ORIGINAL ARTICLE

A retrospective evaluation of delayed diagnosis and misdiagnosis in skeletal muscle ion channelopathy patients

Evaluación retrospectiva del diagnóstico tardío y del diagnóstico erróneo en pacientes con canalopatía iónica del músculo esquelético

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Abstract

Objective: *Skeletal muscle ion channelopathies are a rare genetically inherited orphan disease. Due to the unique characteristics of the symptoms of the disease, misdiagnosis of patients leads to irreversible losses. This study aims to raise awareness on this issue.* **Methods:** *35 patients with a definitive diagnosis of skeletal muscle ion channelopathy were included in the study. The diagnoses of all patients were confirmed by gene analysis. Demographic and clinical characteristics of the patients were examined. After a definitive diagnosis was made, mimic symptoms and misdiagnoses were evaluated separately.* **Results:** *It was determined that 30 of the patients included in the study had multiple different diagnoses until they got the correct diagnosis. It is thought that due to delayed diagnosis or misdiagnosis, patients experience physical and mental loss, are exposed to ineffective drugs, and their daily lives are adversely affected, as well as serious cost losses.* **Conclusions:** *It is stated that the names of misdiagnoses for imitation symptoms have changed with aging, and drug treatments are applied for each diagnosis. It is stated that health authorities should pay attention to this situation to reduce this.*

Keywords: *Channelopathy. Mimic symptoms. Delay in diagnosis. Primary diagnosis.*

Resumen

Objetivo: *La canalopatía iónica del músculo esquelético es una enfermedad huérfana rara que se hereda genéticamente. Debido a las características únicas de los síntomas de la enfermedad, el diagnóstico erróneo de los pacientes conduce a pérdidas irreversibles. Este estudio pretende concienciar sobre esta cuestión.* **Métodos:** *Se incluyeron en el estudio 35 pacientes con diagnóstico definitivo de canalopatía iónica del músculo esquelético. El diagnóstico de todos los pacientes se confirmó mediante análisis genético. Se examinaron las características demográficas y clínicas de los pacientes. Una vez realizado el diagnóstico definitivo, se evaluaron por separado los síntomas mímicos y los diagnósticos erróneos.* **Resultados:** *Se determinó que 30 de los pacientes incluidos en el estudio tuvieron múltiples diagnósticos diferentes hasta que obtuvieron el diagnóstico correcto. Se cree que, debido al retraso en el diagnóstico o a los diagnósticos erróneos, los pacientes experimentan pérdidas físicas y mentales, están expuestos a fármacos ineficaces y su vida cotidiana se ve afectada negativamente, además de graves pérdidas de costes.* **Conclusiones:** *Los diagnósticos erróneos realizados por síntomas mímicos cambian con la edad del paciente, es decir, se realizan diferentes diagnósticos según la edad del paciente, y se aplican tratamientos farmacológicos para cada diagnóstico. Se afirma que las autoridades sanitarias deberían prestar atención a esta situación para reducirla.*

Palabras clave: *Canalopatía. Síntomas mímicos. Retraso en el diagnóstico. Diagnóstico primario.*

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Introduction

Skeletal Muscle Ion Channelopathies (SMICs) are a rare neurological disease affecting the motor structure and causing non-dystrophic, abnormal cell functioning due to gene mutations encoding voltage-gated cell ion channels. In congenital SMICs, mutations develop in the genes encoding the skeletal muscle sodium channel (SCN5A), skeletal muscle calcium channel (CACNA1S), skeletal muscle potassium channel (KCNJ2 and KCNJ18), cation channels, and voltage-gated skeletal muscle chloride (CLCN1) anion channel. Numerous mutations of each of these genes have been described, and many sub-diagnoses exist. It is primarily autosomal dominant. Its diagnosis is made by examination, blood biochemistry examination, electromyography (EMG), and gene analysis[1]. Its classic diseases include myotonia congenita, paramyotonia congenital, hyperkalemic periodic paralysis, and various sodium channel myotonia. The gene locations in SMICs are CLCN1 Cytogenetic location: 7q34 (long arm 34 of chromosome 7), SCN4A Cytogenetic location: 17q23.3, CACNA1S Cytogenetic location: 1q32.1, KCNJ2 Cytogenetic location: 17q24.3, KCNJ18 Cytogenetic location: 17p11.

Clinical response to the disease

The most prominent symptom in the SMICs clinic is myotonia, also defined as a warming phenomenon with delayed relaxation after voluntary contraction. This symptom occurs in 100% of patients. Musculoskeletal symptoms such as persistent weakness, widespread pain, cramping, stiffness, difficulty grasping, painful awakening, warming phenomenon, myalgia, and non-inflammatory pain sensation in the joints are common. In addition to these symptoms, generalized and diffuse symptoms such as difficulty chewing, swallowing, climbing ramps, and overhead work can be seen to varying degrees. Symptoms are episodic and fluctuate depending on triggering factors. Myotonia decreases or disappears after several consecutive warm-up exercises. Symptoms are aggravated at rest, in the cold, and by certain foods[2,3]. Inflammatory Spondyloarthritis, Fibromyalgia (FM), rheumatoid arthritis (RA), idiopathic inflammatory myopathy (IIM), epilepsy, myasthenia gravis (MG), juvenile idiopathic arthritis (JIA), Cervical Spondylotic Myelopathy, Neurogenerative Disease, disc hernia (DH), Vitamin Deficiency are examples of diseases that mimic this disease.

In many diseases overlapping similar complaints, poor differential diagnosis, data collection problems, and inability to synthesize information have led to misdiagnosis[4,5]. Symptoms of the disease usually begin in the first 20 years of life. SMICs are estimated to occur in approximately 1 in 100,000 people worldwide[6]. In defining SMICs, the level of muscle-derived creatine kinase (CK) in plasma may vary from normal to several times higher. Significant abnormalities in blood parameters due to SMICs are not expected. Although changes were observed in the muscle biopsy, it was observed that it did not provide sufficient differential information[7]. Drug therapy in SMICs is symptomatic. It has been reported that there is a rapid change in symptoms and a decrease in the disease burden with correct and regular physical activity, medical rehabilitation, motivation, education, environmental conditions, and nutrition[8]. Mexiletine, phenytoin, and carbamazepine are used in the symptomatic treatment of SMICs.

In this study, the SMICs clinic aims to analyze the patient's misdiagnoses until a definitive diagnosis is made and to raise awareness about SMICs. In addition, the fact that there is no similar study on this subject shows the originality of the study.

Methods

Ethical aspects of the research

Before the study, local ethics committee approval was obtained from the Health Sciences Gazi Yaşargil Training and Research Hospital (No: 306, Date: December 30, 2022). The study group was informed about the purpose and content of the study. Those who agreed to participate in the study signed an "informed consent form" and were included. The demographic characteristics of all patients were recorded.

Participants in the study and processes

Patients admitted to the Neuromuscular Diseases Unit of Health Sciences Gazi Yaşargil Training and Research Hospital between 2013 and 2022 were evaluated by a 30-year Physical Medicine and Rehabilitation specialist and a 15-year Neuromuscular Diseases physician.

- All patients had symptoms of myotonia
- Only patients with mutations in genes encoding the skeletal muscle chloride channel (CLCN1)

– Demographic information on misdiagnosed patients and patients who received diagnostic
– They were included in the study on condition that they received medication treatment

The study included 35 patients; 5 patients were SMICs diagnosed at the onset of their complaints, so only their demographic characteristics were used. 30 patients were examined by more than one physician on different dates until they received the main diagnosis, non-SMICs diagnoses were made, and drug treatment was initiated for the diagnosis. This led to multiple rheumatologic and neurologic misdiagnoses. The misdiagnosis information documents of the patients were obtained by reviewing the notification given by the patient, archival data, and the registry system. Diagnoses made after the main diagnosis was confirmed were investigated. As a result, no other diagnosis other than FM symptoms and changes in plasma vitamin levels was found. FM and vitamin deficiency can be seen in every individual, the reason for inclusion was that the complaints of 30 patients were attributed to FM and vitamin deficiency, and medication was given for a long time, which caused a delay in diagnosis and was therefore included in the misdiagnosis group. CK levels were irregularly mildly elevated.

EMG

It has an important role in detecting the natural activities of the neuromuscular system. A scientifically standardized acquisition protocol has been established. Compound muscle action potential (CMAP) amplitudes are recorded before and after the acquisition[9]. SMICS is evaluated according to the detection of myotonic discharges by needle EMG. All patients underwent EMG, performed in centers licensed by the Ministry of Health and by certified physicians. The physician performing the EMG procedure used short and long exercise tests for diagnostic accuracy. All patients underwent EMG for biceps, fine motor skills, quadriceps, and anterior tibial muscles by a blinded assessor with maximum sensitivity to universal standardized guidelines. Concentric needle EMG was performed. Findings were interpreted in favor of myopathy. Gene molecular analysis was recommended for specific diagnosis and further interpretation. Gene analysis was performed by authorized gene analysis units licensed by the Ministry of Health.

According to the result of gene analysis, among the patients suspected of the SMIC diagnosis, those who returned from patients whose diagnosis was confirmed by the gene center were included in the study in the assessments made. Some of our 52 patients had chloride, and some had sodium channel mutation disorders. The number of patients with a chlorine channel disorder was higher. The gene mutation demographics were not considered necessary because the characteristics of the symptoms did not differ due to the mutation.

Analysis of the data

The SPSS 22.0 package program was used for the data analysis. The measurable variables were expressed as mean ± standard deviation, and the categorical variables were expressed as numbers and percentages.

Findings

When Table 1 was examined, the patients' median age and standard deviation were 29.00 ± 11.95 (min = 16; max = 52). The mean and standard deviation of the visual analog scale (VAS) were 3.77 ± 1.24. 15 (42.9%) patients were female, and 20 (57.1%) were male. Of the patients, 12 (34.3%) are currently smoking, 2 (5.7%) have smoked in the past, and 21 (60%) have never smoked. When the diagnosis was examined after the confirmation by the genetic analysis, the symptoms of SMICs were detected in 6 (17.1%) relatives having different affinities; of these, those who received misdiagnoses and treatment for the diagnosis were included in the study. There was a diagnosis of SMICs in 5 members of the same family, the oldest of whom was 52. It has been determined that 30 (85.7%) patients were misdiagnosed or diagnosed until the primary diagnosis was made, and only 5 (14.3%) patients were correctly diagnosed. All of the patients could walk, and they stated that they were tired. It was determined that 6 (17.1%) patients had inflammatory spondyloarthritis, 30 (85.7%) patients had FM, 4 (11.4%) patients had RA, 7 (20%) patients had IIM, 6 (17.1%) patients had epilepsy, 4 (11.4%) patients had MG, 5 (14.3%) patients had JIA, 3 (8.6%) patients were cervical spondylotic myelopathy, 4 (11.4%) patients were motor neuron disease (MND), and 30 (85.7%) patients were disc herniation and vitamin deficiency (Table 2).

Discussion

SMICs are a group of rare neuromuscular disorders caused by gene mutation and primarily affecting

skeletal muscle. In these patients, it has been observed that the number, severity, age of onset, and course of symptoms are different in family members with the same gene mutation. Misdiagnoses have been reported in many genetic neuromuscular diseases affecting the musculoskeletal system[10]. According to the VAS, patients with myopathy have been reported to experience an unpleasant pain style[11]. Within the scope of this study, all patients had signs of myotonia when evaluated under appropriate conditions. Significantly different clinical findings were found among family members with the same gene analysis result. Although SMICs sub-diagnoses have many different mutations, widespread similarity within different mutations in the same mutation was seen in clinical problems due to the wide symptom network. This may cause serious problems in genotype-phenotype correlation in SMIC patients. Due to the low prevalence of the disease, establishing standard diagnostic criteria can be an important obstacle for physicians.

FM

The etiology of FM is not completely known, and many accusatory factors have been proposed. Symptoms such as multiple tender points, body fatigue, fatigue, and chronic pain have been reported. FM has been described as affecting approximately 2% of the population[12]. The current criteria for defining FM was established by the American College of Rheumatology (ACR) in 1990[13].

It has been observed that it mimics SMICs or secondary FM develops accordingly. It was analyzed that 30 (85.7%) patients admitted to the neuromuscular center were misdiagnosed with myalgia-FM. In one study, 2 (3.2%) of 63 patients diagnosed with FM were reported to have myotonic myopathy[14].

Inflamatory spondyloarthritis

The prototype of inflammatory spondyloarthritis is ankylosing spondylitis. It is a chronic disease and the cause is unknown. Most symptoms are sacroiliac joint involvement, early onset, body stiffness, musculoskeletal pain, and limitation of movement. The establishment of diagnostic and follow-up criteria by the International Spondyloarthropathy Assessment Society for modified features has facilitated patient identification. The drug response of SPA is successful[15]. 6 (17.1%) patients with confirmed SMIC were misdiagnosed as having SPA and were exposed to prolonged drug therapy. There are similarities at the symptom level in the clinic of SPA and SMIC. In some studies, it has been found that SPA and myopathies mimic each other, misdiagnoses have been experienced, and long-term treatments have been applied at the case level[16,17].

RA

RA is a synovial disease with late-onset, predominantly symmetrical, small joint involvement, morning stiffness, fatigue, muscle weakness, and chronic features. Changes compatible with RA develop in the laboratory and joint radiologic evaluation. Classification criteria for RA were developed by the ACR/European League Against Rheumatism in 2010[18]. It was learned that 4 (11.4%) patients were misdiagnosed with RA and were treated with non-steroidal, steroid, non-biologic, and biologic disease-modifying antirheumatic drugs for a long time until the primary diagnosis was made.

In a study, 25 (26%) of 96 patients with myotonic symptoms were misdiagnosed with musculoskeletal rheumatic diseases such as arthritis, chronic fatigue syndrome, FM, RA, and degenerative diseases[19]. One study found that 1 in 26 patients diagnosed with dysferlinopathy had been treated for arthritis long before diagnosis[20].

IIM

IIM is a group of rare autoimmune inflammatory and heterogeneous diseases characterized by joint, muscle inflammation, skin, gastrointestinal, respiratory, and cardiac involvement. These patients may develop loss of strength in the proximal muscles, atrophy, difficulty in overhead work, pain, fever, and in most cases, symptoms of active arthritis. The diagnosis is determined using patient assessment, diagnostic criteria, elevated CK, other muscle enzyme levels, supportive or excluded laboratory parameters, EMG, and muscle histopathology. Response to immunotherapy is good unless there is an underlying malignancy or other cause[21].

It was noticed that 7 (20%) of our patients who were identified as SMIC were identified as IIM and used long-term disease-modifying non-biological and biological disease-modifying antirheumatic drugs. In

some studies, it has been reported that myopathies with primary muscle involvement mimic each other and it has been stated that IIM unknowingly mimics myopathies with muscular dystrophy by applying long-term treatments. In one study, 15 (57.7%) of 26 patients with Limb-Girdle Muscular Dystrophy were misdiagnosed as inflammatory myopathy before the primary diagnosis and 13 (86.7%) of them were given cortisone treatment before the diagnosis; some received immunosuppressive therapy[20].

Epilepsy

In some recent studies, it has been reported that the diagnoses of epilepsy and SMIC are frequently confused, and long-term antiepileptic treatments are used[22]. When the expected improvement could not be achieved with the treatments, it was found that 6 (17.1%) patients were misdiagnosed with epilepsy in the control examination. A study conducted by Ramos-Maqueda et al. found that 8 of 50 patients with cardiac canalopathy were mistakenly diagnosed with epilepsy before definitive diagnosis[23].

MG

MG belongs to autoimmune neuromuscular diseases with unknown neuromuscular synaptic causes. In MG, muscle focalization and weakness with movement are increased; complaints of impaired vision, swallowing, and speech are common, and patients often complain of fluctuations in muscle strength within 24 h. In cases without ocular involvement or with predominantly proximal involvement, it has been confused with other neuromuscular diseases[24].

In 4 (11.4%) patients admitted to the neuromuscular center with a diagnosis of MG, SMIC was diagnosed when the criteria were evaluated appropriately in patients admitted due to uncertainty in the course, lack of response to medication, and suspicion of diagnosis. Neshuku et al. reported that 4 of 31 misdiagnosed patients were diagnosed with genetic myopathy in a 20-year MG database search[25].

JIA

JIA is a systemic chronic rheumatic diagnosis of unknown etiology with early onset. It manifests with clinical symptoms such as pain, limitation of movement, weakness of musculoskeletal tissue, impaired balance control, fatigue, and motor clumsiness[26]. It was found that 5 (14.3%) patients were treated with medication for a long time with the diagnosis of JIA until adulthood. In the evaluation, it was determined that these were SMIC patients.

Since such diagnostic confusion may occur in some studies, it was concluded that it would be practical to use all diagnostic tests together and to bring the diagnosis to mind to minimize misdiagnosis and diagnostic delay[27].

Spinal spondylotic myelopathy (SSM)

SSM presents with complaints such as a change in muscle tone due to pressure on the spinal cord caused by degeneration of cervical anatomical tissues, disc herniation, congenital malformation, atrophy, loss of strength, decrease in muscle dexterity, loss of sensation, neuropathic pain, change in tendon reflex, and sphincter disorder. The basic diagnosis is made by questioning the examination, imaging, EMG, and differential diagnosis method[28]. It was learned that 3 (8.6%) patients with SMIC were diagnosed with spinal stenosis and myelopathy at some point. Robles et al. A patient with SSM was found to have been treated for a long time and with multiple stages of treatment; the diagnosis was incorrect. The patient was diagnosed with amyotrophic lateral sclerosis[29].

MND

MND is a group of progressive neurological disorders characterized by the degeneration of voluntary muscles in the forebrain, upper and lower brain neurons, and spinal cord. This group includes diseases such as amyotrophic lateral sclerosis, hereditary spastic paraparesis, and spinal muscular atrophy. The pathophysiology has not yet been fully elucidated and is mostly focused on genetic mutations. It may have an adult or congenital onset. General symptoms include decreased dexterity, weakness in voluntary muscles, tone disturbance, balance problems, fatigue, and physical and mental problems that make swallowing, speaking, breathing, and activities of daily living difficult. Diagnosis is mainly based on history and examination. Auxiliary methods such as laboratory analysis, EMG, imaging, cerebrospinal fluid analysis, and genetic analysis can be applied[30].

Table 1. Descriptive analysis regarding the patients

Socio-demographic and clinical characteristics regarding the patients		
Age	29.00 ± 11.95 (min: 16; max: 52)	
Visual analog scale score	3.77 ± 1.24	
	n	%
Gender		
Female	15	42.9
Male	20	57.1
Smoking status		
Still Using	12	34.3
Used in the Past	2	5.7
Never Used	21	60.0
SMICs defined family history		
yes	6	17.1
No	29	82.9
Correct diagnosis receiving status		
Yes	5	14.3
No	30	85.7
Walking status		
Walking	35	10.00
Can Not Walk	0	0.0
Tiredness		
Yes	35	100.0
No	0	0.0
Inflammatory		
Misdiagnosed	6	17.1
Spondyloarthritis		
Undiagnosed	29	82.9
Fibromyalgia		
Misdiagnosed	30	85.7
Undiagnosed	5	14.3
Rheumatoid arthritis		
Misdiagnosed	4	11.4
Undiagnosed	31	88.6
Idiopathic		
Misdiagnosed	7	20.0
Inflammatory myopathy		
Undiagnosed	28	80.0
Epilepsy		
Misdiagnosed	6	17.1
Undiagnosed	29	82.9
Myasthenia gravis		
Misdiagnosed	4	11.4
Undiagnosed	31	88.6
Juvenile idiopathic		
Misdiagnosed	5	14.3
Arthritis		
Undiagnosed	30	85.7
Cervical spondylotic		
Misdiagnosed	3	8.6
Myelopathy		
Undiagnosed	32	91.4
Neurodegenerative		
Misdiagnosed	4	11.4
Disease		
Undiagnosed	31	88.6
Disc herniation		
Misdiagnosed	30	85.7
Undiagnosed	5	14.3
Vitamin deficiency		
Misdiagnosed	30	85.7
Undiagnosed	5	14.3
Total	35	100.0

(Continues)

Table 1. Descriptive analysis regarding the patients *(continued)*

In a study conducted in the United States, it was noted that approximately half of patients diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy, a neurologic disorder, who subsequently applied the 2010 diagnostic criteria of the Federation of European Neurological Societies were misdiagnosed, resulting in a significant loss of time in correct diagnosis and exposure to costly treatments. In the United Kingdom, 68% of patients initially diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy were misdiagnosed when re-examined[31].

DH

DH symptoms are manifested by dermatomal pain, motor loss, atrophy, and sensory changes at the level of compression of the nerve tissue. Physical examination and imaging tools are utilized for diagnosis[32]. When we re-examined 30 (85.7%) patients diagnosed with DH, we did not find any compatible findings to support the DH clinic. Madani et al. re-examined 202 patients diagnosed with lumbar DH and found that 146 (72.3%) patients had sacroiliac joint dysfunction disease[33].

It was reported that 3 patients who were followed up for a long time with a diagnosis of DH were reported to have amyotrophic lateral sclerosis in the analysis performed due to worsening of the clinical course[34].

Table 2. Crossover data intended to patient-related variables

Variable	Sub-variable	Female (%)	Male (%)	Total (%)
Cigarette	Still using	3 (25.0)	9 (75.0)	12 (100.0)
	Used in the past	1 (50.0)	1 (50.0)	2 (100.0)
	Never used	11 (52.4)	10 (47.6)	21 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Family history of channelopathy defined	Yes	2 (33.3)	4 (66.7)	6 (100.0)
	No	13 (44.8)	16 (55.2)	29 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Inflammatory	Yes	1 (16.7)	5 (83.3)	6 (100.0)
Spondyloarthritis	No	14 (48.3)	15 (51.7)	29 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Fibromyalgia	Yes	14 (46.7)	16 (53.3)	30 (100.0)
	No	1 (20.0)	4 (80.0)	5 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Rheumatoid arthritis	Yes	4 (100.0)	0 (0.0)	4 (100.0)
	No	11 (35.5)	20 (64.5)	31 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Idiopathic Inflammatory Myopathy	Yes	6 (85.7)	1 (14.3)	7 (100.0)
	No	9 (32.1)	19 (67.9)	28 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Epilepsy	Yes	2 (33.3)	4 (66.7)	6 (100.0)
	No	13 (44.8)	16 (55.2)	29 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Myasthenia gravis	Yes	4 (100.0)	0 (0.0)	4 (100.0)
	No	11 (35.5)	20 (64.5)	31 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Juvenile idiopathic arthritis	Yes	2 (40.0)	3 (60.0)	5 (100.0)
	No	13 (43.3)	17 (56.7)	30 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Cervical spondylotic myelopathy	Yes	0 (0.0)	3 (100.0)	3 (100.0)
	No	15 (46.9)	17 (53.1)	32 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Motor neuron disease	Yes	2 (50.0)	2 (50.0)	4 (100.0)
	No	13 (41.9)	18 (58.1)	31 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Disc herniation	Yes	14 (46.7)	16 (53.3)	30 (100.0)
	No	1 (20.0)	4 (80.0)	5 (100.0)

(Continues)

Table 2. Crossover data intended to patient-related variables *(continued)*

Variable	Sub-variable	Female, n (%)	Male, n (%)	Total, n (%)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Vitamin deficiency	Yes	14 (46.7)	16 (53.3)	30 (100.0)
	No	1 (20.0)	4 (80.0)	5 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)
Correctly diagnosed	Yes	1 (20.0)	4 (80.0)	5 (100.0)
	No	14 (46.7)	16 (53.3)	30 (100.0)
Total		15 (42.9)	20 (57.1)	35 (100.0)

Vitamin deficiency

Vitamin deficiency has been shown to cause neurological symptoms such as pelvic and shoulder muscle weakness, fatigue, skeletal muscle pain, atrophy, muscle cramps, loss of muscle strength, muscle tetany, and impaired balance and movement mimicking ataxia[35,36]. It was found that 30 (86%) patients who were diagnosed late received many vitamin deficiency treatments, especially vitamin D and B vitamins, at different times for their current complaints. In laboratory evaluation, some vitamins were low in all patients, but there were no findings that would mimic the SMIC clinic during the examination. In conclusion, although the treatment did not pose a risk for the patient, it caused a delay in diagnosis.

Conclusion

SMICs are heterogeneous, have no specific owner due to a lack of information about them, and have been referred to as orphan diseases. Inherited SMICs are a group of early-life diseases that are rarely seen and diagnosed under physical and neurological evaluation, laboratory tests, EMG, biopsy, and genetic guidance. International bodies have been unable to define criteria to facilitate diagnosis and treatment because the disease is so different. Despite these difficulties, scientific training, intensive research, advances in gene analysis, inventions in medical technology, and increased awareness have made it easier to reach the correct diagnosis in parallel. Frequent review of the patient in combining the initial and final values will help to reach the truth. Going to the first diagnosis that comes to mind with 1 or 2 symptoms reported by the patient does not permanently repair the damage caused by the wrong diagnosis. During the process, the patient may take many medications and experience emotional exhaustion. This can lead to physical, mental, emotional, social, and economic losses. Considering the prevalence of SMIC included in this study and the prevalence of misdiagnosed diseases, there is a significant rate.

As a result, the majority of SMIC patients are misdiagnosed, different diagnoses are made according to the ageing process, and training specialized health cadres in this field can lead to earlier diagnosis.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of Humans and Animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the Institutional Ethics Committee.

Confidentiality, Informed Consent, and Ethical Approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the Use of Artificial Intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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