Case report

A Case-Report on Double Seronegative Neuromyelitis Optica Spectrum Disorder (DN NMOSD)

ABSTRACT

Neuromyelitis optica spectrum disorder (NMOSD), formerly known as neuromyelitis optica or Devic's disease, affects roughly 0.3 to 4.4 individuals per 100,000. NMOSD is a peculiar inflammatory disease of the central nervous system that manifests clinically as optic neuritis, transverse myelitis, and specific brainstem and brain-inside syndrome. Here we presented a 55-year-old patient who had been normal months prior to developing numbness of the right half of the face and a history of swaying to the right side. He was treated outside with a five-day course of methylprednisolone pulse, and his symptoms improved. However, after three months, he developed the same and came here for further management following a second pulse of steroids. The investigations suggested left-sided facial nerve involvement, sensory loss, and impaired JPS/vibration sense in the toes, positive Romberg's, and gait ataxia. Based on the MRI findings of T2/FLAIR hyperintense lesions, CSF analysis, and other assessments, it indicates a condition that could be consistent with NMOSD. However, the absence of serum Aquaporin-4 (AQP4) antibody and Myelin Oligodendrocyte Glycoprotein (MOG) antibodies makes the diagnosis less certain. The patient was treated effectively for the condition with appropriate glycemic control and monitoring for recurrence and progression for any modifications in the treatment as needed.

Keywords: *Double seronegative; Neuromyelitis Optica Spectrum Disorder; Optic neuritis; Transverse myelitis; Aquaporin 4 antibody; Intravenous Immunoglobulin.*

1. INTRODUCTION

A rare inflammatory condition of the central nervous system (CNS), called neuromyelitis optica spectrum disorder (NMOSD), which was previously thought to be a subtype of multiple sclerosis (MS), is now a widely acknowledged distinct disease entity.[1] NMOSD, formerly known as Neuromyelitis optica or Devic's illness, was initially identified by Dr. Eugene Devic in 1894 while evaluating a patient presented with optic neuritis with neuromuscular manifestations.[2] Roughly 0.3 to 4.4 people per 100,000 were impacted by NMOSD. This condition is typically seen more in women (80%) and is most common among patients aged 30 to 40.[3] The clinical manifestations of NMOSD are optic neuritis, myelitis, and specific brainstem and brain inside syndromes.[4] Presence of pathogenic immunoglobulin G (IgG) antibodies to aquaporin-4 (AQP4), a common CNS water channel, and Myoglobulin Oligodendrocyte Glycoprotein antibodies are linked to NMOSD. Irrespective of ethnicity, there is a significant female preponderance among patients with AQP4-IgG-seropositive status, who constitute a significant proportion of NMOSD, whereas the female:male ratio may vary from 10:1, whereas among seronegative patients, this might reach 3:1.[5] Double-negative NMOSD is a condition in which NMOSD is negative for both aquaporin-4 antibody (AQP4-IgG) and myelin oligodendrocyte glycoprotein antibodies (MOG-IgG). In recent studies, the median onset age of DN NMO/NMOSD ranged from 32 to 43 years with almost equal sex ratios or with a mild female predominance in contrast with the marked female predominance observed in AQP4-IgG+ patients.[6] Most individuals identified as having DN NMOSD will have a combination of brain or brainstem instances typical of NMOSD, longitudinally extensive ON, and

(or) longitudinally extensive transverse myelitis (LETM). The inflammatory response gets more intense in DN NMOSD, as reflected by significantly increased serum proinflammatory cytokines, similar to that in AQP4-IgG+ NMOSD. Several studies have proven that the CSF of DN NMO/NMOSD patients contains a substantial quantity of interleukin 6 (IL-6).[7] Combining strategies may yield further understanding because DN NMOSD is a miscellaneous group without a biomarker. It has been set up that DN NMOSD cases express four distinct patterns: classic NMO-suchlike (high chance of bilateral ON and LETM with normal brain appearance); spinal MS-suchlike (had short-member myelitis and no MS-suchlike brain lesions); NMO-suchlike with brain involvement (a history of NMOSD-brain lesions and LETM); and MS-like (frequently had cortical lesions and central tone signs).[8] Double-seronegative cases exhibited more extended subependymal lesions than Myelin Oligodendrocyte Glycoprotein Antibody-associated Diseases (MOGAD) cases and added extended corpus callosum lesions than MOGAD and AQP4-IgG NMOSD cases. It showed more extended lesions of the optic pathways, with additional parts being affected, particularly in the intracranial regions, and also experienced worse residual disability compared with those with AQP4-IgG NMOSD.[9] The patient who experienced central nervous system (CNS) inflammatory conditions, such as multiple sclerosis or sarcoidosis, could be the obvious cause of DN NMOSD, which could be presented as monophasic or relapsing. Either way, double-negative NMOSD is fluently not a single complaint but a pattern with differing treatment conditions.[10]

2. PRESENTATION OF CASE

A 55 year old male patient who is a known diabetic, was apparently normal months back developed numbness of right half of face and history of swaying to the right side. Patient got outside pulse dose of MPS for 5days and on tapering dose of steroids and patient symptoms improved over a period of time. Patient developed decreased sensation in left half of face and swaying to the left with h/o blurring of vision after three months and got 2nd pulse dose IV steroids and on tapering oral steroids. Now patient came for further management.

2.1 NEUROLOGICAL EXAMINATION:

- EOM: Full, indicating no restriction in eye movements.
- B/L PERL: Change of 3mm, which is within normal limits.
- No relative afferent pupillary defect (RAPD).
- Fundus (BE): Disc margins are visualized bilaterally. Facial sensation reduced in the left half of the face. This suggests a possible lesion affecting the sensory pathways for the left side of the face, likely involving the trigeminal nerve or central pathways.
- Deviation of angle of mouth to right side, possibly due to facial nerve involvement.
- Reduced nasolabial fold on left side. Not able to hold air tightly in mouth due to weakness in the orbicularis oris muscle on the left side.
- Wrinkling present in left forehead and able to close left eye tightly: This suggests that the upper facial muscles are still functioning, indicating that the facial nerve might not be completely affected.
- Motor Examination:
  - Tone is normal in all limbs.
  - Power is 5/5 in both upper limbs, 4-/5 in proximal lower limbs, and 5/5 in distal lower limbs.
  - Deep tendon reflexes (DTR) are likely normal.
- Sensory Examination
  - Touch and pain sensations are intact, but joint position sense (JPS) and vibration sense are impaired in the toes bilaterally, indicating possible peripheral neuropathy or spinal cord involvement.
- Romberg's Test Positive: This indicates a problem with proprioception or vestibular function.
- Cerebellar Examination:
  - Finger-nose test (FNT) and fast finger-nose test (FFNT) are intact.
  - Heel-knee test (HKT) is impaired, suggesting some cerebellar dysfunction.
  - No truncal ataxia, but gait ataxia and broad-based gait are present, indicating possible cerebellar or vestibular issues.
  - Impaired tandem walking further supports this.
- Spine & Cranium Normal: Indicates no structural abnormalities detected. No Signs of Meningeal Irritation.

Further diagnostic imaging (like MRI) and tests may be warranted to determine the underlying cause. Here's a detailed analysis:

(i) CSF Analysis:

- CSF glucose level: 152 mg/dl.
- Protein - 0.1 mg/dl is quite low.

- The presence of occasional RBCs.
- Serum NMO (AQP) and MOG not detected.
- In the follow-up CSF analysis, the protein level increased to 73.40 mg/dl, which is elevated and suggests a possible inflammatory process. The cell count of 10 cells/cu.mm with a DC showing 30% neutrophils and 70% lymphocytes.
- CSF OCB (IgG) – absent.

(ii) MRI Findings:

- The MRI findings of T2/FLAIR hyperintensity in the right medulla, pons, cerebellar peduncles, and peritrigonal region are suggestive of demyelination. The lack of diffusion restriction or significant contrast enhancement may indicate that the lesions are not acutely inflamed.
- The whole spine screening showing no features of demyelination.
- CV Doppler is normal.

(iii). Other Laboratory Findings:

- LFT and RFT are within normal ranges, the elevated blood sugar levels (RBS) indicate possible hyperglycaemia. Monitoring and managing blood sugar levels will be important.

Based on the clinical details and laboratory findings, it appears that the patient is experiencing a complex neurological condition, possibly related to demyelination.

2.2. CLINICAL COURSE:

Based on the course of treatment in the hospital, the patient is being managed for a central demyelinating disorder, specifically suspected DN NMOSD. The treatment regimen includes:

- Intravenous Immunoglobulin (IVIg): Administered at a dose of 2g/kg over 5 days. IVIg to modulate the immune response and reduce inflammation.
- The patient is on a tapering dose of prednisolone 5mg.
- Oral Hypoglycaemic Agents (OHAs) and Human Insulin for managing blood glucose levels.

2.3. ADVICE ON DISCHARGE:

1. Steroids: T.Prednisolone 5mg (3-0-0). To help manage inflammation and symptoms related to the demyelinating disorder.
2. T.Calcium 150mg (0-2-0), to support bone health, especially important when on long-term steroid therapy.
3. Oral Hypoglycaemic Agents:
    - T. Metformin 500mg: To be taken twice a day (1-0-1).
    - T. Vildagliptin 50mg: To be taken once daily (1-0-0).
    - T. Glimepride 2mg: To be taken once daily (1-0-0).
    - T. Voglibose 0.2mg: To be taken once a day (0-0-1).

These medications helps to control blood sugar spikes.

4. Insulin:
    - INJ Regular insulin: Dosage of 14-12-10 to be administered half an hour before meals for immediate control of blood sugar levels.
    - INJ. Monotard insulin: Dosage of 14-0-12 to be administered half an hour after meals. This is a long-acting insulin to provide baseline blood sugar control.

Additionally, the patient is advised to review in the Neuromedicine department on alternative days after 14 days to monitor progress and adjust treatment as necessary.

Challenges in diagnosis: Since the diagnosis of NMOSD is mostly based on the presence of AQPO4 and/or MOG antibody, as approximately 80% of NMOSD patients can be seropositive, the double seronegative assessment along with optic neuritis was a great challenge. The clinical findings are suggestive of NMOSD with AQPO4 and MOG antibody seronegative.

3. DISCUSSION

NMOSD is an autoimmune condition that primarily affects the central nervous system, with a particular affinity for the optic nerves, spinal cord, and brainstem. The autoimmune response is centered around IgG antibodies targeting aquaporin-4. AQP4-IgG antibodies are present in approximately 80% of NMOSD patients. Among those who are negative for AQP4-IgG, about half are classified as having myelin oligodendrocyte glycoprotein (MOG)-antibody positive NMOSD. The characteristics of double-negative NMOSD still require further clarification. The patient met the diagnostic criteria for "NMOSD with unknown AQP4-IgG," as indicated by the presence of two key clinical features: optic neuritis and acute myelitis. [8]

Epidemiology: The incidence and prevalence of NMOSD vary between 0.05–0.40 and 0.52–4.4 per 100,000 individuals, respectively. Prevalence rates were highest in the French West Indies and South Korea, and lowest in Cuba and Australia. In all regions, the rates were higher in females than in males. [9]

Clinical findings: While NMOSD may manifest as monophasic in AQP4-IgG-negative patients, it usually follows a recurrent course in the majority of AQP4-IgG-positive patients. Patients suspected of having myelitis should be assessed for sensory, motor (including respiratory), bladder/bowel, and sexual dysfunction. Additionally, a wide range of brainstem symptoms beyond APS, such as oculomotor disturbances, facial palsy or numbness, and ataxia, has been observed in NMOSD patients, so comprehensive evaluation for brainstem involvement is essential. Even after a single attack, patients may experience significant, lasting disability, particularly if the attack is not promptly and appropriately treated.[10]

Biomarkers: Double seronegative (DN) NMOSD is not a single disease but a syndrome with varying treatment needs. In AQP4-IgG-negative NMOSD cases, the percentage of DN patients varies from 0% to 79%. Like AQP4-IgG-positive NMOSD, DN NMOSD shows an increased inflammatory response, with elevated serum pro-inflammatory cytokines. Studies have found high levels of interleukin 6 (IL-6) in the CSF of DN patients, and CSF neurofilament light chain (NFL) levels are notably higher in DN NMOSD compared to AQP4-IgG-positive NMOSD or MOGAD, suggesting significant neuronal damage. Most DN NMOSD patients experience longitudinally extensive optic neuritis, transverse myelitis, and/or typical brainstem attacks. Approximately 20-50% of these patients suffer from severe visual impairment.[11]

Diagnostic techniques: Due to its heterogeneity and absence of a unique biomarker, DN NMOSD requires a combination of diagnostic techniques. In this case, the patient's clinical findings suggest left-sided facial nerve involvement, potentially from a central lesion affecting the facial nerve pathway, such as a stroke. Sensory loss and impaired JPS/vibration sense in the toes may indicate peripheral neuropathy or CNS involvement. A positive Romberg's test and gait ataxia could point to vestibular or cerebellar issues. Differential count shows lymphocytic predominance. OCB, AQP4, and MOG are negative. MRI reveals T2/FLAIR hyperintense lesions in the right peritrigonal region. All these findings suggest a demyelinating process, possibly DN NMOSD.

Treatment: Treatment for DN NMOSD is based on approaches used for antibody-positive NMOSD and includes glucocorticoids, azathioprine, mycophenolate mofetil, rituximab, methotrexate, and mitoxantrone. A study showed an 86% reduction in relapse rate with tacrolimus. Some DN NMOSD patients may also respond to anti-IL-6R drugs or IV immunoglobulin.[12],[13],[14]

4. CONCLUSION

In conclusion, we presented a rare case of DN NMOSD, a condition that remains challenging to diagnose and treat. It is uncertain whether DN NMOSD is primarily an astrocytopathylike AQP4-positive NMOSD. Diagnosis relies on clinical features, MRI, and antibody testing. Currently, no specific treatments are approved for relapse prevention in DN NMOSD, and it is managed similarly to seropositive NMOSD. If left untreated, the disease can lead to severe disability, including visual impairment and wheelchair dependence. Prompt diagnosis and empirical treatment are essential for better outcomes and improved quality of life for DN NMOSD patients.

CONSENT

The participation was on a voluntary basis and written informed consent was obtained from the individual who participated in the case report.

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author.

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