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CASE REPORT

A Case of Aquaporin-4 (AQP4) Antibody Positive NMOSD without Optic Neuritis

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Abstract:

Neuromyelitis optica spectrum disorders (NMOSD) previously known as Devic disease or Neuromyelitis optica (NMO) are inflammatory disorders of the central nervous system characterized by severe immune-mediated demyelination and axonal damage predominantly targeting optic nerves and spinal cord. Long segment myelitis, severe optic neuritis, and/or bouts of intractable vomiting and hiccups are classic presentations of the disease and may alert the clinician to the diagnosis. Approximately 75% of patients have antibodies against aquaporin-4. Previously, to diagnose NMO, optic nerve involvement was mandatory but in recent times concept of NMO has changed to NMOSD where we can categorize NMOSD even without optic nerve involvement. In this study we have discussed about a 22 years old lady presented to our inpatient department with inability to walk & incontinence of bowel & bladder. MRI spine showed long segment myelitis involving C5 to D6 level & CSF study revealed Aquaporin-4 (AQP4) Ab positive but optic nerves were normal. We diagnosed her as a case of NMOSD. She was put on intravenous methyl prednisolone 1 g daily for 5 days, followed by oral prednisolone and her muscle power improved to a extent that she could walk with assistance. Thereafter she was given azathioprine with good compliance.

Keywords : Neuromyelitis optica (NMO), Neuromyelitis optica spectrum disorder (NMOSD), Aquaporin-4 (AQP4) Ab

Introduction:

Neuromyelitis optica (NMO) is an autoimmune disorder of the central nervous system characterized by optic neuritis and myelitis and was first recognized over a century ago [1,2,3]. The term neuromyelitis optica (derived from neuro-myélite optique aiguë) was first described by Eugène Devic and his doctoral student Fernand Gault in 1894[7].The relation between NMO and multiple sclerosis had been debated for a long time, but after the discovery of NMO-specific aquaporin 4 (AQP4)-antibody [4,5], numerous reports have clarified that NMO has clinical, MRI, laboratory, and immunopathological features distinct from multiple sclerosis[3]. As brain syndromes also occur in NMO, the term NMO spectrum disorders (NMOSD) to cover the entire clinical spectrum was proposed in the international consensus diagnostic criteria in

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2015 [6]The reported incidence and prevalence of NMOSD are dependent on geographical location and ethnicity. Asians and those of African ancestry are at increased risk, with high mortality rates[10,11]. The incidence and prevalence of NMOSD ranges from 0.05–0.40 and 0.52–4.4 per 100,000 people respectively[12]. As with many autoimmune diseases, females are more susceptible than males (3:1–9:1) [13]. AQP4 is the most widely expressed water channel in the brain, spinal cord, and optic nerves. Within the brain, AQP4 is located in regions in contact with cerebrospinal fluid and is specifically localised to the foot processes of astrocytes at the blood brain barrier [14, 15]. In Neuromyelitis optica spectrum disorder (NMOSD) long segment myelitis, severe optic neuritis, and/or bouts of intractable vomiting and hiccoughs (area postrema syndrome) are classic presentations of the disease [8]. Here, we have discussed about an adult case which was diagnosed as a case of NMOSD on the basis of positive aquaporin 4 (AQP4)-antibody, long segment myelitis & other possible causes excluded.

Case summary

A 22-year-old right handed young lady of nonconsanguinous parents presented with weakness of all four limbs for 1 month. Her weakness was insidious in onset, progressed for 20 days and then remained static.Her weakness started in all 4 limbs simultaneously and patient became bed bound within 2 weeks. Weakness was associated with marked sensory loss significantly in lower limbs and prominent bowel and bladder involvement in the form of urinary and fecal incontinence. She also had tingling and paresthesia in her limbs without any significant muscle wasting. There was no history of pain and trauma to her spine. She did not give any history of fever, anorexia, nausea, vomiting, hiccup, weight loss, drowsiness, visual disturbance, headache or difficulty in deglutition. She also gave no history of skin rash photosensitivity, arthralgia or oral ulceration. She had uneventful birth history with normal milestone of development. Her academic performance was also satisfactory. She had no significant family H/O illness.

On general examination her vitals were normal without any skin manifestations and thyromegaly. On nervous system examinations she had normal higher cerebral function and speech. All cranial nerves including fundus were normal. She had no muscle wasting, power was MRC grade 2 in lower limbs and 3 in upper limbs (both proximal and distal). All deep tendon reflexes were exaggerated in upper and lower limbs. Planter response were extensors and Hoffman response were present bilaterally. Her abdominal reflex was lost. All modalities of sensation including touch, pain, position and vibration were lost in both upper and lower limbs. She had normal cerebellar function with no sign of meningeal irritation and spinal tenderness or deformity.

We decided to perform MRI of cervical spine with screening of whole spine which revealed diffuse spinal cord swelling from C5 to D6 level along with T1 iso to hypo and T2 hyper intensity within the cord. Bony structures were normal without any root compression. CSF analysis revealed no WBC and RBC, glucose 6.4mol/l, proten 0.47 g/l, with no oligoclonal band (OCB). Aquaporin-4 IgG was positive with normal IgG index (0.47). Reports of other investigations as follows: MRI of brain normal, Hb 12.0g/dl, ESR 15 mm in 1st hr, WBC 11000/ cumm, random blood glucose 5.1 mmol/l, Serum Na 137 mmol/l, K 4.1 mmol/l, Cl 102 mmol/l, creatinine 0.56 mg/dl. She had normal vasculitic marker including ANA, Anti-ds DNA, p-ANCA and c-ANCA. Colour fundal photograph was normal.

Considering above mentioned scenario she was diagnosed as Neuromyelitis optica spectrum disorder (NMOSD). She was put on intravenous methyl prednisolone 1 g daily for 5 days followed by oral prednisolone and her power improved to a extent that she could walk with assistance. Her sensory symptoms and bowel-bladder incontinence were also showed to improve. We discharged the patient with power MRC grade 4- in lower limbs and 4+ in upper limbs.Her prednisolone dose was gradually tapered and azathioprine started to prevent relapse. About 4 months later she was able to do her daily activities with mild difficulty with no bowel-bladder symptoms.

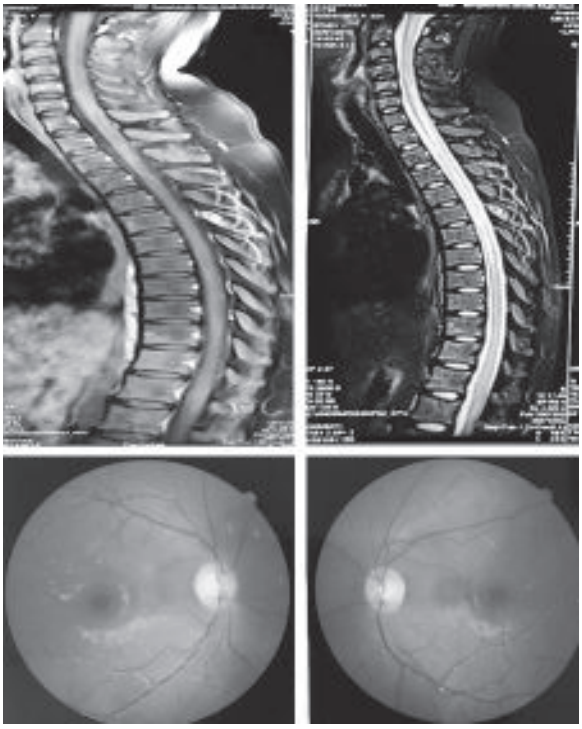

Fig.-1: *MRI of spine and colour fundal photograph of both eyes. T1WI iso to hypo and patchy T2WI hyper intensity with cord swelling from C5-D6. Nomal colour fundal photograph.*

Discussion:

Neuromyelitis optica spectrum disorder (NMOSD) is a central nervous system disease associated with aquaporin-4 antibody but often antibody may not be present (seronegative NMOSD). Diagnostic criteria for NMOSD, which incorporates classic clinical presentations of the disease. Diagnostic criteria for NMOSD with AQP4-IgG incorporate A. At least 1 core clinical characteristic - 1. Optic neuritis, 2. Acute myelitis, 3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting, 4. Acute brainstem syndrome, 5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions, 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions B. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended), C. Exclusion of alternative diagnosis[9].

NMOSD involves regions of the central nervous system (CNS) where AQP4 is most abundantly expressed; spinal cord (longitudinally extensive transverse myelitis), optic nerve (optic neuritis), dorsal medulla (area postrema syndrome), brainstem (acute brainstem syndromes), and thalamus/hypothalamus (acute diencephalic syndromes eg symptomatic narcolepsy). Attacks are frequently severe and often reach nadir in less than a week[8]. In this case we found her maximum deficit within 2 weeks. Longitudinally extensive transverse myelitis (LETM) is the most specific presentation of NMOSD. LETM typically consists of inflammation affecting the central gray matter, extending over three or more contiguous vertebral bodies[16]. LETM often results in para- or tetraplegia depending on the spinal cord level involved[8].

We found her tetraplegic with long segment myelitis (more than 3 vertebral body). Optic neuritis (ON) in NMOSD is also typically longitudinally extensive and has a predilection for posterior optic nerve segments, particularly the optic chiasm. Bilateral simultaneous involvement and painful severe visual loss with poor recovery are often clues for diagnosis [8]. Fortunately, we evaluated her as a case of NMOSD without optic nerve involvement. For diagnosis, one of the six core clinical characteristics (LETM, ON, APS, symptomatic brainstem, diencephalic, or cerebral syndromes) with AQP4-Abs is sufficient to make a diagnosis of NMOSD. AQP4-Ab assays, the cell based assay (CBA) has showed the highest sensitivity (76.7%) and specificity (99.8%)[17]. Furthermore, following an episode of LETM the presence of AQP4-Abs confers a 50% risk of further relapse in the next 12 months [18]. In addition to MRI of whole spine & CSF study (routine, Aquaporin-4 antibody& OCB), other important investigations are MRI of brain (contrast if needed), MOG-antibodies in case of seronegative NMOSD, ANA, anti-ds DNA, c-ANCA, p-ANCA, anti-Ro, anti-La, fundal photograph, visual evoked potentials and optical coherence tomography.

Acute treatment of an NMOSD attack consists of high dose steroids (HDS), typically 1 gram of intravenous methylprednisolone daily for 5 days; oral prednisolone 1 mg/kg is then continued for weeks, followed by gradual taper over months.

Earlier treatment is ideal and with severe neurological deficits, if improvement is not seen within days of HDS, plasma exchange (PLEX; 5 cycles) should be commenced[19]. We treated her accordingly but did not undergo plasma exchange. Her treatment response was satisfactory after giving pulse methylprednisolone.

Approximately 50% of NMOSD patients will be wheelchair dependent and blind if untreated and a third will have died within 5 years of their first attack[20]. So, we must treat all patients with AQP4-Abs at their first attack with long-term immunosuppression. The most commonly used first line immunosuppressants (IS) in NMOSD are mycophenolate mofetil (MMF; 2–3 grams/day) and azathioprine (AZA; 2.5–3 mg/kg)[21]. We prescribed her Azathioprine 50 mg, 1 tab twice daily. On follow up, her drug compliance was good & overall condition improved.

Conclusion:

Neuromyelitis optica spectrum disorder (NMOSD) is a central nervous system disease usually associated with aquaporin-4 antibodies. Common presentations include longitudinally extensive myelitis, severe optic neuritis, and area postrema syndrome. Prompt and aggressive treatment of relapses with high dose steroids +/- plasma exchange improves outcomes. All patients with aquaporin-4 antibodies should be immuno-suppressed indefinitely to prevent further attacks. We should keep it in our mind that NMOSD can be presented without optic neuritis according to 2015 international diagnostic criteria. Life may be jeopardized if we underdiagnose NMOSD, those who have normal optic nerve.

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