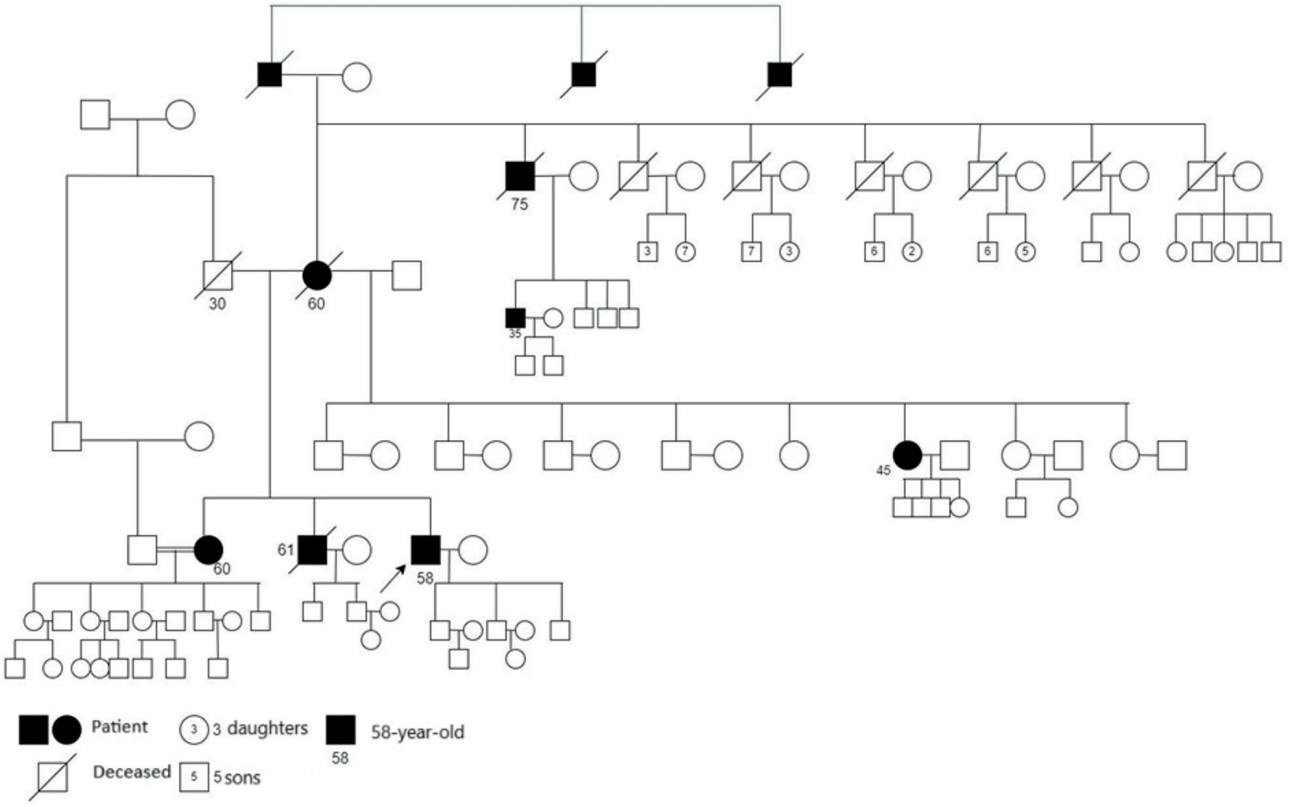

Figure 3. Pedigree

Since frontotemporal dementia can also be seen in this gene positivity, cognitive evaluation was performed.

Standardized Mini Mental Test Score: 10/25 (Subtests that could not be evaluated due to the patient not being able to use both hands were not included in the scoring). The score was observed below normal limits. In the subgroup scoring, the patient lost the most points from recording, attention and delayed recall. (Orientation: 6/10, Record: 1/3, Attention: 1/5, Delayed Recall: 0/3, Language: 2/4).

No lytic lesions or hardening of bone tissue supporting Paget's disease were observed in the knee tomography.

The patient was started on riluzole treatment. No worsening of swallowing difficulty was observed at the 2-year follow-up examination. Previously he was able to walk with a single cane, but now he could walk with a double cane. In muscle strength examination, there was distal and proximal tetraparesis, more dominant in the distal. Atrophy was observed in bilateral thenar and hypothenar muscles. In the deep tendon reflex examination, the biceps could not be obtained on the right and was hypoactive on the left, and reflexes could not be obtained in the lower extremities. Hoffman was bilaterally negative, and plantar skin response was bilaterally flexor.

DISCUSSION

The most important feature of this case report is the description of a previously unidentified variation in the VCP gene that causes a severe syndromic presentation including autosomal dominant myositis, hereditary motor predominant polyneuropathy and motor neuron disease clinics. It is also emphasized that next-generation sequencing alone is not sufficient to overcome the difficulties in differential diagnosis in hereditary forms of neuromuscular diseases, and whole exon sequencing has an important place.

In the family we described, the index case's CK elevation, proximal muscle weakness, significant myogenic MUP changes in the proximal muscles on EMG, and the size-shape difference in myofibers and intercellular edema detected on muscle biopsy can be interpreted in favor of myopathy, while the patient's complaints started with numbness-

tingling in the fingers of four extremities, the absence of deep tendon reflexes despite no apparent atrophy in the early stages, the presence of pes cavus and hammertoe deformities on the feet, and the widespread decrease in the CMAP amplitudes of the motor nerves on nerve conduction study on EMG while the observation of neurogenic MUP changes in the distal areas on needle EMG can be interpreted in favor of polyneuropathy. In addition to the patient's neurogenic MUPs, the detection of denervation potentials in the cervical and lumbar segments, changes in motor amplitudes, and dementia findings with obvious attention deficits could not exclude the motor neuron disease frontotemporal dementia complex. For these reasons, the patient's diagnosis could not be fully established until WES was performed.

The VCP gene is located on chromosome 9. It is a protein that has important roles in chromatin organization, membrane fusion, ubiquitin-dependent protein degradation and autophagy. VCP is a protein that is a member of the AAA+ (diverse activity-associated ATPase) protein family. It exhibits multifunctional properties and expresses in every tissue. Although the exact role of VCP in skeletal muscle is not yet known, VCP mutations lead to the accumulation of ubiquitinated inclusions and protein aggregates in patient tissues, transgenic animal models and in vitro systems [8]. One study found that VCP was localized intranuclearly in differentiated skeletal muscle tissue [9]. VCP has been found to be widespread in the sarcoplasm of skeletal muscle, and also in the perinuclear region and within endomysial vessels [10,11]. In cultured myotubes, VCP is mostly found in the cytoplasm [12]. This may suggest that VCP changes its localization and perhaps its function depending on the differentiation status of the cells.

There are many variations identified in the VCP gene. Paget disease, inclusion body myositis, FTD and ALS complex and CMT2Y diseases have been reported to develop as a result of these variations [2-5].

The most common general features of patients diagnosed with IBMFTD are proximal muscle weakness, which causes morbidity as in our index case, in approximately 90%, Paget disease in 51%, and FTD-type dementia in 32%. Sensory motor axonal neuropathy has rarely been described in these patients. Although muscle biopsies may show vacuoles in some patients, more commonly ubiquitinated sarcoplasmic and myonuclear inclusions associated with VCP and TDP-43 inclusions are observed [2]. However, slight changes can also be detected, as in our patient.

Pathogenic variants in the VCP gene have been newly associated with CMT type 2. A family with a new associated variant (VCP (p.S171R)) was identified. Mild sensory symptoms and findings characterized by chronic progressive motor axonal loss on repeated EMGs were observed in this family [3]. In the case we describe, sensory complaints, hypoactive or absent DTRs on neurological examination, decreased motor amplitudes on EMG, and neurogenic changes in distal muscles on needle EMG suggest that the patient's clinical picture resembles the CMT2Y phenotype.

In a recent study, it was observed that protein aggregates accumulated secondary to mutated SOD1 interact with VCP protein in motor neurons derived from pluripotent stem cells obtained from an ALS patient with SOD1 mutation, and SOD1 toxicity was reduced when VCP was overexpressed. Changes in VCP homeostasis have been highlighted as one of the main factors that may cause faster degeneration in diseased motor neurons [4]. Another study described familial ALS due to VCP mutation [13]. Considering this feature of VCP, it is understandable that ALS could not be excluded in the patient we described. Finally, studies emphasize that VCP mutations can cause the FTD phenotype. Recently, VCP mutations have been shown to lead to abnormal accumulation of enlarged endosomes and lysosomes, as well as to reduce autophagy flux and increase tau phosphorylation. It has been emphasized that tau hyperphosphorylation on these pathways also causes FTD type dementia [5].

The C.-365C>G variant that we identified in our patient was searched in the literature and in databases where genetic variations are stored, but it was determined that it has not yet been identified. It can be said that this variant is a more severe form that phenotypically includes both IBM, CMT2Y and ALS-FTD clinics, based on the patient and family history we reported. However, further studies are required to demonstrate which pathways and cellular dysfunctions are responsible for the clinical manifestation of this variant.

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE REPORT

Thyrotoxic hypokalemic periodic paralysis as the initial manifestation of graves' disease

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ABSTRACT

Thyrotoxic periodic paralysis (TPP) is a rare, potentially life-threatening condition characterized by acute, symmetrical paralysis of proximal muscles coupled with severe hypokalemia, typically arising in the context of thyrotoxicosis, often associated with Graves' disease. We present a case of a 41-year-old male who exhibited sudden-onset quadriplegia following a week of muscle cramps. Initial assessments revealed profound hypokalemia (1.4 mEq/L) and electrocardiographic abnormalities consistent with arrhythmias. Diagnosis was confirmed through positive thyrotropin receptor antibodies and ultrasound findings indicating Graves' disease. The patient was treated with methimazole and propranolol, along with immediate potassium replacement. Remarkably, his motor function improved dramatically post-treatment, with normalization of ECG findings before discharge, highlighting the prompt responsiveness to management and the need for timely diagnosis of this condition. Given the serious implications of untreated hypokalemic periodic paralysis, including respiratory failure and cardiac complications, clinicians must maintain a high index of suspicion for TPP in patients presenting with acute muscle weakness and hypokalemia.

Keywords: Thyrotoxic periodic paralysis, Graves' disease, hypokalemia, acute muscle weakness, thyrotoxicosis complications.

INTRODUCTION

Thyrotoxic periodic paralysis (TPP) is a rare, life-threatening condition characterized by acute, symmetrical paralysis of proximal muscles associated with severe hypokalemia in patients with either known or undiagnosed thyrotoxicosis [1]. The severity of the disease can range from mild weakness to quadriplegia, with bulbar and ocular muscles generally spared in most cases. Patients may present with significant signs of thyrotoxicosis, such as palpitations, tremors, nervousness, unexplained weight loss, and excessive sweating. However, the presentation can vary, and patients may exhibit only mild symptoms of thyrotoxicosis or none at all (Table 1). Unlike hyperthyroidism, the disease is more frequently observed in males, with an average onset age between 20 and 40 years [2].

Various mechanisms are proposed to contribute to hypokalemia-induced paralysis. The most accepted theories include stimulation of Na-K ATPase activity by excessive thyroid hormones or a hyperadrenergic state, as well as intracellular potassium shift caused by hyperinsulinemia [3]. Certain forms of human leukocyte antigen (HLA) are more common in TPP, suggesting a possible immunological link. This association may indicate a connection between the immune system and the disease; however, it is unclear whether HLA directly causes TPP or merely increases susceptibility to Graves' disease, a known autoimmune condition [4].

Any cause of thyrotoxicosis can lead to hypokalemic periodic paralysis. The most common cause is Graves' disease, followed by toxic multinodular

Table 1. Thyrotoxic Periodic Paralysis Clinical Features

1) Young adult male
2) Sporadic
3) Recurrent acute paralysis episodes with complete recovery
4) Limb > trunk involvement
5) Triggered by excessive carbohydrate load, high-salt diet, alcohol, or exertion
6) Family history of hyperthyroidism
7) Clinical features of hyperthyroidism
8) Hypokalemia and reduced potassium excretion rate
9) Normal acid-base balance
10) Decreased phosphate excretion
11) Low-amplitude compound muscle action potential on EMG, unchanged after epinephrine administration

Table 2. Thyrotoxic Periodic Paralysis Etiology

1) Graves' Disease
2) Toxic Nodular Goiter
3) Solitary Toxic Nodule
4) Iodine-Induced Thyrotoxicosis
5) Excessive Exogenous Thyroxine Use
6) Lymphocytic Thyroiditis
7) TSH-Secreting Pituitary Adenoma
8) Amiodarone-Induced Thyrotoxicosis

goiter, solitary toxic nodules, iodine-induced thyrotoxicosis, excessive exogenous thyroxine use, thyroiditis, TSH-secreting pituitary adenoma, and amiodarone-induced thyrotoxicosis (Table 2) [5-7]. Common triggers of periodic paralysis episodes include consumption of carbohydrate-rich foods, intense physical activity, high salt/sodium intake, surgery, trauma, and medications.

This report aims to discuss the pathogenesis, clinical features, laboratory findings, differential diagnosis, and management of thyrotoxic hypokalemic periodic paralysis secondary to Graves' disease through a case presentation.

CASE REPORT

A 41-year-old male with no history of chronic illness presented to the emergency department with sudden-onset muscle weakness following a week of muscle cramps and numbness in his legs. Neurological examination revealed a nervous demeanor, flaccid quadriplegia, and global areflexia. Laboratory tests showed a dangerously low potassium level (1.4 mEq/L). Electrocardiogram (ECG) findings included arrhythmias, ST depression, QT prolongation, and U waves associated with profound hypokalemia (Figure 1). Advanced investigations for the etiology of hypokalemic periodic paralysis revealed thyrotoxicosis. The patient was diagnosed with Graves' disease based on positive thyrotropin receptor antibody (TRAb) findings and ultrasound evidence of increased thyroid size, vascularity, and hypoechogenicity in the parenchyma.

Treatment with methimazole (5 mg, three times daily) and propranolol (80 mg, three times daily) was initiated. Immediate oral and intravenous potassium replacement was administered to normalize serum potassium levels. Following

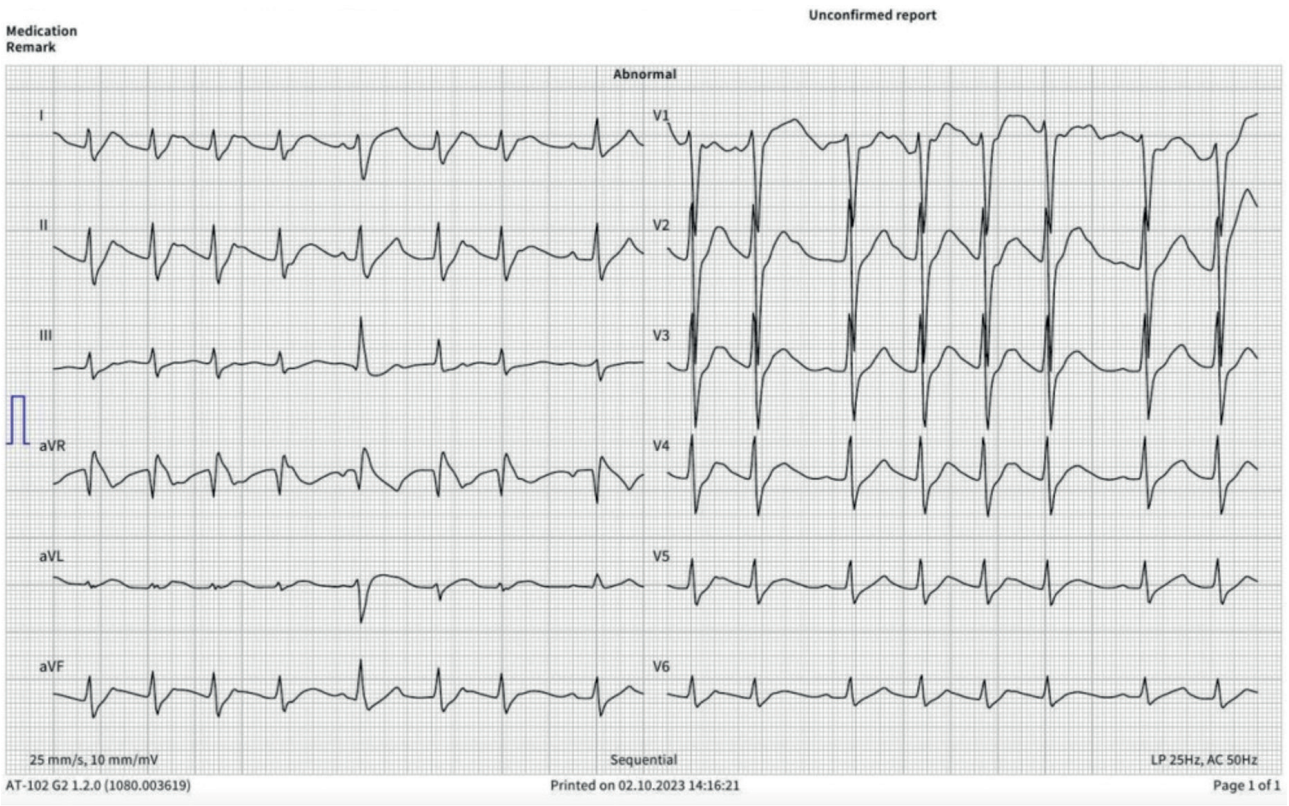

Figure 1. Patient's ECG

potassium normalization, the patient experienced a dramatic improvement in motor function, and ECG abnormalities resolved. The patient was discharged without any residual deficits.

DISCUSSION AND CONCLUSION

Thyrotoxic periodic paralysis (TPP) is defined by the triad of thyrotoxicosis, hypokalemia, and acute muscle weakness. It is most commonly associated with Graves' disease, an autoimmune thyroid disorder. TPP typically affects lower extremity muscles more than upper extremities, with sparing of trunk, ocular, bulbar muscles, and sensory systems. Fatal electrocardiographic findings such as arrhythmias due to hypokalemia may occur. Differential diagnosis should exclude non-thyrotoxic periodic paralysis and familial thyrotoxic periodic paralysis (Table 3) [5].

In the presented case, the rapid resolution of neurological symptoms following potassium replacement and thyrotoxicosis management highlights the treatable nature of the condition. However, untreated hypokalemic periodic paralysis can progress to respiratory failure, arrhythmias, or cardiac arrest, posing a significant risk to life [6]. Prompt diagnosis is therefore critical. Clinicians should thoroughly evaluate laboratory findings in cases of acute paresis and consider hypokalemic periodic paralysis in the differential diagnosis. It is

Table 3. Comparison of Thyrotoxic and Familial

Feature	Thyrotoxic Periodic Paralysis	Familial Hypokalemic Periodic Paralysis
Age (years)	20-40	<20
Gender Distribution	Predominantly male	Equal male-female
Inheritance	Sporadic	Autosomal dominant
Ethnic Background	Asian, American, Hispanic, Caucasian	Caucasian, Asian
Family History	History of hyperthyroidism	History of hypokalemic paralysis
Hyperthyroidism Clinical Signs	Yes	No
Genetic Predisposition	Related to Cav1.1 SNPs (e.g., c.4746G>A, intron mutations)	Cav1.1 mutations (e.g., R528H, R1239H, Na1.4 variants R669H, R672G, K3.4 R83H)

essential to remember that acute-onset tetraparesis may mimic several neurological disorders, with Guillain-Barré syndrome being the most common consideration.

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Conflict of interest

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