

# Isaacs' syndrome: Clinical and paraclinical perspectives in a series of cases

Received: 06 Sep. 2023  
Accepted: 09 Nov. 2023

Payam Sarraf<sup>1,2</sup>, Mahan Shafie<sup>1,2,3</sup>, Ghasem Farahmand<sup>1,2</sup>, Mahsa Mayeli<sup>1,2,3</sup>, Mojtaba Shahbazi<sup>1,2</sup>, Hana Magrouni<sup>1,2</sup>, Melika Jameie<sup>1</sup>, Babak Ghelichnia Emrani<sup>1,2</sup>, Maryam Rashidi-Jazani<sup>1,2</sup>

<sup>1</sup> Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran

<sup>2</sup> Neuromuscular Department, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

<sup>3</sup> School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

## Keywords

Isaacs' Syndrome; Neuromyotonia; Paraneoplastic Syndromes; Neuromuscular Disorder

## Abstract

**Background:** Isaacs' syndrome is a form of generalized peripheral nerve hyperexcitability (PNH) causing increased and continuous muscle activity characterized by muscle twitching, stiffness, cramps, myokymia, and pseudomyotonia. Herein, we aimed to review the clinical and paraclinical aspects of Isaacs' syndrome in a number of cases.

**Methods:** We reported a series of 12 patients with Isaacs' syndrome, including their clinical features, electrophysiological findings, laboratory parameters, malignancy work-up, and therapeutic management.

**Results:** In all cases, clinical and electrodiagnostic assessment was suggestive of Isaacs' syndrome. Of the 12 studied cases, 5 patients were positive for both leucine-rich glioma inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) antibodies, 5 patients were CASPR2 positive and LGI1 negative, and 1 had borderline positive titers for CASPR2 with

negative LGI1 antibody. The search for underlying malignancies was inconclusive in all subjects. After symptomatic treatment, mostly with carbamazepine or gabapentin, immunotherapies with double filtration plasmapheresis or Intravenous immunoglobulin (IVIG) provided favorable outcomes. Ultimately, all subjects fully recovered after 3-6 months of follow-up and all signs and symptoms resolved.

**Conclusion:** Despite the rarity of the disease, our results provide valuable information for understanding the epidemiological, clinical, and paraclinical features of Isaacs' syndrome.

## Introduction

Isaacs' syndrome is a form of generalized peripheral nerve hyperexcitability (PNH) characterized by increased and continuous muscle activity.<sup>1</sup>

**How to cite this article:** Sarraf P, Shafie M, Farahmand G, Mayeli M, Shahbazi M, Magrouni H, et al. Isaacs' syndrome: Clinical and paraclinical perspectives in a series of cases. *Curr J Neurol* 2024; 23(1): 1-14.

Muscle twitching, stiffness, cramps, myokymia, and pseudomyotonia are the main clinical symptoms, and sensory complaints including pain and paresthesia are also reported. Delayed relaxation of muscle voluntary contraction such as handgrip and eye closure, referred to as pseudomyotonia, has been reported in about one-third of patients, and muscle weakness might also be experienced by affected patients. Muscle hypertrophy, mainly calf muscles, may usually be experienced due to continuous muscle activity.<sup>2</sup> Weight loss and signs of autonomic disturbance including hyperhidrosis, tachycardia, and diarrhea are also associated with this disorder.<sup>2</sup> The presence of encephalopathy manifesting as confusion, hallucinations, agitation, and insomnia alongside neuromyotonia and hyperhidrosis is considered Morvan's syndrome in PNH group disorders.<sup>3</sup>

Dysfunction of voltage-gated potassium channels (VGKCs)-complex proteins is the main cause of Isaacs' syndrome pathophysiology, which could be associated with a genetic basis or acquired factors.<sup>4</sup> Antibodies against VGKC-complex have been identified to be associated with the acquired forms, and contactin-associated protein-like 2 (CASPR2) and leucine-rich glioma inactivated 1 (LGI1) are considered to be the two main VGKC complex targets.<sup>5</sup> Isaacs' syndrome can occur as a paraneoplastic syndrome in various hematologic and non-hematologic malignancies, mainly thymoma and small cell lung cancer, as well as with autoimmune disorders such as myasthenia gravis, Hashimoto's thyroiditis, pernicious anemia, celiac disease, and rheumatoid arthritis.<sup>2,6</sup> An inherited form of the disease, associated with KCNA1, KCNA2, KCNA6, KCNQ2, and potassium channel gene mutations, has also been described.<sup>7</sup>

On electrodiagnostic investigations, nerve conduction studies (NCS) are usually normal, except after discharges on motor NCS and late response. Electromyography (EMG) however, reveals various spontaneous discharges including fasciculation and fibrillation potentials, myokymic discharges, and neuromyotonic discharges.<sup>2,8</sup> The origin of involuntary activity is considered to be one or more segments of the peripheral motor axon which could be eliminated by neuromuscular blocking agents, but not general anesthesia. All these may occur spontaneously or be triggered by muscle contraction.<sup>9</sup> Management usually consists of treatment of underlying malignancy or associated autoimmune disorder if detected, symptomatic therapy, and immunomodulation

therapy with intravenous immunoglobulin (IVIG) and plasma exchange. Maintenance therapy with an immunosuppressive drug is also recommended.<sup>2,8</sup>

Herein, we have presented 12 patients with symptoms suggestive of PNH who were referred to our center and were treated with the diagnosis of Isaacs' syndrome within the past 3 years. The patients' demographic characteristics, symptoms, signs, laboratory parameters, and EMG findings, and malignancy work-up have been presented.

## Materials and Methods

The study was approved by the Institutional Review Board at Tehran University of Medical Sciences, Iran. The protocol of this study corresponded to the 2013 Helsinki Declaration. All participants provided a written informed consent and were considered anonymously, and all data was registered confidentially with no personal information. The study consisted of all patients with confirmed Isaacs' syndrome diagnosis, who were referred to our neuromuscular clinic within the past 3 years from March 2020 to September 2022. The diagnosis was made by expert neuromuscular specialists based on clinical presentation and EMG.

Data were collected retrospectively from the hospital medical records. Demographic data consisted of age, gender, past medical history (autoimmune, connective tissue, malignancy, neurodegenerative, and other disorders), drug history, and family history. Clinical variables included age of diagnosis, onset of symptoms, clinical manifestations, and neurological physical examination. Laboratory data, imaging findings, and electrodiagnosis data were also extracted. In-hospital and maintenance treatments and medications received by patients, and outcomes after 3 months to 3 years of follow-up were also obtained.

## Results

Clinical features of the 12 patients, who presented with Isaacs' syndrome during the study period, are detailed in table 1. Their mean age was  $32.75 \pm 11.21$  years, ranging from 21 to 63 years. Moreover, 10 patients (83%) were women. The median time from the onset of symptoms to diagnosis was 2.3 months.

One of the patients had a history of hypothyroidism and one of them reported a history of epileptic seizures.

**Table 1.** Part I: Demographics, clinical manifestations, and physical examination

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
<b>Demographics and clinical characteristics</b>						
Sex	F	F	F	F	M	M
Time from symptoms to diagnosis	2 weeks	2 months	4 months	40 days	2 years	2 months
Age at diagnosis	21	23	24	26	63	45
Past medical history (Autoimmune/connective tissue/malignancy/neurodegenerative/etc.)	-	-	-	-	Laminectomy, seizure, HTN	Nephrolithiasis, COVID-19, UTI
Drug history	Gabapentin, Carbamazepine, Baclofen	Gabapentin, Carbamazepine	Pregabalin, Pramipexole, Clonazepam	Gabapentin	Valsartan, Lamotrigine, Amlodipine	Gabapentin, Acetaminophen, Clindamycin
Family history	-	-	-	-	MS in daughter	Malignancy
<b>Clinical manifestations</b>						
Primary affected muscles (Chief complaint)	Back and LL (P = D)	Back and LL (P = D)	LL (P = D)	Back and LL (P = D)	LL pain (D > P)	UL and LL (LL > UL, P > D)
Other affected muscles	UL	UL	UL	UL, lips, tongue	UL	-
Rippling sensation	+	+	+	+	+	+
Pain	+	+	+	+	+	+
Stiffness	+	+	+	-	+	+
Muscle cramps	-	-	-	-	+	+
Fatigability	+	-	+	-	+	+
Exercise intolerance	+	+	+	+	+	+
Muscle twitching	+ (P = D)	+ LL (P = D)	+ (P = D)	+ (P = D)	+ LL (P)	+ LL (P = D)
Muscle weakness	-	-	-	-	-	-
Paresthesia	+ LL (D)	+ LL (D)	+ LL (D)	-	+ LL > UL (D)	+ LL > UL (D)
Wight loss	-	-	-	-	+	+
Fever	-	-	-	-	-	+ (Concomitant UTI)
Hyperhidrosis	-	-	-	-	-	+
Bulbar symptoms	-	-	-	-	-	-
Sphincter involvement	-	-	-	-	-	-
Autonomic symptoms	-	-	-	-	-	+
<b>Physical examination</b>						
Cranial nerves	NL	NL	NL	NL	NL	NL
<b>Muscle force</b>						
Upper proximal	5	5	5	5	5	5
Upper distal	5	5	5	5	5	5
Lower proximal	5	5	5	5	5	5
Lower distal	5	5	5	5	5	5
Rigidity	-	-	-	-	-	-

**Table 1.** Part I: Demographics, clinical manifestations, and physical examination (continue)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Muscle hypertrophy (Calf, etc.)	-	-	-	-	-	+ (calf hypertrophy)
Fasciculation	+ (LL dominant)	+ (LL dominant)	+ (LL dominant)	+ (Widespread, hands, lips)	+ (Widespread)	+ (LL and UL)
Myokymia	+ (LL dominant)	+ (LL dominant)	+ (LL dominant)	+ (LL dominant)	+ (Widespread)	+ (LL dominant)
Sensory examination	NL	NL	NL	NL	NL	NL
<b>DTR</b>						
Upper	3+	2+	3+	3+	1+	0
Lower	3+	2+	2+	3+	0	0
Plantar reflexes	Down	Down	Down	Down	Down	Down
Coordination	HTS: impaired	NL	NL	NL	NL	NL
Gait	Unsteadiness	Slight unsteadiness	NL	NL	NL	NL

**Table 1.** Part II: Demographics, clinical manifestations, and physical examination

	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12
<b>Demographics and clinical characteristics</b>						
Sex	F	F	F	F	F	F
Time from symptoms to diagnosis	2 months	3 months	1 month	40 days	3 months	5 months
Age at diagnosis	30	27	37	34	28	35
Past medical history (Autoimmune/ connective tissue/ malignancy/ neurodegenerative/ etc.)	Hypothyroidism	-	-	-	COVID-19 vaccination (2 weeks before)	Raynaud phenomenon just before neurologic symptoms
Drug history	Levothyroxine, Baclofen, Gabapentin	Gabapentin, Carbamazepine, Duloxetine, Doxepin	-	Baclofen, Pregabalin	-	-
Family history	-	-	-	-	-	-
<b>Clinical manifestations</b>						
Primary affected muscles (Chief complaint)	LL (P = D)	LL (P = D)	Back and LL (P = D)	Back and LL (P = D)	Back and LL (P = D)	Back and LL (P = D)
Other affected muscles	UL (P)	UL, face	UL, face, abdomen	LL, UL, tongue	-	UL
Rippling sensation	+	+	+	+	+	+
Pain	+	+	+	+	+	+
Stiffness	+	+	+	+	-	+
Muscle cramps	-	+	+	+	+	+
Fatigability	-	-	-	+	-	+
Exercise intolerance	+	-	-	+	+	+
Muscle twitching	+ (P = D)	+ (P = D)	+ (P = D)	+ LL (P = D)	+ (P = D)	+ (P = D)
Muscle weakness	-	-	-	-	-	-

**Table 1.** Part II: Demographics, clinical manifestations, and physical examination (continue)

	<b>Case 7</b>	<b>Case 8</b>	<b>Case 9</b>	<b>Case 10</b>	<b>Case 11</b>	<b>Case 12</b>
Paresthesia	+ (LL > UL)	+(L = U)	-	+ (LL > tongue)	-	+ (LL)
	D	D				D
Wight loss	-	+	+	-	-	+
Fever	-	+	+	-	-	+
Hyperhidrosis	-	-	-	-	-	-
Bulbar symptoms	+	+	-	+	+	+
Sphincter involvement	-	-	-	-	-	-
Autonomic symptoms	-	-	-	-	-	-
<b>Physical examination</b>						
Cranial nerves	NL	NL	NL	NL	NL	NL
<b>Muscle force</b>	5	5	5	5	5	5
Upper proximal	5	5	5	5	5	5
Upper distal	5	5	5	5	5	5
Lower proximal						
Lower distal	5	5	5	5	5	5
Rigidity	-	-	-	-	-	-
Muscle hypertrophy (Calf, etc.)	-	-	-	+ (calf hypertrophy)	-	-
Fasciculation	+ (LL dominant)	+ (LL dominant)	+ (LL dominant)	+ (LL dominant)	+ (LL dominant)	+ (LL dominant)
Myokymia	+ (LL dominant)	+ (LL dominant)	+ (LL dominant)	+ (LL dominant)	+ (LL dominant)	+ (LL dominant)
Sensory examination	NL	NL	NL	NL	NL	NL
<b>DTR</b>						
Upper	1+	2+	2+	2+	+2	+2
Lower	1+	2+	2+	2+	+2	+2
Plantar reflexes	Down	Down	Down	Down	Down	Down
Coordination	NL	NL	NL	NL	NL	NL
Gait	NL	NL	NL	NL	NL	NL

HTN: Hypertension; UTI: Urinary tract infection; MS: Multiple sclerosis; NL: Normal; HTS: Heel to shin examination; LL: Lower limb; UL: Upper limb; P: Proximal; D: Distal

One of the patients had experienced Raynaud's phenomenon just before the occurrence of neurologic symptoms and another had received the coronavirus disease 2019 (COVID-19) vaccine [Sinopharm (Vero Cell)] 2 weeks prior to the onset of symptoms. Drugs used for symptom relief before admission were gabapentin (50%), carbamazepine (25%), baclofen (25%), pregabalin (16%), pramipexole (8%), clonazepam (8%), duloxetine (8%), and doxepin (8%). However, 4 of the patients had not received any medications. Additionally, patients' family histories were insignificant except for 2 patients with a family history of malignancy and multiple sclerosis (MS) in a first-degree relative.

The most common symptoms were rippling sensation, pain, and muscle twitches, which were reported in all of the studied patients. Other symptoms including stiffness/spasm (83%), exercise intolerance (83%), and paresthesia of lower limbs (75%) were also reported. Muscle twitches were seen mostly in the distal and proximal muscles of the lower extremities. Other clinical presentations included muscle cramps (58%), fatigability (50%), hyperhidrosis (50%), autonomic symptoms (50%), and weight loss (42%). None of the patients experienced weakness and none had bulbar or sphincter involvement. Initially affected muscles were mainly lower extremities in all patients and paraspinal muscles in 58% of the patients. On neurological examination, the most common abnormal findings were fasciculation and myokymia which were presented in all cases. Furthermore, 2 patients had an unsteady gait, 3 subjects (25%) had diminished deep tendon reflex (DTR), and 2 (16%) had calf hypertrophy.

Table 2 shows the laboratory and imaging findings, as well as malignancy work-up for each subject. The level of creatine kinase (CK) and thyroid function were within the normal range for all patients. Antinuclear antibody (ANA), rheumatoid factor (RF), anti-double-stranded DNA (anti-dsDNA) antibody, and antineutrophil cytoplasmic antibodies (ANCA) were negative in all patients. The autoimmune and paraneoplastic panels were determined for all patients; 5 patients (42%) were positive for both LGI1 and CASPR2 antibodies. Additionally, 5 patients were CASPR2 positive and LGI1 negative, and 1 had borderline positive titers for CASPR2 with negative LGI1 antibody. Only 1 case was negative for CASPR2 and LGI1; however, further evaluation illustrated that he had an elevated titer of anti-VGKC complex antibody. The patient with borderline CASPR2

antibody was also positive for the anti-Yo antibody. The search for underlying malignancies was performed using whole-body positron emission tomography (PET) scan, which was inconclusive in all subjects. Only 1 patient had reactive lymph nodes in the para-aortic and right renal pelvis, splenomegaly, and a lytic lesion in the right ischium in abdominopelvic computed tomography (CT), which was suggestive of possible metastasis. The patient also reported a family history of malignancy and no antibody was found during the investigation of his serum. Further investigations reported hypercellularity with reactive change in bone marrow flow cytometry. In spite of these findings, no evidence of malignancy was detected even after repetitive follow-up during 3 years of monitoring for this patient.

Table 3 reports electrodiagnostic and needle examination findings. All EMG-NCV results were suggestive of Isaacs' syndrome. The most common finding in NCS was after discharge in F response especially in both lower limbs in all cases. Other examinations were within normal limits. All patients had fasciculation, myokymia, and neuromyotonia during the needle examination.

Treatments and medications received by each subject during and after hospitalization are reported in table 4. The most prescribed drugs for symptom relief were gabapentin (75%) and carbamazepine (66%). Half of the patients received plasmapheresis (mean = 7 times) and the other half received IVIG (mean dose = 142.5 g). All were prescribed immunosuppressant with prednisolone and azathioprine after discharge. In the 3-to-6-month follow-up sessions, all of the studied patients yielded a remarkable recovery and response to the immunotherapy, and all symptoms and signs including myokymia and twitching resolved. Patients were monitored for up to 3 years following the initial visit. No relapse was observed in patients after tapering the medications within the follow-up period.

## Discussion

Herein, we have presented 12 cases of PNH with the final diagnosis of Isaacs' syndrome. As the syndrome is relatively uncommon, there are heterogeneous findings from an epidemiological aspect. According to existing literature, the reported cases of paraneoplastic Isaac's syndrome are quite limited.<sup>8,10-16</sup> Furthermore, a few studies have documented cases of Isaac's syndrome linked to autoimmune disorders, infections, vaccines, and exposure to metallic toxins.<sup>17-21</sup>

**Table 2.** Part I: Frequency distribution of deleted exons in patients with dystrophinopathy

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
<b>Laboratory</b>						
CK	NL	NL	NL	NL	NL	NL
TSH	NL	NL	NL	NL	NL	NL
ESR	NL	NL	NL	NL	NL	NL
CRP	NL	NL	NL	NL	NL	NL
ANA	-	-	-	-	-	-
RF	-	-	-	-	-	-
Anti-dsDNA	-	-	-	-	-	-
ANCA	-	-	-	-	-	-
<b>Autoimmune panel</b>						
Anti-VGKC complex Abs (pmol/l) (Potassium channel-complex) (< 85:NL)	N/A	290.1 (Elevated)	N/A	N/A	N/A	N/A
NMDA	-	-	-	-	-	-
LGI1 Abs	+	-	-	-	-	-
CASPR2 Abs	+	-	Borderline	+	+	+
Glutamate receptor 1 (AMPA1)	-	-	-	-	-	-
Glutamate receptor 2 (AMPA2)	+	+	+	+	+	+
GABA receptors 1, 2	+	+	+	+	+	+
DPPX	+	+	+	+	+	+
<b>Underlying malignancy work-up</b>						
Paraneoplastic panel (Ampiphysin, PNMA2/Anti CRMP5/Ri- ANNA-2/Yo-PCA-1/Hu-ANNA- 1/recoverin/AGNA/titin/ Zic4/GAD 65/PCA-Tr)	-	-	Yo-PCA-1: + (2+) Other: -	-	-	-
Pelvic examination		NL				
Pap-smear				NL		
Chest CT	NL	NL	NL	NL	NL	NL
Thymoma	No	No	No	No	No	No
Abdominal CT	Liver hemangioma, uterus myoma	NL	NL	NL	NL	Axillary lymph node, reactive lymph node in para-aortic and right renal pelvis, splenomegaly, 3 hepatic cysts, no adenopathy Lytic lesion in the right ischium possible of metastasis
Pelvic CT	NL	NL	NL	NL	NL	
Abdominopelvic sonography	N/A	NL	N/A	NL	NL	N/A
Mammogram	NL	N/A	N/A	N/A	NL	NL
Breast sonography		BIRADS 2	BIRADS 1	BIRADS 1	N/A	N/A
Whole-body PET	N/A	N/A	NL	N/A	NL	NL
Bone scan	N/A	N/A	N/A	N/A	N/A	-
Other	Lumbosacral MRI: NL	Lumbosacral MRI: NL	Lumbosacral MRI: NL	Lumbosacral MRI: NL	Lumbosacral MRI: NL	Bone marrow flow cytometry: hypercellular with reactive change



**Table 2.** Part II: Frequency distribution of deleted exons in patients with dystrophinopathy

	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12
<b>Laboratory</b>						
CK	NL	NL	NL	NL	NL	NL
TSH	NL	NL	NL	NL	NL	NL
ESR	NL	NL	NL	NL	NL	NL
CRP	NL	NL	NL	NL	NL	NL
ANA	-	-	-	-	-	-
RF	-	-	-	-	-	-
Anti-dsDNA	-	-	-	-	-	-
ANCA	-	-	-	-	-	-
<b>Autoimmune panel</b>						
Anti-VGKC complex Abs (pmol/l) (Potassium channel-complex) (< 85:NL)	N/A	N/A	N/A	N/A	N/A	N/A
NMDA	-	-	-	-	-	-
LGI1 Abs	-	+	+	+	+	-
CASPR2 Abs	+	+	+	+	+	+
Glutamate receptor 1 (AMPA1)	-	-	-	-	-	-
Glutamate receptor 2 (AMPA2)	+	+	+	+	+	+
GABA receptors 1, 2	+	+	+	+	+	+
DPPX	+	+	+	+	+	+
<b>Underlying malignancy work-up</b>						
Paraneoplastic panel						
(Ampiphysin, PNMA2/Anti CRMP5/Ri- ANNA-2/Yo-PCA-1/Hu-ANNA- 1/recoverin/AGNA/titin/ Zic4/GAD 65/PCA-Tr)	-	-	-	-	-	-
Pelvic examination						
Pap-smear						
Chest CT	NL except for thyroid lobes heterogeneity	NL	Emphysema	NL	NL	NL
Thymoma	No	No	No	No	No	No
Abdominal CT	NL except for umbilical hernia	NL	NL	NL	NL	NL
Pelvic CT	NL	NL	NL	NL	Bilateral ovaries are enlarged and heterogenic	NL
Abdominopelvic sonography	N/A	NL	N/A	NL	A homogenic and hypo-echoic lesion in right ovary in favor of hemorrhagic cyst or endometrium	N/A
Mammogram	N/A	N/A	NL	NL	NL	NL
Breast sonography	BIRADS 2 (Benign findings)	BIRADS 1	N/A	N/A	N/A	N/A



**Table 2.** Part II: Frequency distribution of deleted exons in patients with dystrophinopathy (continue)

	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12
Whole-body PET	N/A	N/A	N/A	N/A	N/A	N/A
Bone scan	N/A	N/A	N/A	N/A	N/A	N/A
Other	Lumbosacral MRI: disc protrusion,	Brain MRI: NL	Lumbosacral MRI: NL	Lumbosacral MRI: NL	Lumbosacral MRI: NL	Lumbosacral MRI: NL

CK: Creatine kinase; TSH: Thyroid-stimulating hormone; TFT: Thyroid function tests; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ANA: Antinuclear antibody; RF: Rheumatoid factor; dsDNA: double-stranded DNA; ANCA: Antineutrophil cytoplasmic antibodies; VGKC: Voltage-gated potassium channel; NMDA: N-methyl-D-aspartate; LGI1: Leucine-rich glioma inactivated-1; CASPR2: Contactin-associated protein-like 2; AMPA: Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA: Gamma-aminobutyric acid; DPPX: Dipeptidyl-peptidase-like protein-6; BI-RADS: Breast imaging-reporting and data system; NL: Normal; PET: Positron emission tomography; CT: Computed tomography; MRI: Magnetic resonance imaging; N/A: Not applicable

**Table 3.** Part I: Electrodiagnosis and needle examination results

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
<b>Electrodiagnosis</b>						
EMG-NCV	Hyperexcitability	Hyperexcitability	NL Hyperexcitability	Hyperexcitability	Hyperexcitability	Hyperexcitability
NCS (CMAPs, Snaps, CV)	NL	NL	NL	NL	NL	NL
F response (After-discharge)	+	+	+	+	+	+
MUAPS	NL	NL	NL	NL	NL	NL
<b>Needle examination</b>						
Myokymic discharges	+ (Especially in LL)	+ (Especially in LL)	+ (Especially in LL)	+ (Especially in LL)	+ (Especially in LL)	+ (Especially in LL)
Fasciculation	+ (Especially in LL)	+ (Especially in LL)	+ (Especially in LL)	+ (Especially in LL)	+ (Especially in LL)	+ (Especially in LL)
Neuromyotonia	+	+	+	+	+	+

**Table 3.** Part II: Electrodiagnosis and needle examination results

	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12
<b>Electrodiagnosis</b>						
EMG-NCV	Hyperexcitability	Hyperexcitability	Hyperexcitability	Hyperexcitability	Hyperexcitability	Hyperexcitability
NCS (CMAPs, Snaps, CV)	NL	NL	NL	NL	NL	NL
F response (After- discharge)	+	+	+	+	+	+
MUAPS	NL	NL	NL	NL	NL	NL
<b>Needle examination</b>						
Myokymic discharges	+ (Especially in LL)	+ (Especially in LL)	+ (Especially in LL)	+ (Especially in LL)	+ (Especially in thoracic paraspinal and LL)	+ (Especially in lumbar paraspinal and LL)
Fasciculation	+ (Especially in LL)	+ (Especially in LL)	+ (Especially in LL)	+ (Especially in LL)	+ (Especially in LL)	+ (Especially in LL)
Neuromyotonia	+	+	+	+	+	+

EMG-NCV: Electromyography nerve conduction velocity; NCS: Nerve conduction study; MUAPS: Motor unit action potential; NL: Normal; LL: Lower limb

**Table 4.** Part I: Treatments and medications

<b>Treatment</b>	<b>Case 1</b>	<b>Case 2</b>	<b>Case 3</b>	<b>Case 4</b>	<b>Case 5</b>	<b>Case 6</b>
Carbamazepine		+		+		+
Gabapentin	+	+		+		+
Pregabalin			+		+	
Clonazepam			+			
Pramipexole			+			
Prednisolone	+	+	+	+	+	+
Azathioprine	+	+	+	+	+	+
Plasmapheresis (Course)	+ (6)				+ (5)	+ (8)
IVIg		+ (135g)	+ (150gr)	+ (160g)		
Response to treatment (after 3-6 months follow-up)	Complete improvement	Complete improvement	Complete improvement	Complete improvement	Complete improvement	Complete improvement

**Table 4.** Part II: Treatments and medications

	<b>Case 7</b>	<b>Case 8</b>	<b>Case 9</b>	<b>Case 10</b>	<b>Case 11</b>	<b>Case 12</b>
Carbamazepine	+	+	+		+	+
Gabapentin	+	+	+		+	+
Pregabalin						
Clonazepam						
Pramipexole						
Prednisolone	+	+	+	+	+	+
Azathioprine	+	+	+	+	+	+
Plasmapheresis (Course)				+ (8)	+ (6)	+ (7)
IVIg	+ (140g)	+ (130g)	+ (140g)			
Response to treatment (after 3-6 months follow-up)	Complete improvement	Complete improvement	Complete improvement	Complete improvement	Complete improvement	Complete improvement

IVIg: Intravenous immunoglobulin

Overall, the prevalence is almost double in men compared to women, the mean age of onset is in the 40s, and the mean time from onset of symptoms to diagnosis is about 3 to 4 years.<sup>22</sup> Meanwhile, a large part of our sample were women, the mean age at the time of diagnosis was 32 years, and the average time from onset of symptoms to confirmed diagnosis was much lower, except for 1 patient with about 2 years from symptoms onset to diagnosis. This could be related to early referral to a neuromuscular specialist at our tertiary center, and also the limited number of subjects in previous studies.

A variety of muscle-related symptoms and signs is usually presented in Isaacs' syndrome. Muscle pain and cramps, which are usually worsened with voluntary movements, as well as widespread muscle twitching are typically the most common complaints. However, paresthesia and weakness are rarely reported. On the physical examination, generalized fasciculations and myokymia are indicated, while muscle forces, DTR, and sensory examination usually remain intact. Muscle hypertrophy due to continuous excitation of muscle is noted, specifically in the calf muscles.<sup>2</sup> A similar pattern of muscle involvement was observed among our studied sample.

The dysfunction of the VGKC complex is the main pathology observed in Isaacs' syndrome, in which the peripheral, autonomic, or central nervous system (CNS) could be affected and exhibit a spectrum of PNH.<sup>23</sup> Briefly, impairments in the VGKCs induce nerve excitability, which ultimately might result in repetitive neuron discharges, which is observed as the various mentioned muscle symptoms and signs in PNH syndromes.<sup>22</sup> Accordingly, an autoimmune basis, a paraneoplastic association, or a genetic disorder have been suggested as underlying etiologies of this syndrome.<sup>23</sup> Based on current evidence, antibodies against VGKC have been reported in approximately half of patients with Isaacs' syndrome, among which LGI1 and CASPR2 antibodies are the most replicated.<sup>24</sup> It is noteworthy that CASPR2 is more prevalent in the peripheral neurons and several patients could have two or more antibodies against the complex subunits.<sup>24,25</sup> However, in our study, anti-VGKC antibodies were found in all 12 patients, among whom 5 patients were positive for both anti-LGI1 and CASPR2 antibodies. There is also other evidence underpinning the autoimmune process of the syndrome. Previous studies have associated

Isaacs' syndrome with various autoimmune disorders such as myasthenia gravis, thymoma, Addison's disease, Hashimoto's thyroiditis, vitamin B12 deficiency, and celiac disease.<sup>17,25,26</sup> Studies have also estimated that 50% of VGKC antibody-positive subjects will demonstrate other positive antibodies such as acetylcholine receptor antibodies and anti-glutamic acid decarboxylase (anti-GAD) antibodies.<sup>22,26,27</sup> Additionally, vaccination and infection have also been reported as a trigger.<sup>18-20</sup> Among our subjects, 1 patient reported a history of recent COVID-19 and urinary tract infections, and another patient reported a recent COVID-19 vaccination, which could be related to the development of the disease.

Regarding the association with malignancies, as a part of a paraneoplastic condition, some studies have reported that about 16-25% of patients with PNH syndromes had neoplasms.<sup>5,22,28</sup> This is probably due to the cross-reaction of the VGKC complex with tumor antigens during an immune response.<sup>26</sup> Considering the level of antibodies against VGKC, it has been reported that borderline titers are more commonly found in patients with underlying neoplasms without known autoimmune bases.<sup>29</sup> Notably, 1 of our patients had borderline titer for the anti-CASPR2 antibody and was positive for the anti-Yo-PCA-1 antibody, which could be associated with a paraneoplastic condition. However, further comprehensive work-up for her was negative for any underlying malignancy. Moreover, although it has been reported that 40% of patients with double positive antibodies and 20% with anti-CASPR2 antibodies have a diagnosis of thymoma, none of our patients were so.<sup>30,31</sup> Additionally, 1 patient had evidence of suspicious underlying malignancy with reactive lymphadenopathy and lytic bone lesions; however, further repetitive work-up revealed no evidence of malignancy in this patient. Other patients all yielded negative results through malignancy work-up. These discrepancies between our findings and previous reports are probably the result of small sample sizes due to the extreme rarity of the disease. Ultimately, in addition to mutations in the histidine triad nucleotide-binding protein 1 (HINT1) gene,<sup>32</sup> some studies reported toxins-associated neuromyotonia including exposure to lead and silver.<sup>21</sup>

There are a number of differential diagnoses that are crucial to consider alongside Isaacs' syndrome in patients with symptoms of PNH. Morvan's syndrome is defined as encephalopathy

presented with headaches, drowsiness, and hallucinations in addition to findings of Isaacs' syndrome. Antibodies against VGKC and acetylcholine receptor is associated with this syndrome.<sup>3</sup> Similarly, limbic encephalitis manifested as memory loss, confusion, and seizures has also been reported, while these patients less commonly exhibit clinical or electrophysiological neuromyotonia.<sup>33</sup> Among our subjects, no symptoms of encephalopathy with underlying Morvan's syndrome or limbic encephalitis were observed. There are also some other syndromes with hyperexcitability, which share some similarities with Isaacs' syndrome. Cramp-fasciculation syndrome may show after-discharges on repetitive nerve stimulation and fasciculation potentials on needle examination, similar to Isaacs' syndrome, but without myokymic and neuromyotonic discharges, and VGKC antibodies.<sup>34</sup> Stiff-person syndrome is also characterized by repetitive motor excitation, because of GAD autoantibodies in the CNS. However, in this syndrome, NCS is normal without neuromyotonic and myokymic discharges.<sup>35</sup>

Laboratory assessments of underlying autoimmune or paraneoplastic conditions should be performed after the diagnosis of Isaacs' syndrome. The level of CK is not sensitive nor specific for Isaacs' syndrome, and it is usually normal to moderately high in most patients.<sup>36</sup> An autoimmune panel including antibodies against VGKC complex and specific antibodies for LGI1 and CASPR2 should be checked for underlying autoimmunity; however, in many cases, the targeted autoantigen is not known despite the detection of autoantibodies.<sup>2,36</sup> Additionally, a comprehensive investigation of paraneoplastic autoantibodies could be illustrative of an underlying neoplasm. Thoracic, abdominal, and pelvic CT, a pelvic examination, a pap smear and mammography, and an evaluation of prostate-specific antigen are recommended as parts of the malignancy work-up. Ultimately, a whole-body PET scan could be utilized if malignancy is suspected despite negative screenings.<sup>2</sup> In our population, all subjects were positive for at least one of the anti-VGKC, LGI1, and CASPR2 antibodies. Paraneoplastic screening showed one patient positive for anti-Yo-PCA-1. A malignancy work-up was thoroughly performed, which was negative for all patients. Genetic evaluation is not mandatory for Isaacs' syndrome and was not performed in the current study; however, future

studies could include these investigations.<sup>2</sup> Electrodiagnosis study on Isaacs' syndrome is usually normal except for after-discharge which has been reported to have 79% sensitivity and 88% specificity for diagnosis of PNH.<sup>37</sup> Needle examination of patients with the syndrome typically reveals myokymic and neuromyotonic discharges.<sup>38</sup> Electrodiagnosis and needle examination results of our studied patients were in line with these findings.

Management of Isaacs' syndrome comprises treatment of the underlying disorder, often malignancy, and symptomatic therapy. Studies have reported that the treatment of malignancies if identified, may slightly affect the clinical severity of the symptoms.<sup>26</sup> In symptomatic treatment, the use of carbamazepine as the first-line and phenytoin or gabapentin as the second-line medications is recommended. Carbamazepine is recommended as a first-line medication of symptomatic treatment with an initial dose of 400-600 mg per day in divided doses, which could be increased up to 1200 mg per day as tolerated. Gabapentin could be started at 300 mg per day and increased to 1800 mg per day or higher as tolerated. Phenytoin should be initiated from a daily dose of 200 to 300 mg and could be titrated up to a maximally tolerated dose. Complete blood count and serum level of the drug should be assessed regularly to avoid possible toxicity. Some other medications including valproate, acetazolamide, lamotrigine, and clonazepam have also been used in patients with favorable outcomes.<sup>2</sup> However, it should be noted that all treatments in PNH syndromes are off-label as a part of an expert opinion, commonly at doses approved for other disorders. If the symptoms are not controlled with these agents, plasma exchange or IVIG should be considered concurrently with oral steroids (prednisone) and immunosuppressive medications (azathioprine).<sup>39</sup> In the present-day literature, plasmapheresis has been reported to be more effective and is considered the first line of immunomodulatory therapy.<sup>39</sup> Plasma exchange or IVIG could be maintained from weeks to months based on the patient's therapeutic response and could be tapered or discontinued after 3 to 6 months to allow the patient to be on oral medications. Studies have recommended that prednisone be initiated with a daily dose of 10 mg, increased up to 60 mg per day, and azathioprine with a daily dose of 2 to 3 mg/kg, as tolerated.<sup>2</sup> In our study, however, half

of the patients received plasmapheresis and the other half received IVIG, and eventually, both groups achieved remarkable recovery and had a significant response to these therapies. However, future interventional studies are warranted to compare the ultimate effect of each treatment. All of our patients received maintenance immunosuppressive therapy as recommended in previous studies, consisting of prednisolone and azathioprine which is the most recommended drug regimen. As for symptomatic treatment, gabapentin and carbamazepine were almost equally prescribed for our patients, followed by pregabalin. Although carbamazepine is suggested as the first line for symptomatic management, it seems that both drugs are valid choices alongside pregabalin, phenytoin, valproate, and some other options.<sup>8,40</sup> All studied patients fully recovered by the time of the follow-up visit and no relapse was observed in the 3 years of follow-up among the studied population.

All observations should be interpreted carefully

## References

- Sawhani K, Katirji B. Peripheral nerve hyperexcitability syndromes. *Continuum (Minneapolis)* 2017; 23(5, Peripheral Nerve and Motor Neuron Disorders): 1437-50.
- Ahmed A, Simmons Z. Isaacs's syndrome: A review. *Muscle Nerve* 2015; 52(1): 5-12.
- Barber PA, Anderson NE, Vincent A. Morvan's syndrome associated with voltage-gated K<sup>+</sup> channel antibodies. *Neurology* 2000; 54(3): 771-2.
- Arimura K, Sonoda Y, Watanabe O, Nagado T, Kurono A, Tomimitsu H, et al. Isaacs' syndrome as a potassium channelopathy of the nerve. *Muscle Nerve Suppl* 2002; 11: S55-S58.
- Vincent A, Pettingill P, Pettingill R, Lang B, Birch R, Waters P, et al. Association of leucine-rich glioma inactivated protein 1, contactin-associated protein 2, and contactin 2 antibodies with clinical features and patient-reported pain in acquired neuromyotonia. *JAMA Neurol* 2018; 75(12): 1519-27.
- Park SB, Thurbon R, Kiernan MC. Isaacs's syndrome: The frontier of neurology, psychiatry, immunology and cancer. *J Neurol Neurosurg Psychiatry* 2020; 91(12): 1243-4.
- Falace A, Striano P, Manganelli F, Coppola A, Striano S, Minetti C, et al. Inherited neuromyotonia: A clinical and genetic study of a family. *Neuromuscul Disord* 2007; 17(1): 23-7.
- Rana SS, Ramanathan RS, Small G, Adamovich B. Paraneoplastic Isaacs' syndrome: A case series and review of the literature. *J Clin Neuromuscul Dis* 2012; 13(4): 228-33.
- Isaacs H, Frere G. Syndrome of continuous muscle fibre activity. Histochemical, nerve terminal and end-plate study of two cases. *S Afr Med J* 1974; 48(38): 1601-7.
- Walsh JC. Neuromyotonia: An unusual presentation of intrathoracic malignancy. *J Neurol Neurosurg Psychiatry* 1976; 39(11): 1086-91.
- Zifko U, Drlicek M, Machacek E, Jellinger K, Grisold W. Syndrome of continuous muscle fiber activity and plasmacytoma with IgM paraproteinemia. *Neurology* 1994; 44(3 Pt 1): 560-1.
- Caress JB, Abend WK, Preston DC, Logigian EL. A case of Hodgkin's lymphoma producing neuromyotonia. *Neurology* 1997; 49(1): 258-9.
- Toepfer M, Schroeder M, Unger JW, Lochmuller H, Pongratz D, Muller-Felber W. Neuromyotonia, myocloni, sensory neuropathy and cerebellar symptoms in a patient with antibodies to neuronal nucleoproteins (anti-Hu-antibodies). *Clin Neurol Neurosurg* 1999; 101(3): 207-9.
- Hayat GR, Kulkarnakorn K, Campbell WW, Giuliani MJ. Neuromyotonia: Autoimmune pathogenesis and response to immune modulating therapy. *J Neurol Sci* 2000; 181(1-2): 38-43.
- Forte F, Pretelegiani E, Battisti C, Sicurelli F, Federico A. Neuromyotonia as paraneoplastic manifestation of bladder carcinoma. *J Neurol Sci* 2009; 280(1-2): 111-2.
- Issa SS, Herskovitz S, Lipton RB. Acquired neuromyotonia as a paraneoplastic manifestation of ovarian cancer. *Neurology* 2011; 76(1): 100-1.
- Taylor PW. Isaacs' syndrome (autoimmune neuromyotonia) in a patient with systemic lupus erythematosus. *J Rheumatol* 2005; 32(4): 757-8.
- Cerami C, Corbo M, Piccolo G, Iannaccone S. Autoimmune neuromyotonia following human papilloma virus vaccination. *Muscle Nerve* 2013; 47(3): 466-7.
- Odabasi Z, Joy JL, Claussen GC, Herrera GA, Oh SJ. Case of the month: Isaacs' syndrome associated with chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve* 1996; 19(2): 210-5.
- Liu YC, Wu ZA, Wang SJ, Shan DE, Lin KP. Transient syndrome of continuous muscle fiber activity associated with staphylococcal infection. *Mov Disord* 1998; 13(3): 609-11.
- Chaurasia R, Shukla R. Toxin induced continuous muscle fiber activity syndrome. *Ann Neurosci* 2008; 15(4): 118-9.
- Hart IK, Maddison P, Newsom-Davis J, Vincent A, Mills KR. Phenotypic variants of autoimmune peripheral nerve hyperexcitability. *Brain* 2002; 125(Pt 8): 1887-95.
- Gallin WJ, Boutet PA. VKCDB: Voltage-gated K<sup>+</sup> channel database updated and upgraded. *Nucleic Acids Res* 2011; 39(Database issue): D362-6.
- Irani SR, Alexander S, Waters P, Kleopa KA, Pettingill P, Zuliani L, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome

as only a limited number of patients were studied. Further studies with a longitudinal view could also assess antibodies and their alterations through follow-up visits to provide a better understanding of the therapeutics' response.

## Conclusion

This overview aimed to describe the syndrome by presenting a series of cases and discussing the existing evidence regarding its pathogenesis, diagnosis, and its management. Despite the rarity of the disease, our results offer valuable insights into the epidemiological, clinical, and paraclinical features of Isaacs' syndrome, along with recommendations for its management.

## Conflict of Interests

The authors declare no conflict of interest in this study.

## Acknowledgments

None.

- and acquired neuromyotonia. *Brain* 2010; 133(9): 2734-48.
25. Hart IK, Waters C, Vincent A, Newland C, Beeson D, Pongs O, et al. Autoantibodies detected to expressed K<sup>+</sup> channels are implicated in neuromyotonia. *Ann Neurol* 1997; 41(2): 238-46.
  26. Maddison P. Neuromyotonia. *Clin Neurophysiol* 2006; 117(10): 2118-27.
  27. Tan KM, Lennon VA, Klein CJ, Boeve BF, Pittock SJ. Clinical spectrum of voltage-gated potassium channel autoimmunity. *Neurology* 2008; 70(20): 1883-90.
  28. Vernino S, Lennon VA. Ion channel and striational antibodies define a continuum of autoimmune neuromuscular hyperexcitability. *Muscle Nerve* 2002; 26(5): 702-7.
  29. Paterson RW, Zandi MS, Armstrong R, Vincent A, Schott JM. Clinical relevance of positive voltage-gated potassium channel (VGKC)-complex antibodies: Experience from a tertiary referral centre. *J Neurol Neurosurg Psychiatry* 2014; 85(6): 625-30.
  30. Boyko M, Au KLK, Casault C, de Robles P, Pfeffer G. Systematic review of the clinical spectrum of CASPR2 antibody syndrome. *J Neurol* 2020; 267(4): 1137-46.
  31. Samogalskyi V, Alcalay Y, Gadoth A, Eilam A, Gilad R. Case report: Isolated muscle neuromyotonia, as presenting feature of Isaacs' syndrome. *J Neuroimmunol* 2021; 353: 577491.
  32. Zimon M, Baets J, Almeida-Souza L, De Vriendt E, Nikodinovic J, Parman Y, et al. Loss-of-function mutations in HINT1 cause axonal neuropathy with neuromyotonia. *Nat Genet* 2012; 44(10): 1080-3.
  33. Vincent A, Buckley C, Schott JM, Baker I, Dewar BK, Detert N, et al. Potassium channel antibody-associated encephalopathy: A potentially immunotherapy-responsive form of limbic encephalitis. *Brain* 2004; 127(Pt 3): 701-12.
  34. Harrison TB, Benatar M. Accuracy of repetitive nerve stimulation for diagnosis of the cramp-fasciculation syndrome. *Muscle Nerve* 2007; 35(6): 776-80.
  35. Levy LM, Dalakas MC, Floeter MK. The stiff-person syndrome: an autoimmune disorder affecting neurotransmission of gamma-aminobutyric acid. *Ann Intern Med* 1999; 131(7): 522-30.
  36. Rubio-Agusti I, Perez-Miralles F, Sevilla T, Muelas N, Chumillas MJ, Mayordomo F, et al. Peripheral nerve hyperexcitability: A clinical and immunologic study of 38 patients. *Neurology* 2011; 76(2): 172-8.
  37. Benatar M, Chapman KM, Rutkove SB. Repetitive nerve stimulation for the evaluation of peripheral nerve hyperexcitability. *J Neurol Sci* 2004; 221(1-2): 47-52.
  38. Maddison P, Mills KR, Newsom-Davis J. Clinical electrophysiological characterization of the acquired neuromyotonia phenotype of autoimmune peripheral nerve hyperexcitability. *Muscle Nerve* 2006; 33(6): 801-8.
  39. Merchut MP. Management of voltage-gated potassium channel antibody disorders. *Neurol Clin* 2010; 28(4): 941-59.
  40. Kanmaz S, Ozcan M, Simsek E, Serin HM, Aydogdu I, Gokben S, et al. A rare case of peripheral nerve hyperexcitability in childhood: Isaacs's syndrome. *J Pediatr Neurosci* 2020; 15(2): 153-6.