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Case Report

Neuropathic pruritus: an early indicator of neuromyelitis optica spectrum disorders

Pradeep Kumar Bansal*, C. L. Nawal, Aradhana Singh, Radheyshyam Chejara, Sebastian Marker, Pankaj Mangal

Department of Medicine, SMS Medical College, Jaipur, Rajasthan, India

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***Correspondence:**
Dr. Pradeep Kumar Bansal,
E-mail: drpkbansal22@gmail.com

ABSTRACT

Neuromyelitis optica is a relapsing, inflammatory astrocytopathic disorder, affecting predominantly the optic nerves and spinal cord. It is associated with antiaquaporin-4 immunoglobulin G (AQP4-IgG) in up to 70% of patients. Spinal cord involvement typically presents as a longitudinally-extensive transverse myelitis, with associated sensorimotor and sphincter dysfunction. Sensory symptoms such as numbness, dysaesthesia, pain and tonic spasms are common. Here, we present a case of a 25years old female who came to the medicine OPD, with the chief complaints of intense itching over face and forehead, which was later on progressed to quadriparesis after 3 weeks. This case highlights neuropathic pruritus as an under-recognised early feature of neuromyelitis optica.

Keywords: AQP4-IgG, NMOSD, Neuropathic pruritus

INTRODUCTION

Neuromyelitis optica (NMO) is an inflammatory disorder affecting the central nervous system (CNS). Previously it was thought to be closely related to multiple sclerosis (MS), but more recently, it was found to represent a distinct clinical and pathophysiologic entity.

Early in the course of the disease, it may be difficult to distinguish between neuromyelitis optica and multiple sclerosis because both may cause optic neuritis and myelitis as symptoms. However, the optic neuritis and myelitis tend to be more severe in neuromyelitis optica; the brain MRI is more commonly normal, and the spinal fluid analysis does not usually show oligoclonal bands in neuromyelitis optica, which are features that help distinguish it from MS. The characteristic symptoms of neuromyelitis optica are either optic neuritis or myelitis; either may occur as the first symptom.

The diagnosis of neuromyelitis optica spectrum disorders is based on the typical clinical and MRI features of the core clinical syndromes as well as laboratory evidence of the disease. The core clinical features of neuromyelitis optica spectrum disorders include optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome, and symptomatic cerebral syndrome. Optic neuritis that is simultaneously bilateral or severe with poor recovery (acuity 20/200 or worse) despite treatment should raise suspicion for a neuromyelitis optica spectrum disorder. The hallmark of myelitis in a neuromyelitis optica spectrum disorder is that it is typically longitudinally extensive, spanning at least three vertebral segments on MRI. The identification of antibodies to aquaporin -4, a water channel present on astrocytic foot processes, heavily expressed in the optic nerves, brainstem, and spinal cord, and their subsequent demonstration that these antibodies are pathogenic increases its diagnostic significance.[1-4]

An area postrema syndrome, characterized by intractable hiccups, nausea, and vomiting, occurs in up to 43% of patients with neuromyelitis optica spectrum disorders.[5-7] A single attack of neuromyelitis optica spectrum disorder may leave a patient blind or paraplegic or may result in death due to respiratory compromise. Effective preventive therapy is therefore of utmost importance, and therapy initiation should be viewed as urgent.

As NMO carries significant morbidity and, at times, mortality, prompt and accurate diagnosis, followed by swift initiation of therapy for acute exacerbations, and then, prevention of further relapses, is critical. The revised diagnostic criteria's suggest simplification of previously used terminology, such that all patients, now fall under the umbrella of NMO spectrum disorders.

CASE REPORT

A 25-year-old woman presented to out patient department with severe itching sensation all over face and forehead (Figure 1A and 1B). There was no rash, or swelling over the area. She denied any history of drug intake, insect bite, fever, jaundice, previous allergies, or other systemic symptoms. She was prescribed some antihistaminics, and adviced to review in skin opd. Her symptoms persisted, and she returned to emergency department after one week, with same complaint, along with nausea and vomiting. She was prescribed some injectable PPI and antiemetics and discharged with oral antiemetics and PPI. After discharged from emergency she visited many times to local physician for same symptoms but did not get relieved.

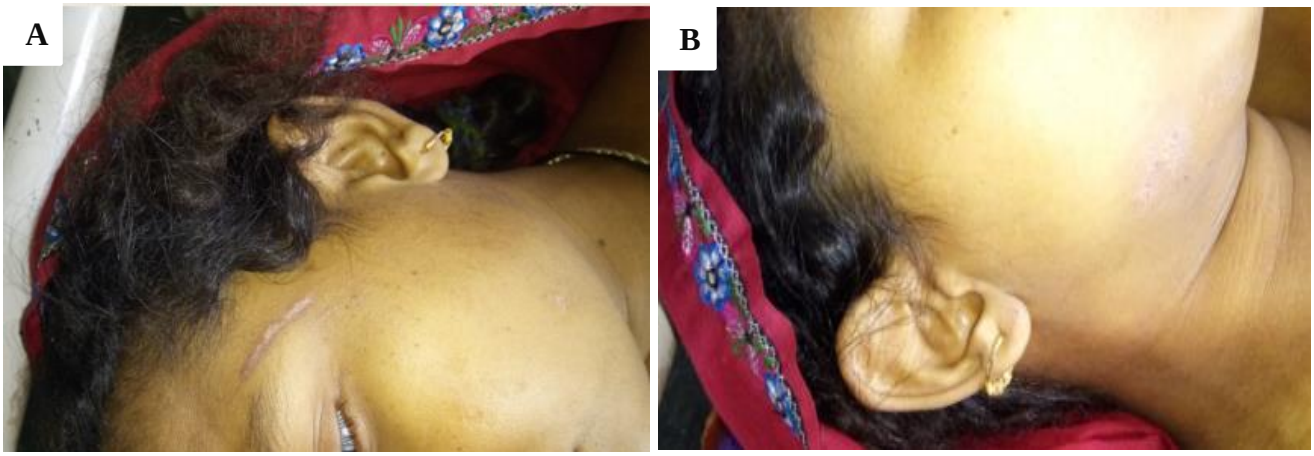

Figure 1: Itching scratch. A) Itching scratch marks above eyebrow. B) Itching scratch marks below chin.

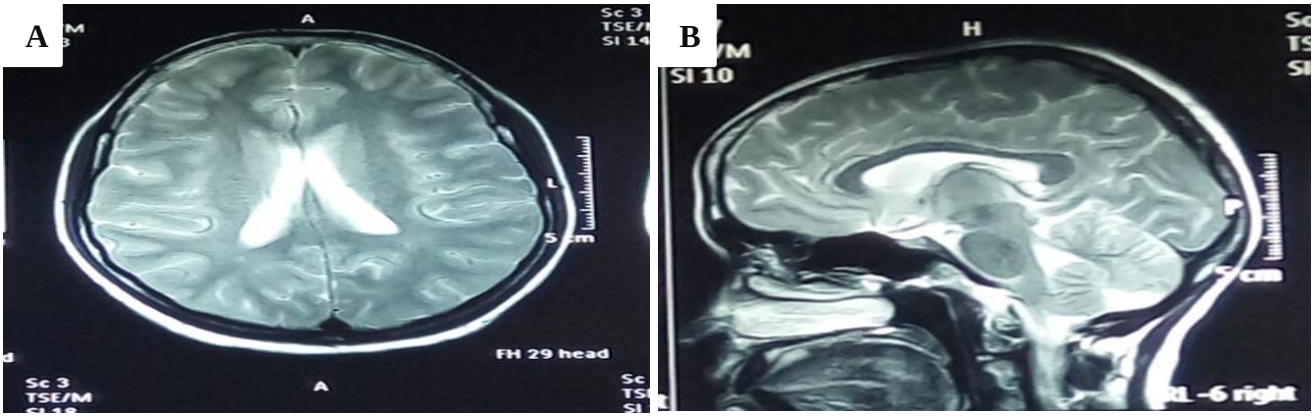

Figure 2: MRI. A) MRI of the brain axial. B) MRI of sagittal view show normal study.

After three weeks, patient returned to the emergency department with severe vomiting, headache, and weakness of left upper and lower extremity for last 2 days, which gradually progressed to involve right extremity also after two days of admission. She also started having urinary retention during the period of admission. She denied trauma, recent infection, paresthesia, cramps, dysphagia, facial droop, visual symptoms, aphasia, bowel involvement, and there were no constitutional symptoms. Her history did not suggest any malignancy and autoimmune disorders.

On examination, the patient had a regular heart rate of 84/min, respiratory rate of 16/min, blood pressure was 134/96mmhg in right arm supine position, and an oxygen saturation of 96% on room air. On neurological examination, mentation and cranial nerves were normal, tone was increased in bilateral lower limb, power in

bilateral shoulder and wrist joint was 3/5, bilateral elbow 4/5, bilateral hip, knee, ankle was 2/5. Deep tendon reflexes in biceps, triceps, supinator, knee, ankle were brisk. Plantars were bilaterally extensor. Abdominal reflexes were absent in all the quadrants.

On sensory examination, pain and touch sensation were decreased till clavicle, joint position, vibration and temperature sensation were normal. Signs of meningeal irritation were absent. Gait was unsteady. Coordination could not be assessed. Other systemic examination were within normal limit.

Given focal neurological findings, magnetic resonance imaging (MRI) of the brain, MRI of the cervical spine and lumbar puncture (LP) were performed. Magnetic resonance imaging of the brain, with and without contrast, showed no acute intracranial event (Figure 2A and 2B).

Lumbar puncture showed normal glucose and protein, with no pleocytosis. Cerebrospinal fluid was negative for any microorganisms, or neoplastic cells. Serologic testing was negative for cytomegalovirus, human immunodeficiency virus, Lyme, syphilis, and herpes simplex virus. Complete blood count and biochemistry examination were within normal limit. Based on these findings, there was suspicion for first episode of multiple sclerosis or transverse myelitis causing symptoms. Neoplasm or vasculitis profile was negative. Keeping this in mind, VEP was done, which showed delayed latencies on both the sides (Figure 3).

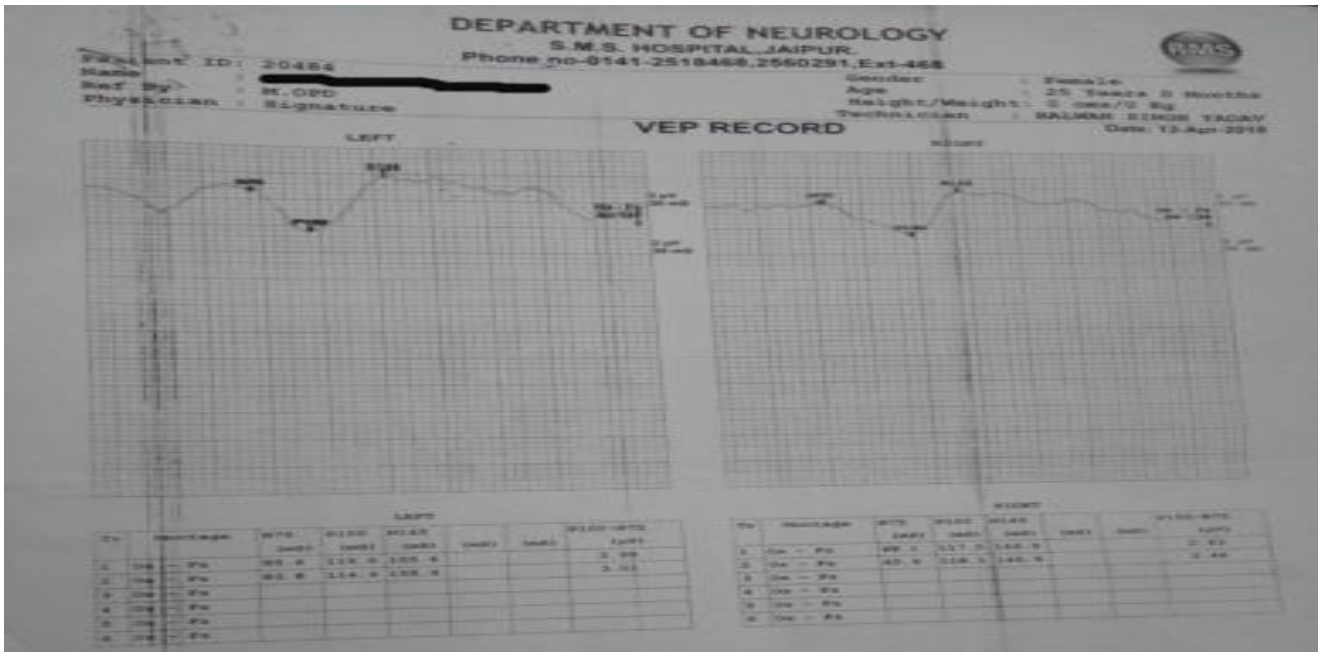

Figure 3: VEP study shows delayed P100 wave peak latencies on both sides.

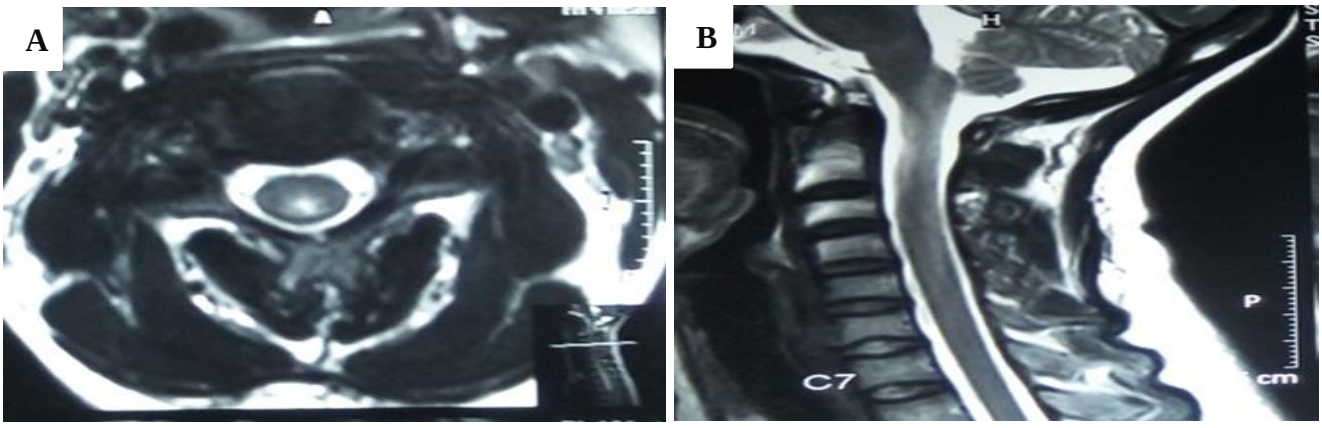

Figure 4: Various postcontrast view of the cervical spine. A) Postcontrast axial view of the cervical spine showing intramedullary signal intensity suggesting transverse myelitis. B) Postcontrast sagittal view of the cervical spine showing intramedullary signal intensity seen extending from cervicomedullary junction to C5, suggesting long segment transverse myelitis.

Our patient met the diagnostic criteria for NMO by having two of the absolute criteria (acute myelitis and optic neuritis) and two of the supportive criteria (brain MRI not meeting criteria for multiple sclerosis diagnosis and longitudinally extensive transverse myelitis on T2-weighted imaging on MRI) (Figure 4A and 4B). She was was negative for AQP4-Ab, so the diagnosis of seronegative NMOSD was made. The patient was started on methylprednisolone 1gm for 5 days. Due to the severity of NMO, with no improvement after steroids, the decision was taken for plasma exchange. After two sessions of plasma exchange, the patient's condition improved, and she regained some strength in her lower extremity. Patient completed five cycles of plasma exchange, and was discharged with steroid and azathioprine, with follow-up in neurology clinic.

DISCUSSION

Neuromyelitis optica, also known as Devic's disease, is an autoimmune demyelinating disorder of the central nervous system. The disorder was first described in 1870 and was confused with MS for many years. The distinction between NMO and MS is based on pathogenesis, antibody studies, imaging, and response to treatment. The advent of NMO-IgG/AQP4 was pivotal in differentiating the two disease entities. This distinction is important not only for nomenclature, but also for therapeutic decisions, as some immunotherapeutic agents used for treatment of MS can aggravate the symptoms of NMO.[8]

The International Panel for NMO Diagnosis (IPND) revised diagnostic criteria defined the term NMOSD. The term NMOSD was introduced in 2007, to include those patients presenting with atypical form of the disease, and were positive for AQP4-IgG serology, those with AQP-IgG seropositivity and concomitant autoimmune disorders, and those with cerebral, diencephalic, and brainstem lesions occurring in patients with typical NMO. In 2015, IPND unified the term NMO and NMOSD, and developed the new diagnostic criteria of NMOSD, based on the occurrence of core clinical characteristics with or without detection of AQP4 antibody.[9] The core clinical characteristics include the following:

- Optic neuritis,
- Acute myelitis,
- Area postrema syndrome,
- Acute brainstem syndrome,
- Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions, and
- Symptomatic cerebral syndrome with NMOSD-typical brain lesions.[9]

Patients without AQP4-IgG seropositivity have more strict criteria which include 2 or more core clinical characteristics and specific MRI characteristics. A longitudinally extensive transverse myelitis (LETM) extending over 3 or more vertebral segments, as in our patient, is the most specific neuroimaging characteristic of NMOSD, and very uncommon in patients with MS.[10]

Brainstem syndromes occur frequently in NMO spectrum disorders. A multicentre international study noted brainstem symptoms in 81 of 258 patients (31.4%).[11] Of these, vomiting (33.1%) and hiccups (22.3%) were most common; oculomotor abnormalities (19.8%) and pruritus (12.4%) were also frequently reported. Less commonly reported were hearing loss, facial palsy, and trigeminal neuralgia (2.5% each); vertigo or vestibular ataxia (1.7%); and other cranial nerve abnormalities (3.3%).

Neuropathic pruritus was reported in only 4.5% of a series of multiple sclerosis patients while in other two case series, patients with neuromyelitis optica reported neuropathic pruritus much more frequently, between 12% and 27%.[11-13]

Neuropathic pruritus in neuromyelitis optica may reflect the typical central cord lesions affecting dorsal horn neurones, the dorsal horn being rich in mediators of pruritus,or lesions surrounding periaqueductal grey matter.[14]

The AQP4 serum autoantibody, also known as NMO-IgG, has a sensitivity of 91% and specificity of 100% for NMO, and is positive in up to 80% of patients.[9] The AQP4 is a water channel in the brain, which is highly localized in astrocytes. These antibodies may be responsible for a variety of immune events which includes immunoglobulin deposition, demyelination, and complement-mediated cytotoxicity.[15] The development of new antigenic targets, such as AQP1 and myelin oligodendrocyte glycoprotein in AQP4-seronegative patients, may allow for novel treatment options.[16]

Acute attacks are treated with intravenous glucocorticoids, followed by plasma exchange for refractory cases, as our patient. Recurrent attacks are treated with long-term immunosuppression. There are multiple empiric immune-modulating therapeutic options employed. However, none have been proven effective in prospective trials, or led to the development of complicated infections.[17] Immunosuppression is continued for at least 5 years in seropositive patients presenting with an initial attack, as they are at high risk for relapse. As of now, there is no consensus over the total duration of therapy.

The recommended agents include oral azathioprine or mycophenolate mofetil, with or without oral steroids.[18]At present, seronegative and seropositive NMOSDs are managed similarly. The complement fixation pathway, which includes antibody formation and activating the membrane attack complex, plays a key role in NMOSD

relapses. Thus, restoring the loss of immune tolerance is fundamental in developing novel NMOSD treatment modalities.[19] New therapies such as anti-IL6 receptor, anticomplement, and anti-AQP4 antibody biologicals are promising future options.[20] The long-term disability and mortality rates of NMOSD are high and there is a stepwise deterioration of function.

Our patient presented with a protean manifestation of NMOSD, that is, pruritus. We highlight the importance of recognizing unusual presentations of NMOSD, and the need for early identification and treatment.

CONCLUSION

NMO should be thought of in the differential diagnosis in any patient presenting with transverse myelitis and other unusual manifestation regardless of the gender and race. Negative AQP4-Ab cannot exclude the diagnosis, but rather, it should trigger further evaluation of pathophysiology, manifestation, and prognosis. Treatment is similar between seropositive and seronegative NMO; however, new studies showed promising results using rituximab as an alternative first-line therapy. Future studies and research are still needed to evaluate the prognostic outcome of both groups.

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