Sakarya Tıp Dergisi
Sakarya Med J

E-ISSN: 4146-409X
Publisher: Sakarya University

Vol. 14, No. 3, 327-333, 2024
DOI: http://doi.org/10.31832/smj.1525167

Case Report

A Case of Autoimmune Encephalitis Presenting with CASPR-2 Antibody Positivity

Nilüfer Büyükkoyuncu Pekel[1]*, Demet Yıldız[1], Zeynel Abidin Karakaş[1]

[1] Department of Neurology, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Türkiye

niluferbuyuk@hotmail.com
demetyildiz@gmail.com
znlkarakas@gmail.com

* Corresponding Author

Received:
30.07.2024
Accepted:
11.09.2024
Available Online Date:
30.09.2024

Objective: In parallel with the increase in awareness about the disease the number of patients diagnosed with autoimmune encephalitis has been increasing in recent years. Diagnosis is delayed in cases of autoimmune encephalitis where symptoms such as fever, neck stiffness, nausea, vomiting and confusion, which we are used to seeing in central nervous system infections, are more in the background and cognitive disorders, behavioral problems and psychiatric findings are at the forefront. The prognosis is good with early diagnosis and treatment especially in cases with the formation of antibodies against cell surface antigens.

Methods: In this article a case of autoimmune encephalitis with Contactin-related protein-2 (CASPR-2) antibody positivity, which is in the group of autoimmune encephalitis with the formation of antibodies against cell surface antigens is presented.

Results: Our patient responded well to immunotherapy, no recurrence was observed during the following 1 year and no malignancy was detected.

Conclusion: In patients presenting with confusion, epileptic seizures, hallucinations and non-specific sensory symptoms during a subacute process autoimmune encephalitis should be considered in the differential diagnosis. The chance for early diagnosis and treatment should not be missed.

Keywords: Autoimmune encephalitis, Contactin-Related Protein-2 (CASPR-2), Early diagnosis and treatment

1. INTRODUCTION

Central nervous system (CNS) infections can be grouped under four headings: inflammation of the meninges (meningitis), inflammation of the brain parenchyma (encephalitis), inflammation of the brain parenchyma with a limited area around it (abscess) and inflammation of vascular structures (vasculitis/phlebitis). Encephalitis is mainly divided into two categories: infectious and autoimmune. Fever, headache, nausea, vomiting, altered consciousness, neck stiffness, meningeal irritation findings, focal neurological findings, epileptic seizures which are frequently seen in CNS infections may have an insignificant course in autoimmune encephalitis.[1,2] Subacute course, vagueness of clinical findings, difficulties in differential diagnosis, occasional confusion with psychiatric diseases and the late results of related antibody panels cause delays in the diagnosis and treatment of autoimmune encephalitis. Autoimmune encephalitis is divided into two main groups: syndromes associated with antibodies against neuron surface antigens or intracellular antigens. There are some differences between these two groups. Forms associated with neuron surface antigens are less associated with malignancy and respond better to immunotherapy. Autoimmune encephalitis with contactin-associated protein-2 (CASPR-2) antibody positivity are among the syndromes associated with neuron surface antigens and their prognosis is generally good.[3]

Cite this article: Büyükkoyuncu N., Yıldız D., Karakaş Z. A. A Case of Autoimmune Encephalitis Presenting with CASPR-2 Antibody Positivity. Sakarya Med J 2024; 14(3): 327-333 DOI: 10.31832/smj.1525167

This case report aims to draw attention to encephalitis with CASPR-2 antibody positivity due to delays in diagnosis.

2. CASE REPORT

A 39-year-old male patient was admitted to the emergency room on July 15, 2023 with complaints of meaningless speech, confusion and seizures. His complaints started approximately 1 month before he applied to our hospital. He had difficulty in finding words. Then absence seizures lasting for a few seconds were added and progressed over the days. His communication with his environment decreased, his reaction time increased, memory problems were added, absence seizures became more frequent, meaningless speech and complaints of repeating the same word were added. 2-3 weeks after the onset of complaints, he had a short-term attack accompanied by involuntary contractions in the arms and legs and loss of consciousness after screaming in his sleep. He applied to various polyclinics with these complaints. He was referred to the Internal Medicine unit upon detection of high blood sugar and was diagnosed with Diabetes Mellitus (DM). During this period, he applied to the Brain Surgery unit due to pain starting from his left arm and radiating to his neck, cranial and cervical Magnetic Resonance Imaging (MRI) were performed, no pathology was detected. Electroencephalography (EEG) performed at an external center on 12.07.2023 revealed "15-20 seconds 1-2 Hz spike slow wave activity" after hyperventilation (Figure-1) and anti-seizure treatment (valproate 1000 mg/day) was started. His medical history included newly diagnosed DM, hypertension (HT) and smoking 1 pack/day for 10 years. He did not describe substance use or exposure to toxins.

On his first admission to the emergency room, his fever was 36.7 C°, his blood sugar was 197 mg/dl and his electrocardiogram (ECG) was in normal sinus rhythm. His neurological examination revealed confusion. He was able to produce words but he was repeating the same words. He did not understand simple commands. His naming was impaired. There was no neck stiffness. Cranial nerves were intact. His motor examination was normal. Deep tendon reflexes (DTR) were normoactive. The plantar reflex was bilaterally flexor. Routine laboratory tests were normal. Sedimentation and C reactive protein (CRP) were within normal values. No pathology was detected in the first brain computed tomography taken in the emergency room on 15/07/2023. In the cranial MRI, a hyperintense area was seen in the medial part of the left temporal lobe in the diffusion sequence. The image was isointense in the Apparent Diffusion Coefficient (ADC) sequence (Figure-2). Lumbar puncture was unremarkable. No cells were seen in the cerebrospinal fluid (CSF). Glucose in CSF was 104 mg/dl (simultaneous blood sugar was 122 mg/dl), protein was 21 mg/dl, Na was 144 mmol/liter, K was 2.6 mmol/liter. Viral meningitis and autoimmune encephalitis panels were performed. After the evaluation in the emergency room, CNS infection, autoimmune encephalitis, post-ictal confusion, metabolic encephalopathy due to hyperglycemia, encephalopathy due to substance use, exposure to toxic substances, cerebrovascular disease and conversion disorder were considered, and the patient was admitted to the Neurology ward. No significant pathology was seen in the first contrast-enhanced cranial MRI taken on 17/07/2023. In the 2nd contrast-enhanced cranial MRI taken on 21/07/2023, mild contrast enhancement was seen in the medial part of the left temporal lobe (Figure-3). Both EEG's taken in our hospital were normal. On the 3rd day of his admission to our clinic his comprehension was completely impaired, agitation developed and his speech consisted entirely of word repetitions.

Visual hallucinations were added to the picture during his hospitalization. During the morning visit he stated that someone he did not know sat in the chair next to him and then got up and left. The patient was evaluated by the Psychiatry unit. Since the content of the hallucinations were "vivid hallucinations incompatible with psychotic hallucinations" psychotic disorder was not considered at the forefront. It was recommended to continue investigating organic causes. During his follow-up in the clinic complex partial seizures accompanied by oroalimentary automatism in the mouth and forced head-eye deviations of less than 1 minute were observed. After the adjustment of anti-seizure medication the seizures decreased and stopped. He complained of a burning sensation in his head. 1000 mg/day intravenous methylprednisolone treatment for 5 days was given with a preliminary diagnosis of possible autoimmune encephalitis. After the symptoms improved, the patient was discharged with recommendations. Contrast-enhanced thoracic and abdominal computed tomography (CT) scans for malignancy screening were normal. Tumor markers were negative. In the outpatient clinic follow-up his clinical condition was good, he had no new complaints and no treatment was given. Cranial MRI and EEG taken during the follow-up were normal. The viral and bacterial meningitis panel that ended after discharge was negative. CASPR2 positivity was detected in the autoimmune encephalitis panel studied from the serum.

Figure 1.

In the EEG taken in an external center, "15-20 seconds of 1-2 Hz spike slow wave activity after hyperventilation" was detected

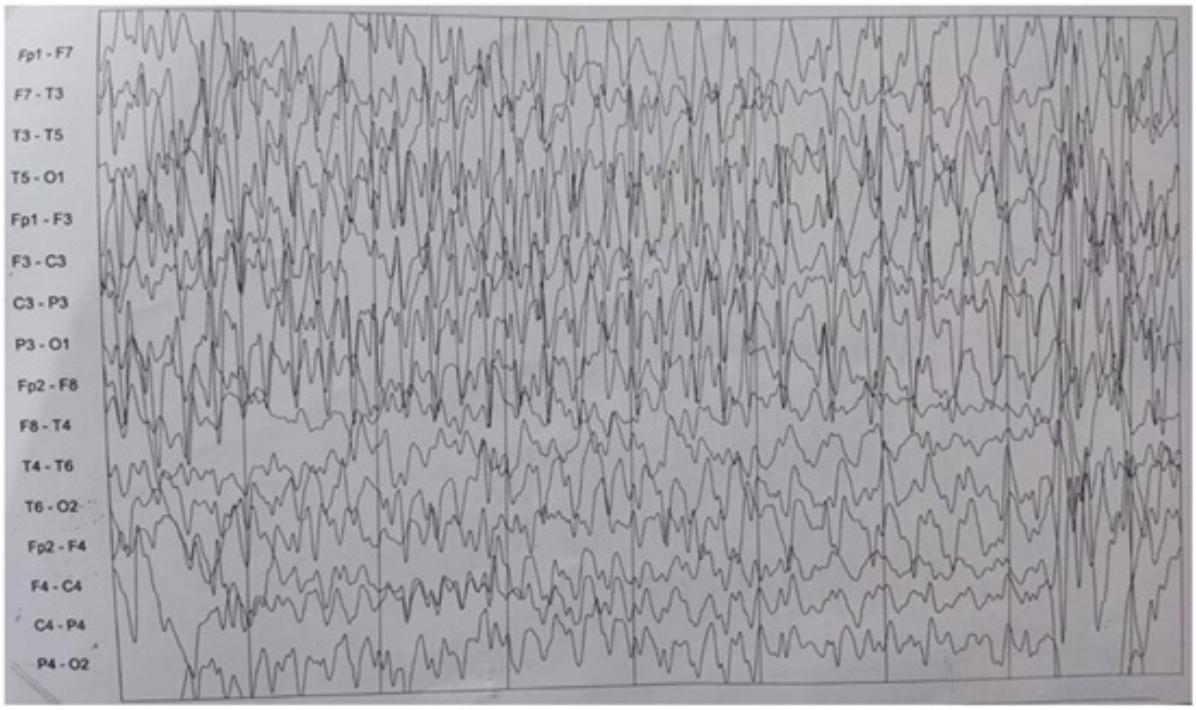


Figure 2.

A hyperintense area was seen in the medial part of the left temporal lobe in diffusion MRI. Its counterpart was isointense in the ADC sequence

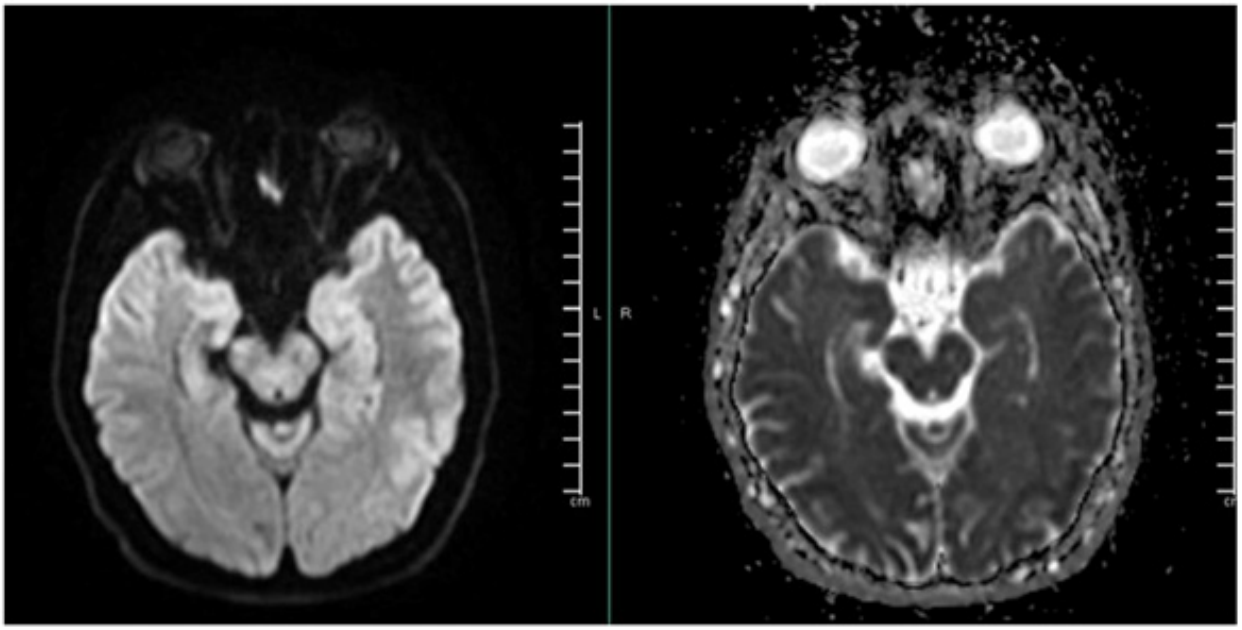
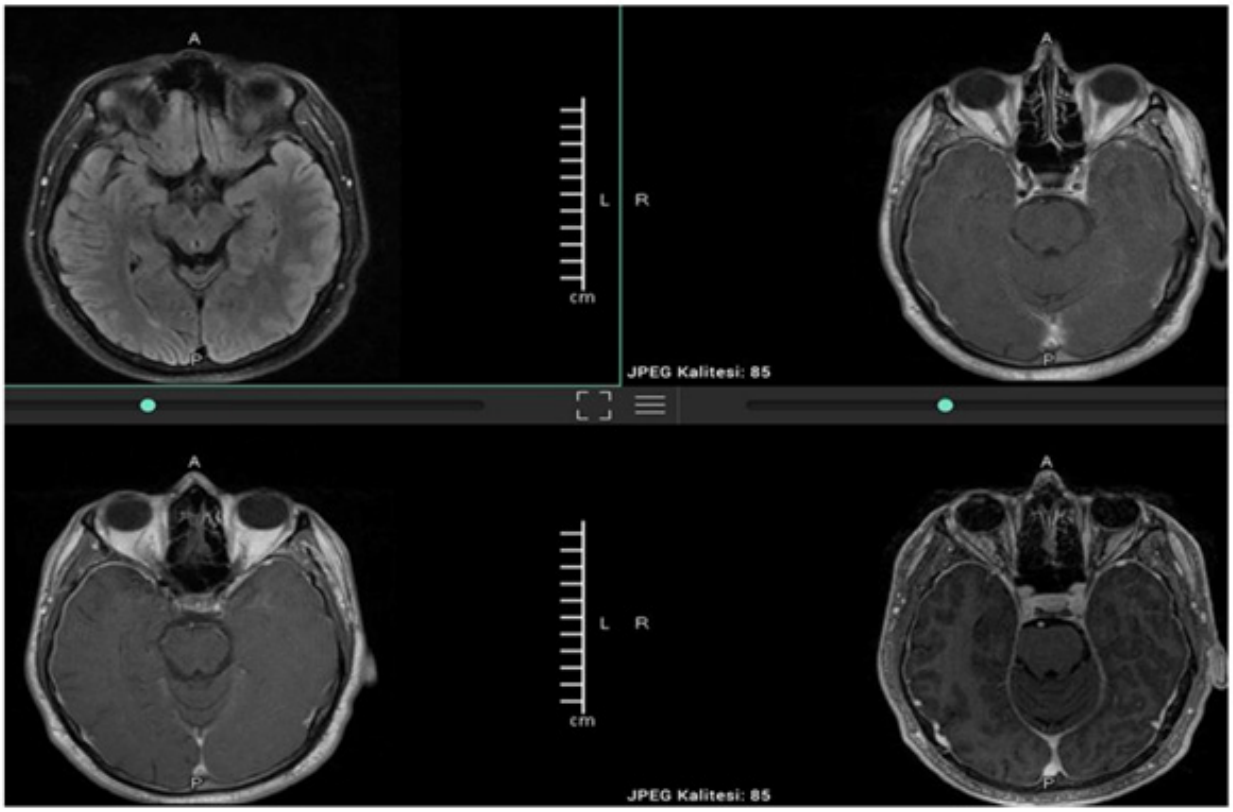


Figure 3.

Contrast-enhanced MRI showed mild contrast enhancement in the medial part of the left temporal lobe



3. DISCUSSION

Delays in the diagnosis and treatment of autoimmune encephalitis have brought the definition of "possible autoimmune encephalitis" to the agenda. Possible autoimmune encephalitis diagnostic criteria can be grouped under three main headings. The first is subacute (less than 3 months) memory loss, mental status change or psychiatric findings. For the second item, new focal CNS findings, new-onset seizures, CSF pleocytosis (WBC>5 cells/mm^3) and at least one of the encephalitis findings on cranial MRI must be present. The third item includes the exclusion of other causes that would cause these findings.[4]

CASPR2 is a cellular adhesion molecule in the neuroxin family. It is associated with ankyrin protein called 4.1B and PDZ binding motif with its C-terminal end.[5] It is located in the juxta-paranodal region of Ranvier node on the axon. CASPR2, contactin2 protein and potassium (K) channels form the voltage-sensitive K channel complex.[5–7] It is thought that the blockage of the relationship between CASPR2 and contactin-2 due to the formation of antibodies is involved in the pathogenesis of the disease. Due to this blockage the expression of K channels is impaired. This causes a an increase in the expression of K channels in some regions such as hippocampus and decrease in the expression of K channels in some regions such as the dorsal root ganglion. This is thought to lead to hyperexcitability and seizures.[8] Voltage-gated potassium channels (VGKC) are associated with the repolarization of the synaptic membrane. Blockage of these channels causes excitability in the nerves.[9] CASPR2 is abundant in the limbic system, basal ganglia, other motor areas, sensory pathways and especially the temporal lobe. The widespread presence of CASPR2 in both the CNS and peripheral nervous system (PNS) leads to the observation of different clinical findings related to the disease. These findings can be listed as ataxia, epilepsy, psychiatric symptoms, encephalitis, Morvan syndrome, neuropathic pain and Isaac syndrome.[10] Morvan Syndrome is an autoimmune disease that can affect the CNS, PNS and autonomic nervous system (ANS). Symptoms such as neuromyotonia (cramps, rigidity, fasciculation), seizures, fever, encephalopathy, insomnia, dysautonomic signs, especially hyperhidrosis and cardiovascular instability, neuropathic pain, skin lesions or pruritus may be observed.[11-12] Isaac syndrome is an acquired peripheral nerve hyperexcitability. Its main findings can be summarized as myokymia, cramps, fasciculation, twitching, rigidity and pseudomyotonia. Muscle activity may continue even when the patient is asleep. This condition can cause muscle hypertrophy. Dysautonomia (hyperhidrosis, sialorrhea), Trousseau and Chvostek signs may also be present, sensory findings are rare, reflexes are usually normal. Symptoms are usually insidious and develop over years.[13,14]

In a multicenter retrospective study of 25 cases of CASPR encephalitis, it was seen that the disease was mostly seen in men (68%), and the age of symptom onset was 42. The average time from the onset of complaints to admission of hospital was 17 days, ranging from 2 days to 6 months. Fever was the initial symptom in 6 of the patients. The most common symptom was cognitive impairment, seen in 17 of 25 patients. 8 patients met the criteria for limbic encephalitis. 6 of the 8 patients diagnosed with limbic encephalitis had epileptic seizures. 4 patients were diagnosed with Morvan syndrome. All patients had positive anti-CASPR-2 antibodies in serum. Antibodies were shown in both CSF and blood in 6 patients. White blood cells were high in CSF in 8 patients. While 10 patients had high protein levels in CSF, 7 patients had low protein levels and

8 patients had normal protein levels in CSF. Slow background activity and epileptic patterns were observed as EEG findings. Cranial MRI showed abnormal signal increase in bilateral hippocampus in 3 patients with cognitive impairment. Positron emission tomography (PET-CT) showed increased metabolism in bilateral basal ganglia and mesial temporal lobe in 1 patient with limbic encephalitis. Relapse was observed in 4 out of 25 patients after 2 months. This study showed that both CNS and PNS findings are seen in CASPR-2 encephalitis. Lung tumor was detected in only 1 patient and there was a good response to immunotherapy.[10] In our case confusion, hallucinations, epileptic seizures and sensory symptoms such as numbness in the left arm at the beginning of the complaints, burning in the head were observed during the hospitalization, and these were consistent with the literature. It is known that the diagnosis process of the disease can take up to 6 months. Our patient who applied to our clinic 1 month after the onset of his complaints was diagnosed quickly. The patient responded well to immunotherapy, no recurrence was observed during the following 1 year and no malignancy was detected.

In patients presenting with confusion, epileptic seizures, hallucinations and non-specific sensory symptoms during a subacute process autoimmune encephalitis should be considered in the differential diagnosis. It should be remembered that the prognosis is good especially in those with antibody formation against surface antigens. The chance for early diagnosis and treatment should not be missed. Due to the late results of autoimmune encephalitis-related antibody panels the diagnostic criteria for "possible autoimmune encephalitis" should be known and treatment should be started before the antibody panel is completed in clinically appropriate cases. Due to its association with malignancies, malignancy screening should also be performed while the diagnosis and treatment process is ongoing. It should not be forgotten that relapses may be seen and tumors may be detected in the post-disease period, patients should be closely monitored in this regard during outpatient clinic follow-up and it should not be forgotten that there may be cases where immunotherapy should be continued for a long time.

There is no conflict of interest between the authors. The type of the study is case report so we did not get ethical approval. The informed consent form was signed by the patient. All off the authors have participated in the design and writing of the manuscript.

Ethical Approval

Presented as an electronic poster (EP-627) at the 59th National Neurology Congress held at Kaya Plaza Hotel, Antalya, December 13-18, 2023.

REFERENCES

1. Kocasoy Orhan E, Çakar A, Akman-Demir G. Sinir Sistemi İnfeksiyonları. Öge AE, Baykan B, Bilgiç B (Ed). Nöroloji Ders e-kitabı. 4. baskı. İstanbul: Nobel Tıp Kitapevleri, 2020.
2. Dervişoğlu P, Kösecik M. Meninks İrritayon Bulgularıyla Başvuran Atipik Kawasaki Hastalığı. Sakarya Tıp Dergisi 2016, 6(3):175-178.
3. Nissen MS, Ryding M, Meyer M, Blaabjerg M. Autoimmune Encephalitis: Current Knowledge on Subtypes, Disease Mechanisms and Treatment. CNS & Neurological Disorders-Drug Targets. Volume 19, Issue 8, 2020. Page:572-583.
4. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016;15(4):391-404
5. Saint-Martin M, Joubert B, Pellier-Monnin V, Pascual O, Noraz N, Jérôme Honnorat. Contactin-associated protein-like 2, a protein of the neurexin family involved in several human diseases. Eur J Neurosci 2018; 48:1906-1923.
6. Pinatel D, Hivert B, Saint-Martin M, Noraz N, Savvaki M, Karagogeos D et al. The Kv1-associated molecules TAG-1 and Caspr2 are selectively targeted to the axon initial segment in hippocampal neurons. J Cell Sci 2017;130(13):2209-2220.

7. Arancibia-Carcamo IL, Attwell D. The node of Ranvier in CNS pathology. Acta Neuropathol 2014;128:161-75.
8. Breis LC, Schlindwein MAM, Gonçalves MVM. Anti-CASPR2 antibodies clinical significance and its main phenotypes. Neurosciences 2020;7:330-334.
9. Ahmed A, Simmons Z. Isaacs syndrome: a review. Muscle Nerve 2015;52:5-12.
10. Qin X, Yang H, Zhu F, Wang Q, Shan W. Clinical Character of CASPR2 Autoimmune Encephalitis: A Multiple Center Retrospective Study. Front Immunol. 2021; 12: 652864. https://doi.org/10.3389/fimmu.2021.652864.
11. Nikolaus M, Jackowski-Dohrmann S, Prüss H, Schuelke M, Knierim E. Morvan syndrome associated with CASPR2 and LGI1 antibodies in a child. Neurology 2018;90:183-185.
12. Irani SR, Pettingill P, Kleopa KA, Schiza N, Waters P, Mazia C et al. Morvan syndrome: Clinical and serological observations in 29 cases. Ann Neurol 2012;72(2):241-255.
13. Song J, Jing S, Quan C, Lu J, Qiao X, Kai Qiao et al. Isaacs syndrome with CASPR2 antibody: A series of three cases. J Clin Neurosci 2017;41:63-6.
14. Sawlani K, Katirji B. Peripheral nerve hyperexcitability syndromes. Continuum (Minneap Minn) 2017; 23:1437-50.