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NEUROMYELITIS OPTICA (AQUAPORIN-4 ANTIBODY-POSITIVE) WITH OVERLAPPING ANTI NMDAR ENCEPHALITIS

Neurology

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ABSTRACT

Neuromyelitis Optica (NMO) is an inflammatory CNS syndrome distinct from multiple sclerosis (MS) that is associated with serum aquaporin-4 immunoglobulin G antibodies (AQP4-IgG) or rarely with Anti -MOG antibodies (Myelin Oligodendrocyte Glycoprotein-IgG). Anti-NMDAR encephalitis classically presents with Neuro-psychiatric symptoms, including memory deficits, seizures, frequent dyskinesia, autonomic dysfunction, reduced consciousness, and hypoventilation. Although rare, the coexistence of autoimmune encephalitis with demyelinating disorders should be considered in presence of atypical symptoms.

We present a case of a patient with overlapping clinical features of NMOSD and Anti-NMDAR encephalitis presenting with difficulty in voiding urine, constipation, abnormal behavior, and cognitive impairment as the chief findings on presentation.

KEYWORDS

Neuromyelitis Optica, Anti-aquaporin 4, Anti-NMDAR encephalitis, CNS Demyelinating diseases, Psychosis

INTRODUCTION

Neuromyelitis Optica is an Autoimmune demyelinating CNS disorder characterized by severe relapsing episodes of optic neuritis and transverse myelitis. Although earlier in the evolution of the disease, other parts of the CNS are spared, later on, however, it is not uncommon to have widespread involvement encompassing Area postrema, Brainstem, Hypothalamus, and Cerebral hemispheres [1].

Anti-NMDAR encephalitis affects predominantly children and young adults, with female to male case ratio of 4:1, and presents with sleep disturbances, seizures, dyskinesias, or altered behavior such as irritability, temper tantrums, agitation, and reduction of verbal output [2].

Clinical manifestations of NMO are myriad depending on the involvement of the particular areas of the brain and spinal cord with a propensity to affect both the gray matter and white matter. Consideration should be given for co-existing Anti-NMDAR encephalitis in presence of atypical symptoms like abnormal behavior, psychiatric manifestations, cognitive dysfunction, autonomic dysfunction, or atypical supratentorial lesions [3].

We present a case of a 16-year-old girl with no previous psychiatric history, who presented with the chief findings of difficulty in voiding urine, constipation, altered mental status, and cognitive impairment with CSF testing positive for Anti-aquaporin 4 and Anti-NMDAR antibodies on evaluation.

CASE STUDY

A 16-year-old girl presented to our hospital with difficulty in voiding urine, constipation, behavioral changes, and altered mental status for 2 weeks. She was relatively asymptomatic until two weeks back, when she endorsed difficulty in passing urine and stools. Her family members also reported marked changes in her behavior over the last few days which included episodes of irrelevant talking, anger, irritability, confusion, temper tantrums, disorientation, and incoherent speech. She denied having fevers, chills, cough or sputum production, arthralgias, myalgias, rashes, bruising, headaches, weight loss, back pain, chest pain, abdominal pain, pain on passing urine or stools, oral ulcers, dizziness, visual blurring, diplopia, hearing loss, hemoptysis, or hematochezia.

Her past medical history was significant for an episode of left-sided weakness six months back when an MRI of her brain and spine revealed hyperintensity on T2W/FLAIR sequences of the right thalamo-capsular region and entire cervical spinal cord, medulla, and pons extending caudally up to the T1 segment, without any significant enhancement of the lesions. Overall, findings were suggestive of the diffuse demyelination, most likely to be ADEM (Acute disseminated Encephalomyelitis). She subsequently showed marked improvement after treatment with plasma exchange and steroids.

History was otherwise unremarkable for TB, Hypertension, thyroid disorders, psychiatric diseases, or any autoimmune diseases. Her family history was also unrevealing for any autoimmune or chronic diseases. She was not sexually active and denied alcohol consumption or illicit drug usage.

On physical examination, she was disoriented to time and place. Her vitals were remarkable for pulse rate fluctuating between 80-120 beats/min and systolic blood pressure values ranging from 130mm of Hg to 110mm of Hg with the component of postural hypotension. Evaluation of the respiratory, gastrointestinal, and cardiovascular system was unremarkable. Neurological examination revealed the power of +3 in the lower limbs and +4 in the upper limbs. The tone was normal in all extremities. Babinski sign was absent bilaterally. There was no evidence of hyperreflexia on examination of upper and lower limb deep tendon reflexes. Sensory examination was negative for a sensory level but was positive for diffuse hyperaesthesia. Pupils were bilaterally symmetric and reactive to light and no evidence of nystagmus was seen. Examination of cranial nerves was normal. Nuchal rigidity was absent. There was evidence of cognitive impairment with short term memory loss. The psychiatric evaluation revealed elevated mood, confusion, disorganized and incoherent speech, delusions, and hallucinations.

INVESTIGATIONS:

Thyroid function tests and Vitamin B12 levels were within the normal range. HIV antigen-antibody screening test was non-reactive as was the serum testing for Anti HBsAg and Anti HCV antibodies. Urinalysis was within the normal range. Tests for ANA and ANCA were unrevealing.

CSF analysis revealed mild lymphocytic pleocytosis with a total cell count of 15 cells/mm3 (100% lymphocytes), elevated protein levels at 61.6 mg/dl, a glucose level of 91 mg/dl, and absence of oligoclonal bands.

CSF testing for aquaporin-4 immunoglobulin G antibodies (AQP4-IgG) was positive and testing for Anti-MOG antibodies (Myelin Oligodendrocyte Glycoprotein-IgG) was negative. CSF testing for Anti NMDAR encephalitis returned positive while testing for Anti LGI1, Anti Caspr2, Anti AMPAR, and Anti GABA-B was negative.

IMAGING STUDIES:

MRI of the brain revealed patchy, irregular, confluent T2W/FLAIR hyperintensity involving both caudate nuclei, hippocampus, cerebral peduncles, both thalami, both temporal lobes, midbrain, pons, bilateral periventricular white matter, and corpus callosum.

Few lesions show patchy restriction of diffusion. No significant enhancement was noted in the post-contrast study.

MRI of the spine revealed multifocal patchy T2W/STIR hyperintensity in the entire spinal cord extending from cervical segments to the conus medullaris. Lesions predominantly involved the central cord with mild patchy peripheral involvement. There was no significant enhancement in the post-contrast study.

Linear T2W/ STIR hyperintense signal was also seen in dorsal cord extending from D4 up to D11 level with a maximum width of 2mm.

Cauda equina nerve roots were unremarkable without any enhancement.

MRA was unrevealing for any regions of dilatation or stenosis in the intracranial vasculature.

Imaging studies of the chest, abdomen, pelvis, and ovaries were otherwise unrevealing for the presence of any malignancy.

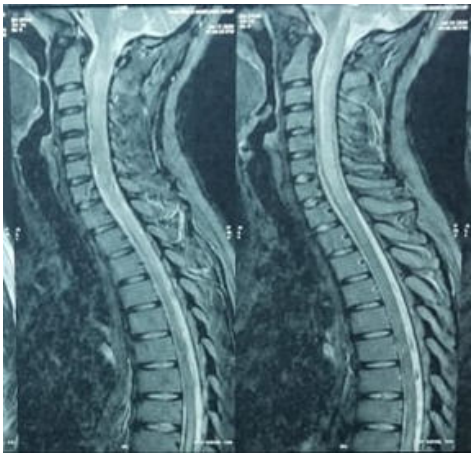

Figure-1

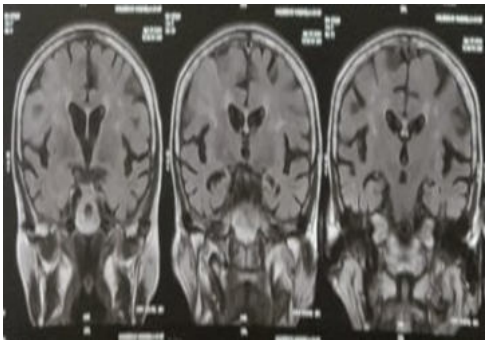

Figure-2

TREATMENT:

She was ultimately diagnosed with Neuromyelitis Optica overlapping with Anti NMDAR Encephalitis.

She showed remarkable improvement after being treated with five cycles of plasma exchange and pulse IV Methylprednisolone therapy (1gm) for five days. She was discharged on Prednisone (1g/kg/day) tablets, Azathioprine (50 mg bid), and Risperidone (5mg/day), and Melatonin with the plan to follow up in one month.

DISCUSSION:

Around 1%–4% of demyelinating diseases in Caucasians are accounted for by NMOSD but between 20% and 48% in southeast Asians [4, 5,]. The average age of onset is 40 years with females accounting for 70%–90% of affected individuals [6]. NMOSD typically involves inflammation of those regions where expression of Aquaporin-4 channels on astrocyte foot processes is predominant as seen in optic nerves, spinal cord, periventricular regions, and brainstem [7]. Complement activation through the binding of antibodies to the astrocyte foot processes is thought to be the primary event in pathogenesis, which ultimately culminates in the activation of other components of the immune system.

Antibody-mediated encephalitides constitute a group of inflammatory brain diseases that are associated with prominent neuropsychiatric symptoms and movement disorders [2]. Young children typically present with sleep disturbances, seizures, dyskinesia, or altered behavior such as irritability, temper tantrums, agitation, and reduction of verbal output. Young children typically present with sleep disturbances, seizures, dyskinesia, or altered behavior such as irritability, temper tantrums, agitation, and reduction of verbal output. Psychiatric symptoms like agitation, hallucinations, delusions, and catatonia are more frequent in teenagers and adults [2]. Autonomic instability manifests as excess salivation, temperature disturbances, fluctuations of blood pressure, tachycardia, or central hypoventilation. Clinical manifestations of NMO are myriad depending on the involvement of the particular areas of the brain and spinal cord with a propensity to affect both the gray matter and white matter. Optic neuritis in NMO is usually bilateral and can cause severe vision loss, unlike Multiple sclerosis. The symptoms and signs of transverse myelitis depend on the spinal level and completeness of the inflammatory changes ranging from motor and sensory changes in extremities, respiratory failure (Cervical myelitis) to bowel and bladder dysfunction (lumbar myelitis). Brainstem involvement manifests with intractable hiccups, vomiting, facial numbness, dysphagia, double vision, and cranial nerve palsies [7]. Lesions of the hypothalamus can present with autonomic instability, SIADH, or endocrinologic disturbances like diabetes insipidus and pubertal disturbances [7].

A demyelinating disease can present simultaneously with anti-NMDAR encephalitis or occur at a distant time [9]. The presence of atypical symptoms for NMOSD like psychiatric symptoms, dysautonomia, and cognitive impairment warrants further investigation for coexisting autoimmune encephalitis such as Anti NMDAR encephalitis. Anti-NMDAR encephalitis has been reported in association with the central nervous system demyelinating diseases, such as ADEM [10], and neuromyelitis optica spectrum disorder [11].

The clinical and radiographic features in our case suggest features of both NMO and Anti NMDA receptor encephalitis. Clinical and radiographic features that could be consistent with NMO include the involvement of the brainstem, hypothalamus, and myelitis. Similarly, psychiatric features, cognitive impairment, and dysautonomia along with the radiographic features of encephalitis might be due to Anti NMDA receptor antibodies.

The initial treatment in patients with such overlapping disorders remains the same as that with either antibody alone. First-line immunotherapy consists of corticosteroids, IVIG, PLEX, or a combination of all of them [12]. In patients with anti-NMDAR encephalitis associated with malignancy, tumor excision should also be performed. Although the initial treatment approach for anti-NMDAR encephalitis and demyelinating disorders is similar, subsequent management and prognosis can be highly variable, which highlights the importance of diagnosing both conditions[12].

CONCLUSION:

Our case represents the rare coexistence of NMOSD and Anti NMDAR encephalitis. The presence of atypical symptoms including psychiatric changes, dysautonomia, cognitive disturbances, or dyskinesias necessitates testing for overlapping autoimmune encephalitis.

Given the potentially deleterious consequences of delay in diagnosis and prompt treatment, it is prudent to have a high index of suspicion for such overlapping conditions in patients presenting with signs and symptoms that can't be explained alone by either NMOSD or Anti NMDAR encephalitis.

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