Case Report

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Isaacs Syndrome in A Patient with Positive CASPR2 And LGI1 Antibodies: A Case Report and Literature Review

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ABSTRACT

Isaacs Syndrome (IS) is an autoimmune disease characterized by fasciculations, dysautonomia, and hyperactivity of muscle fibers due to hyperexcitability of the peripheral nerve system. Patients with IS often express voltage-gated potassium channels (VGKCs), contactin-associated protein 2 (CASPR2), and leucine-rich glioma-inactivated protein (LGI1) antibodies. Slower rates of grouped fasciculation, known as myokymia, are a common presentation in IS patients. Recently, carbamazepine has been considered as the first-line treatment to alleviate the symptoms of IS patients. In this report, the authors present a case of a female patient with ramps and unintended movements in the abdomen and both lower limbs. She was diagnosed with IS after the detection of myokymia in the needle electromyography (EMG) and a positive paraneoplastic panel for CASPR2 and LGI antibodies. The patient is now symptom-free due to the administration of Carbamazepine, Gabapentin, and Baclofen. Additionally, due to her potential risk for solid tumors, she is under regular follow-up.

Introduction

Isaacs Syndrome (IS) is an autoimmune disease caused by hyperexcitability of the peripheral nerve system [1]. Alongside autoimmunity, paraneoplastic disorders, genetic predisposition, and toxin exposure are considered as other causes of IS. IS predominantly affects males with a prevalence of 67% and a median age of 55 years old [2]. Patients with IS may present with continuous activity of muscle fiber, muscle hypertrophy, fasciculations, dysautonomia, and even paresthesia and sleep disorders [3,4]. Other symptoms can include constipation, pseudo-obstruction of the intestine, and lower urinary tract problems [5,6]. Previous studies have shown that this syndrome can accompany other disorders such as ALS and hypoparathyroidism [7,8]. Morvan syndrome can also affect muscle contraction, however, unlike IS, it has characteristic neuropsychiatric involvements [9].

It is reported that 45-50% of patients with IS show voltage-gated potassium channels (VGKCs) antibodies

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which affect contactin-associated protein 2 (CASPR2), leucine-rich glioma-inactivated protein (LGI1), and contactin-2 [1,10,11]. Among the mentioned proteins, CASPR2 is considered as the most involved one in IS [12]. These proteins are mostly found in several parts of the CNS such as the hypothalamus, locus coeruleus, and thalamus which can better explain some symptoms such as insomnia in IS patients [12]. Also, the involvement of locus coeruleus as a norepinephrine producer can be the cause of dysautonomia in these patients. In addition, hippocampus impairments in these patients can disrupt the process of memory formation in IS patients [13]. It is shown that 21-25% of IS patients present with malignancies suggesting that IS is correlated with paraneoplastic syndromes [10].

As mentioned above, fasciculation is a common symptom in IS patients. Myokymia is a kind of grouped fasciculation which presents at slower rates and can be seen on the skin's surface [14]. However, neuromyotonic patients reflect faster rates of grouped fasciculations [15]. There is no absolute cure for this syndrome according to the National Institute of Neurological Disorders and Stroke [16]. However, recent studies suggested carbamazepine as the first-line treatment to alleviate symptoms of IS patients with phenytoin and gabapentin as the second line [14]. Moreover, the aforementioned medications are shown to be effective in this syndrome: acetazolamide, lamotrigine, and clonazepam [14].

In this study, the authors are going to present a female with an IS diagnosis who was positive for CASPR2 reflecting a high possibility for solid tumors in terms of paraneoplastic syndrome, especially for thymoma.

Case presentation

A 32-year-old female presented with pain, cramps, and unintended movements in the abdomen and both lower limbs. These movements were progressive and evoked pregnancy in the patient. With 14 days of the mentioned symptoms, psychological disorders were diagnosed for the patient. With continuous pain and unintended movements, the patient was referred to the Kosar hospital of Sanandaj. In the physical examination, she reflected normal MMSE and intact cranial nerves. However, in the motor examination, undulating movements were seen in the lower limbs, especially in leg muscles, as well as anterior abdomen muscles. There were no signs of atrophy in the upper and lower limbs. Moreover, no abnormalities were reported in the sensory examination. Also, the tendon reflex was normal for the patient. The patient was complaining of progressive cramps in the lower limbs, making difficulties in her gait process. Due to fasciculation and myokymia, electromyography was ordered for the patient. In the needle EMG, there was evidence of fasciculation, myokymia, and myotonia suggesting hyperexcitability in motor fibers. 125g IVIG and 3 g corticosteroid pulse were administered as the primary treatment for the patient. With the primary diagnosis of IS, a paraneoplastic panel was checked for the patient which reported the aforementioned results: Glutamate receptor (NMDA type): negative, Glutamate receptor (AMPAR1/2 type): negative, GABARB1/B2: negative, Dipeptidyl Aminopeptidase-like protein6: negative, Anti-Hippocampus reactivity: negative, Anti-cerebellum: negative, Voltage-Gated Potassium channel Ab: negative, CASPR2: 1/32 (positive), LGI1: 1/10 (positive) (Table 1). Based on positive CASPR2, IS was diagnosed for this patient. Since CASPR2 was positive for the patient, she was evaluated for possible solid tumors in the chest and abdomen by CT scan and MRI, especially in terms of thymoma, revealing no abnormalities. For now, the patient is under follow-up for potential solid tumors every six months by total monitoring. The patient receives Carbamazepine 200 mg every eight hours, Gabapentin 150 mg every eight hours, and Baclofen 10 mg every 12 hours which were successful in the alleviation of myokymia, cramps, and muscle twitching, and she is symptom-free on this regimen.

Table 1. The result of the paraneoplastic panel

Antibodies	Result
Glutamate receptor (NMDA type)	Negative
Glutamate receptor (AMPAR1/2 type)	Negative
GABARB1/B2	Negative
Dipeptidyl Aminopeptidase-like protein6	Negative
Anti-Hippocampus reactivity	Negative
Anti-cerebellum	Negative
Voltage-Gated Potassium channel Ab	Negative
CASPR2	1/32 (positive)
LGI1	1/10 (positive)

Discussion

IS was first described by Hyam Isaacs through symptoms such as muscle twitching and stiffness in needle EMG [17]. It is more common in males than in females [18]. Patients with IS reflect muscle cramping and fasciculation, especially during voluntary contraction which can be similar to stiff person syndrome [32]. The severity of these symptoms highly depends on several factors like immune function, genetics, and sensitivity level of CNS [19]. Moreover, some chemical materials including lead, silver, and penicillamine are shown to affect these symptoms [20, 21]. EMG, especially the needle EMG, is known as the most useful method in the detection of IS symptoms including neuromyotonic discharges and myokymia [22,23]. Mentioned symptoms were reported in the needle EMG of our case.

CASPR2 is a kind of neurotoxin that can be expressed in both central and peripheral nervous system neurons [24]. This transmembrane protein is involved in the localization of voltage-gated potassium channel (VGKC) complex and maintenance of the axon stability through facilitating K channel accumulation [25]. The appearance of CASPR2 in the blood increases the risk of CNS involvement and symptoms such as insomnia [26]. Antibodies against CASPR2 can cause autoimmune disease with different symptoms including movement disorders, psychosis, and paraneoplastic syndromes such as thymoma [27]. Alongside IS, CASPR2 is associated with Morvan syndrome which can be presented with encephalopathy and hallucinations distinguishing it from IS [14]. The patient in our study didn't reveal any symptoms resulting from LGI1 antibodies such as cognitive dysfunction, limbic encephalitis, and seizures [28].

Table 2. CASPR2 antibody status in patients with IS

References	Number of patients	Symptoms	CASP2 antibody status	LGI1 antibody status
Patel et al. 2023	N=1	Decrease in his routine activities and ambulation difficulties associated with weakness and cramping	-	-
Rebello et al. 2022	N=1	fatigue, low back ache, and dragging sensation in both his lower limbs	Positive	-
Surana et al. 2019	N=3	Case1: muscle twitching in his legs; pain in his lower back, gluteal muscles, and posterior thigh muscles; and cramps Case2: leg weakness and twitching and a diarrhea, and cramps Case3: leg pain and the inability to walk short distances without a wheelchair	All of cases were positive	All of cases were positive
Samogalskyi et al. 2021	N=1	pain and muscle stiffness in both calves	Positive	Positive
Fleisher et al. 2013	N=1	muscle twitching and weight loss	Positive	Positive

Table 3. IS associated paraneoplastic syndromes

Studies	Malignancies	CASPR2 antibody status
Walsh et al. 1976	Small-cell lung cancer	-
Partanen et al. 1960	Small-cell lung cancer	-
Li et al. 2022	Thymoma	Positive
Viallard et al. 2005	Thymoma	-
García-Merino et al. 1991	Thymoma	-
Perini et al. 1994	Thymoma	-
Tsivgoulis et al. 2014	Thymoma	Positive
Paul et al. 2010	Thymoma	Positive
Caress et al. 1997	Hodgkin's lymphoma	-
Zifko et al. 1994	Plasmacytoma with IgM paraproteinemia	-
Issa et al. 2011	Ovarian cancer	Positive
Forte et al. 2009	Bladder cancer	-
Rana et al. 2012	Thymoma, lymphoplasmacytic lymphoma, and hemangioblastoma	-

Several cases of IS were reported in relation to CASPR2 antibody (Table 3) [13]. Rebello et al. in their case report explained a patient with myokymia and pulling sensation in his lower limbs who was diagnosed as IS by finding CASPR2 antibodies in his blood sample [29]. Surana et al. reported three patients with CASPR2 positive revealing a correlation between these antibodies and acute-onset myokymia especially in the lower limbs [30]. Samogalskyi et al. reported a CASPR2 and LGI1 positive patient who presented with neuromyotonia in gastrocnemius muscles reflecting a significant response to high-dose steroids [31]. Fleisher et al. in their study presented an old man with myasthenia gravis accompanied by neuromyotonia who was positive for CASPR2 and LGI1 [32]. The case of our study was positive for both LGI1 and CASPR2.

The existence of CASPR2 antibodies in the blood of IS patients increases the risk of paraneoplastic syndrome in these patients increasing the risk of other cancers [33,34,35]. Walsh et al. and Partanen et al. in their studies reported the coexistence of IS and small-cell carcinoma of the lung [36,37]. Also, some studies reported IS patients suffering from thymoma [3, 5, 38-41]. Moreover, cases of Hodgkin's lymphoma [42], plasmacytoma with IgM paraproteinemia [43], ovarian cancer [44], bladder cancer [45], and lymphoplasmacytic lymphoma and hemangioblastoma were reported in previous studies (Table 3) [46]. The patient of our study didn't reflect paraneoplastic syndrome in the complete evaluation including imaging methods.

Several studies have reported possible treatments for CASPR2-positive IS patients. Song et al. reported three IS cases with positive CASPR2. One of these patients was a 43-year-old female complaining of cramps and twitching and she was positive for CASPR2 antibody. This patient was controlled by methylprednisolone. The second patient was a 25-year-old male with additional symptoms including trunk and limb stiffness alongside myokymia of both lower and upper limbs. This patient didn't respond to methylprednisolone and thus double filtration plasmapheresis (DFPP) was administered to him. This plasma exchange method was shown to be effective in IS patients [47]. After three times of DFPP, the patient was CASP2 free with alleviated IS symptoms. The third patient of this study was a 46-year-old man presenting with limb and trunk myokymia and a past medical history of thymoma, myasthenia gravis (MG), and pure red cell aplasia (PRCA). He was strongly positive for CASPR2 (++++) in the examination. This patient showed no significant response to DFPP and thus was treated with intravenous rituximab [48]. Li et al. in their study reported a male patient with IS symptoms who was also positive for CASP2 and LGI1. In this report, IS was accompanied by thymoma type B2 and the patient was controlled through administration of concurrent chemoradiotherapy (CCRT) and high dose steroid [3]. The effectiveness of immune system-targeted therapies in CASPR2-positive IS patients was also reported by other studies [49]. Horiuchi et al. in their study reported an IS patient with neuromyotonia in his left leg who was positive for CASPR2 and LGI1 antibodies. This study showed that unlike methylprednisolone (IVMP), intravenous immunoglobulin (IVIg), and DFPP, rituximab can provide a long-term response in these patients [50]. The case in this study showed a significant response to IVIG and corton pulse therapy followed by Carbamazepine, gabapentin, and baclofen.

In summary, the authors reported a patient with IS who was positive for CASPR2 and LGI1 antibodies which are reliable biomarkers in the diagnosis of IS. The patient is symptom-free by administrating a combination of carbamazepine, gabapentin, and baclofen. Due to the given information, the presence of CASPR2 antibodies can be a strong predictor of paraneoplastic syndrome incidence, especially thymoma in this patient. Thus, the patient is under regular follow-up for potential solid tumors. However, more clinical trial studies are needed to shed light on the absolute and long-term treatments for IS patients to prevent its improvement and further consequences especially paraneoplastic syndromes.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

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Conflict of Interests

The authors have no conflict of interest to declare.

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