

## Caspr 2 antibody associated disease—An unusual presentation

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### Abstract

**Introduction:** Antibodies to Voltage Gated Potassium Channels (VGKC) are directed against Leucine-rich Glioma- Inactivated1 (LGI1) and Contactin Associated Protein like 2 (Caspr2). Common presentations of Caspr2 antibody associated diseases include limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. New clinical phenotypes are being considered to the spectrum of Caspr2 antibody associated disease. Here we report a case of Caspr2 antibody associated disease with an unusual clinical presentation.

**Case Report:** 40 year old male presented with distal symmetrical sensorimotor neuropathy of 4 months duration. Subsequently he had developed neurobehavioral symptoms in the form of irritability, episodic memory impairment and seizures. After medical evaluation he was diagnosed to have anti Caspr2 antibody associated disease. Patient showed improvement with an immunosuppressive therapy, but had recurrence of autoimmune encephalitis 1 month later. Along with that, he had also developed right vocal cord palsy, for which no other cause was identified. Patient improved with second line immunosuppressive therapy. He had no further recurrence and is under follow up.

**Keywords:** Voltage gated potassium channels, Leucine-rich Glioma-inactivated 1, Contactin associated protein, Limbic encephalitis, Neuromyotonia.

### Introduction

Antibodies to voltage gated potassium channels (VGKC) were reported in patients with neuromyotonia, Morvan's syndrome and limbic encephalitis (LE). These antibodies are not directed against the VGKC subunits but against VGKC associated proteins. Two of these proteins were identified in 2010 as Leucine-rich Glioma- Inactivated1 (LGI1) and Contactin Associated Protein like 2 (Caspr2).<sup>1</sup> Antibodies to LGI1 are present only in the central nervous system and are associated with limbic encephalitis and faciobrachial dystonic seizures<sup>2</sup>. Caspr2 is a membrane protein present in both central nervous system (CNS) and peripheral nervous system (PNS). This protein is essential for clustering of potassium channel in juxtaparanodes of myelinated axon.<sup>3</sup> Hence Caspr2 antibody spectrum disorders can affect both CNS and PNS. The clinical spectrum of Caspr2 autoimmunity is not well defined and is more diverse. There are reports of LE, Morvan's syndrome and acquired neuromyotonia associated with antibodies against Caspr2 protein in the literature.<sup>4</sup> Here we report a case of Caspr2 antibody associated disease with an unusual clinical presentation.

### Case Report

40 year old gentleman without any co-morbidities presented with insidious onset, slowly progressive tingling sensation and numbness of both lower limbs of 4 months duration, which were started in the toes and then gradually ascended symmetrically up to knee. This was followed by development of similar symptoms of both hands. One month later he has developed unsteadiness of gait during night. He had also developed motor weakness in the form of bilateral foot

drop and was unable to grip objects tightly with hands. Then he got admitted to our institution with forgetfulness, irritability and aggressive behavior of 3 weeks duration.

On examination patient was conscious and irritable. Folstein MMSE was 18/30 with disorientation to time and place, impaired attention and recall, with normal language. Distal muscles of upper and lower limbs showed asymmetrical wasting and weakness (Image 1, 2). Ankle jerk and superficial abdominal reflex were absent; with positive Babinski sign. There was symmetrical sensory loss in distal parts of lower limbs up to knee and both hands. Romberg's test was positive.

Complete blood count, liver function test, renal function test, serum electrolytes, urine routine and C - reactive protein were within normal limits.

On 3<sup>rd</sup> day of admission, he had developed recurrent myoclonic jerks of left upper limb and facial grimacing. This was followed by generalized tonic clonic seizures, which got controlled only after 30 to 40 min, with multiple antiepileptic drugs (lorazepam, levetiracetam and sodium valproate). He was drowsy even after control of seizures.

Electroencephalography (EEG) showed diffuse theta to delta slow waves and periodic lateralized epileptiform discharges from right temporal leads (Image 3). MRI Brain with contrast revealed non-specific T2 FLAIR white matter hyper intensity in the frontal lobes (Image 4). CSF study was normal.

After ruling out meningitis, he was started on intravenous (IV) methylprednisolone 1 gm, considering the possibility of autoimmune encephalitis/ systemic

vasculitis with CNS involvement. Patient improved significantly over a period of 3 days. His sensorium became normal and he was shifted out of intensive care unit. IV methylprednisolone was continued for 5 days.

ANA profile including double stranded DNA, serum angiotensin converting enzyme, anti TPO antibody titre and serum electrophoresis were within normal limits. Hepatitis B and C serology and examination of serum and CSF for anti HSV 1 and 2 antibodies were negative. HIV and blood and CSF VDRL were non-reactive. Autoimmune and paraneoplastic encephalitis panel of antibodies were done; test results for CASPR 2 antibody came as positive.

Contrast enhanced CT thorax was done in view of positive Caspr2 antibody, to rule out thymoma<sup>5</sup> and was found to be normal. Nerve conduction study was suggestive of sensory motor axonal neuropathy with absent Compound Muscle Axon Potential (CMAP) and Sensory Nerve Axon Potentials (SNAP) of lower limbs and reduced CMAP and SNAP amplitudes in upper limb. Electromyography (EMG) showed Fibrillation potentials, large motor unit action potentials and reduced recruitment in both lower and upper limbs distally. Biopsy of right sural nerve was suggestive of chronic axonopathy.

Our final diagnosis was Caspr2 antibody associated - limbic encephalitis with distal symmetrical sensor motor neuropathy. Patient was discharged on steroids at a dose of 1 mg/kg of prednisolone. At discharge his sensorium improved. Folstein MMSE was 28/30 with impaired recall 1 out of 3. There was residual motor and sensory deficit over distal upper and lower limbs.

1 month later, patient was readmitted with recurrence of symptoms in the form of altered sensorium and hallucinating behavior. On examination patient was conscious, but disoriented to time and place with impaired attention and recall (Folstein MMSE 20/30). Motor system examination showed persistent weakness and sensory impairment in both upper and lower limbs. Patient developed hoarseness of voice for which flexible laryngoscopy was done and it suggested right vocal cord palsy (Image 5).

Extensive evaluation, including blood and CSF study failed to identify any secondary cause for encephalopathy. MRI brain with contrast showed few non-specific T2 FLAIR hyper intensities similar to previous imaging. MRI of thorax and nasopharynx were taken in view of right vocal cord palsy and was found to be normal.

Considering all these findings, a possibility of recurrence of autoimmune encephalitis was considered. He was given intravenous methylprednisolone 1 gm daily for 3 days followed by oral steroids. In view of recurrence of his symptoms with steroids alone, he was also started on rituximab 500mg iv infusion once weekly for 4 weeks and was maintained on oral

steroids. With this line of management, patient's condition improved well with attainment of normal sensorium.

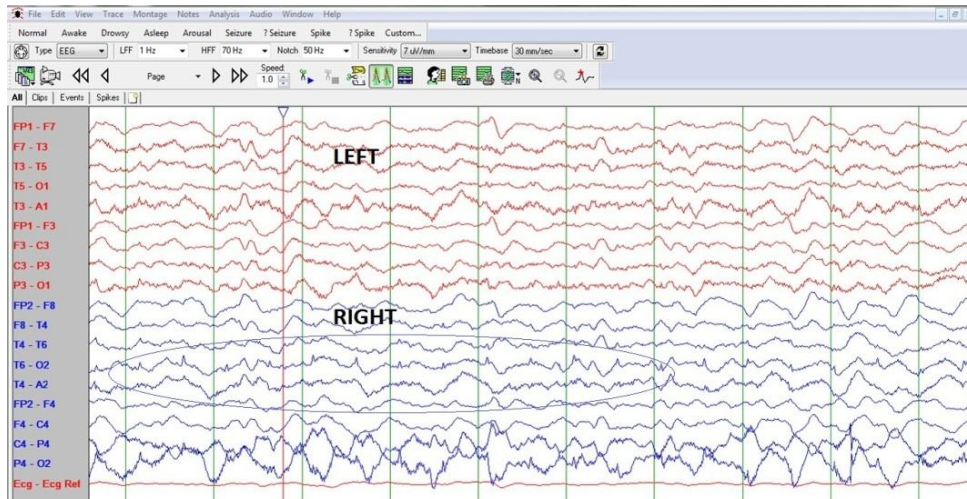
The follow up period was uneventful. On re-evaluation after 3 months, Folstein MMSE was 29/30 with recall 2 out of 3. Hoarseness of voice resolved and repeat flexible laryngoscopy showed normal vocal cord mobility. Sensory symptoms and signs subsided. Residual weakness in the form of bilateral foot drop and small muscle weakness of lower limbs was persisting and he is still under follow up.



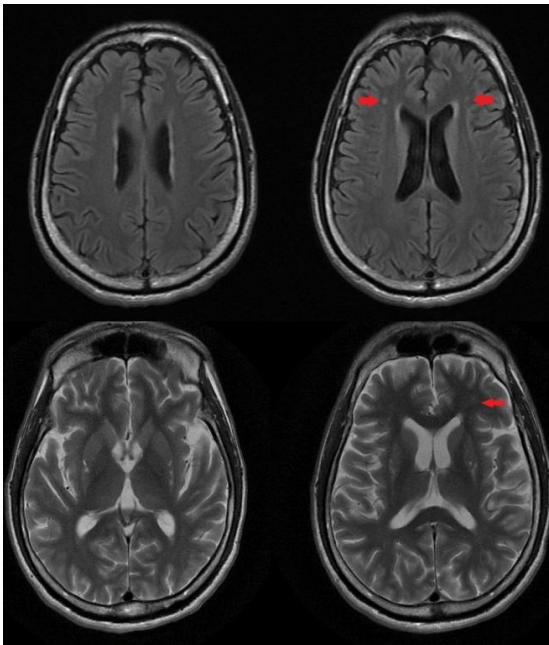
**Fig. 1: Showing asymmetrical small muscle wasting of hands (red arrow)**



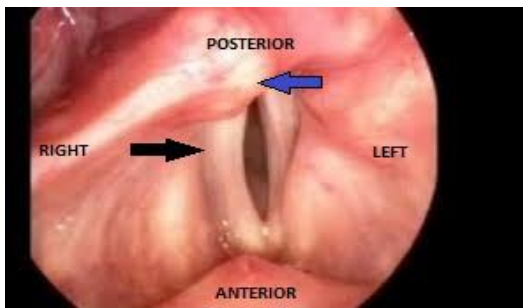
**Fig. 2: Showing bilateral extensor digitorum brevis wasting (red arrow)**



**Fig. 3:** Awake EEG showing diffuse theta to delta slow waves and periodic lateralised epileptiform discharge (marked in EEG) from right temporal leads.



**Fig. 4:** MRI Brain (T2 and T2 Flair) showing non specific white matter hyperintensity in the frontal white matter (red arrow)



**Fig. 5:** Flexible laryngoscopy showing bowing of right vocal cord (black arrow) and right arythenoid pulled medially (blue arrow) suggestive of right vocal cord palsy

**Discussion**

Caspr2 antibody associated disease is a treatable disorder with high recurrence rate of about 25%.<sup>4</sup> The clinical presentation of this immune disorder is complicated by a combination of symptoms involving the CNS and PNS.

Involvement of CNS can manifest as amnesia, behavioural disorders, hallucinations, psychosis, epilepsy and insomnia. PNS manifestations include features of peripheral nerve hyperexcitability like cramps, muscle twitching (fasciculations or myokymia), stiffness, pseudomyotonia (delayed muscle relaxation after contraction) and pseudotetany (spontaneous or evoked carpal or pedal spasm, or Chvostek’s sign) or neuropathic pain usually described as a burning sensation in the hands or feet; other types of pain include joint and muscle pain, thoracic pain, and lumbocoxalgia.<sup>6</sup>

Our patient presented with distal symmetrical sensorimotor neuropathy causing sensory ataxia and distal weakness of upper and lower limbs causing significant functional impairment, and later progressed to involve central nervous system in the form of episodic memory impairment, behavioral abnormality and focal seizure with secondary generalization suggestive of limbic encephalitis. There were no clinical or electrophysiological features to qualify peripheral nerve hyperexcitability. A final diagnosis of Caspr2 antibody associated - limbic encephalitis with distal symmetrical sensory and motor neuropathy was made. One month later he presented with recurrence of limbic encephalitis along with right vocal cord palsy, from which he recovered completely with aggressive immunosuppressive therapy. Recurrence of Caspr2 autoimmune encephalitis is well described in literature. But we could not find any report of vocal cord palsy in

Caspr2 antibody associated disease, even after thorough literature search.

Neuropathic pain and peripheral neuropathic features are mostly seen with Morvan's syndrome and are very rare in Caspr2 antibody associated limbic encephalitis.<sup>5</sup> Significant peripheral neuropathy causing disability in association with Caspr2 antibody limbic encephalitis is not yet described in literature. In addition vocal cord palsy in association with Caspr2 is a new entity. Hence our case is novel and gives value adding to the expanding spectrum of Caspr2 antibody associated diseases.

**Conflicting Interest:** Nil

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