International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Is Dystonia A Rare Manifestation of Neuromyelitis Optica Spectrum Disorder (NMOSD) - A Case of Varicella-Zoster Virus (VZV) Triggering Aquaporin-4 Antibodies?

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Abstract: ***NeuromyelitisOptica Spectrum Disorder is an autoimmune disease characterised by demyelination of CNS affecting optic nerve, spinal cord and brain stem region simultaneously or separated by variable period. This case highlights the atypical presentation of NMOSD as dystonia which was triggered by Aquaporin-4 Antibodies due to varicella-zoster virus (VZV) infection. Case Presentation: 42 year old female presented with paroxysmal dystonia, weakness of all 4 limbs and urinary incontinence. Spinal MRI: longitudinally extensive transverse myelitis (Fig. 1). Brain MRI: demyelination in medulla. Visual evoked potential examination abnormal. Serum AQP4-IgG positive, anti-MOG negative. Diagnosis of NMOSD confirmed. Patient improved on pulse methylprednisolone therapy and immunosuppressant Inj. Rituximab and was discharged on tapering dose of corticosteroid. She remained stable on this treatment in her follow up visits. Conclusion: NMOSD can present as movement disorder which can be major cause of disability and often mislabelled or undertreated. And since it is a treatable condition high index of suspicion is required to diagnose and treat this condition.***

Keywords: NeuromyelitisOptica, Rituximab, Methylprednisolone, Immunosuppressant, Radiculomyelitis, varicella-zoster virus (VZV) AntiAQP4 autoantibody

1. Introduction

Neuromyelitis Optica Spectrum Disorder (NMOSD) previously known as Devic disease is a rare autoimmune disease characterised by severe demyelinating disease of CNS affecting optic nerve, spinal cord and brain stem region simultaneously or separated by variable period. It has been estimated that between 0.5 - 4.4/100,000 people has a Neuromyelitisoptica spectrum disorder. It has been reported to be more prevalent in Asians and Africans[1].

Neuromyelitis Optica with its partial forms are referred as NMOSD. NMOSD predominantly affects adult females. NMOSD is associated with auto-antibodies against Aquaporin 4 (antiAQP4 autoantibody), which is present in 70-80% patients[2]. Here, we report a case of NMOSD which presented as movement disorder (paroxysmal dystonia).

2. Case

A 42 year old female known case of hypothyroidism presented with multiple episodes of abnormal posturing, involuntary repetitive and twisting movements (dystonia) of all 4 limbs (Right>Left) since 1 month, lasting few minutes. Later patient gave history of gradually progressive subacute asymmetrical distal weakness of limbs (Right>Left), bladder incontinence without any sensory symptoms, bowel and cranial nerve involvement. Interestingly patient had history of painful blisters varicella-zoster virus (VZV) on right upper limb 1 month ago.

Patient was conscious, oriented to time, place and person with GCS 15/15 with stable vitals. Neurological examination revealed normal higher mental functions with increased tone in all four limbs, power 4/5 on right upper limb, lower limb and normal on left side. Deep tendon reflexes were brisk. Right plantar was extensor with mute left plantar. Bilateral Relative Afferent Pupillary Defect was detected. Other cranial nerves, cerebellar system and sensory examination were normal without signs of meningismus. Other systemic examination was unremarkable.

Routine lab investigations showed increased TLC-12,800; ESR-8mm/hr; LFT, KFT and TSH, CSF were normal; serologic test for HIV, ANA by ELISA, hepatitis markers and CSF PCR for herpes were negative. CXR, EEG and Initial NCCT head revealed no abnormality. On detail history and examination other causes of dystonia like Parkinson's disease, Huntington's disease, Wilson's disease, Traumatic brain injury, stroke, brain tumor or paraneoplastic syndromes, hypoxia, carbon monoxide poisoning, tuberculosis, encephalitis, consumptions of certain medications or heavy metal poisoning were ruled out. In view of recent exposure to of VZVpossibility of post-infectious myelitis & autoimmune myelitis was kept along with NMOSD and antiviral (inj. acyclovir) and corticosteroids were given.

CEMRI brain and spine was done later which revealed LETM (C2-C7) (Fig. 1), few punctuate T2/FLAIR hyperintensities in bilateral frontal, parietal white matter and increase signal intensity on FLAIR images suggestive of demyelination in medulla. VEP was consistent with bilateral visual pathway defect. AQP4IgG was positive. Anti-MOG was negative. Based on above findings, lab reports diagnosis of NMOSD was confirmed. Patient received methylprednisolone 1000mg iv q 24 hourly for 5 days and 2 doses of inj. Rituximab (1gm infusion each, 2 weeks apart). Patient improved symptomatically and discharged on tapering dose of oral steroids. Patient showed improvement on 2 month follow-up.

3. Discussion

NMOSD includes 6 core characteristics including Optic neuritis (ON), acute transverse myelitis (ATM), area postrema syndrome, acute brainstem syndrome, diencephalic syndrome & symptomatic cerebral syndrome. ON & ATM are typical manifestations. NMOSD can occur as monophasic or polyphasic illness and relapses are common. Immunopathogenesis involves AQP4IgG, complement & antibody dependant cell mediated cytotoxicity (ADCC)[3]. AQP4IgG are detected in upto 70-80% cases. Diagnosis requires 2 core clinical characteristics in AQP4IgG negative/unknown status.

Differential diagnosis of NMOSD includes Multiple Sclerosis, SLE and Neurosarcoidosis which were ruled out by investigations. Acute myelitis in NMOSD is severe with typically longitudinally extensive (LETM) myelitis, whereas patchy and short spinal segments are involved in Multiple Sclerosis[4,5]. NMDAR-ab encephalitis with dystonia was ruled out in view of normal mental function. Our patient who presented with dystonia had ON and acute myelitis; positive AQP4IgG serology and CEMRI findings supported the diagnosis of NMOSD. Review of literature suggests a causal association between VZV and radiculomyelitis[6,7].

Asymptomatic AQP4-IgG seropositive status may exist for years before clinical NMOSD presentation and need "trigger" to develop the disease. Proposed mechanism is AQP4-abundant spinal cord tissue damage due to the direct invasion of VZV activated AQP4-IgG or blood-brain barrier breakdown, which allows the autoantibody to cross the blood-brain barrier which may play a role in the production of AQP4-IgG[7].

Management of NMOSD includes Immunosuppressant, steroids, plasma exchange, managing acute attacks and maintenance therapy. Acute attacks are usually treated pulse dose of Methylprednisolone. In case of poor response, treatment escalation with 2,000 mg IVMP may improve outcome. Rituximab (RTX) regimen is given intravenously as 2 doses 1,000mg with an interval of 2 weeks followed by 6-monthly dosages of 1,000mg. Alternatively, initially 375 mg/m^2 body surface every week over a period of 4 weeks can be administered.

Maintenance therapy includes oral prednisone, azathioprine, Mycophenolatemofetil and RTX therapy along with steroids. Another immunotherapy approved for NMOSD includes eculizumab, satralizumab and Inebilizumab. Few novel immunotherapies are under clinical evaluation includes Sivelesat, Ravulizumab, Ublituximab and Aquaporumab[8]. For relapsing NMOSD, combination therapy of immunosuppressant, corticosteroids and plasma exchange should be used. Long term immunosuppressive treatment, e.g., with RTX or Azathoprine has emerged to be the most effective therapies, RTX being increasingly used as a first-line drug[9]. Long term rehabilitation is also needed along with management of depression, anxiety and pain management.

Few cases of dystonia reported in literature[10] in NMO while our case had dystonia triggered by VZV infection as NMO with LETM.

4. Conclusion

NMOSD can present as movement disorder which can be major cause of disability and often mislabelled or undertreated. A meticulous history and high index of suspicion is required for AQP4-IgG seropositivity in female patient with dystonia after VZV exposure for prompt management.

5. Funding

This research did not receive any financial support.

6. Ethics statement

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Conflict of interest:
Nil

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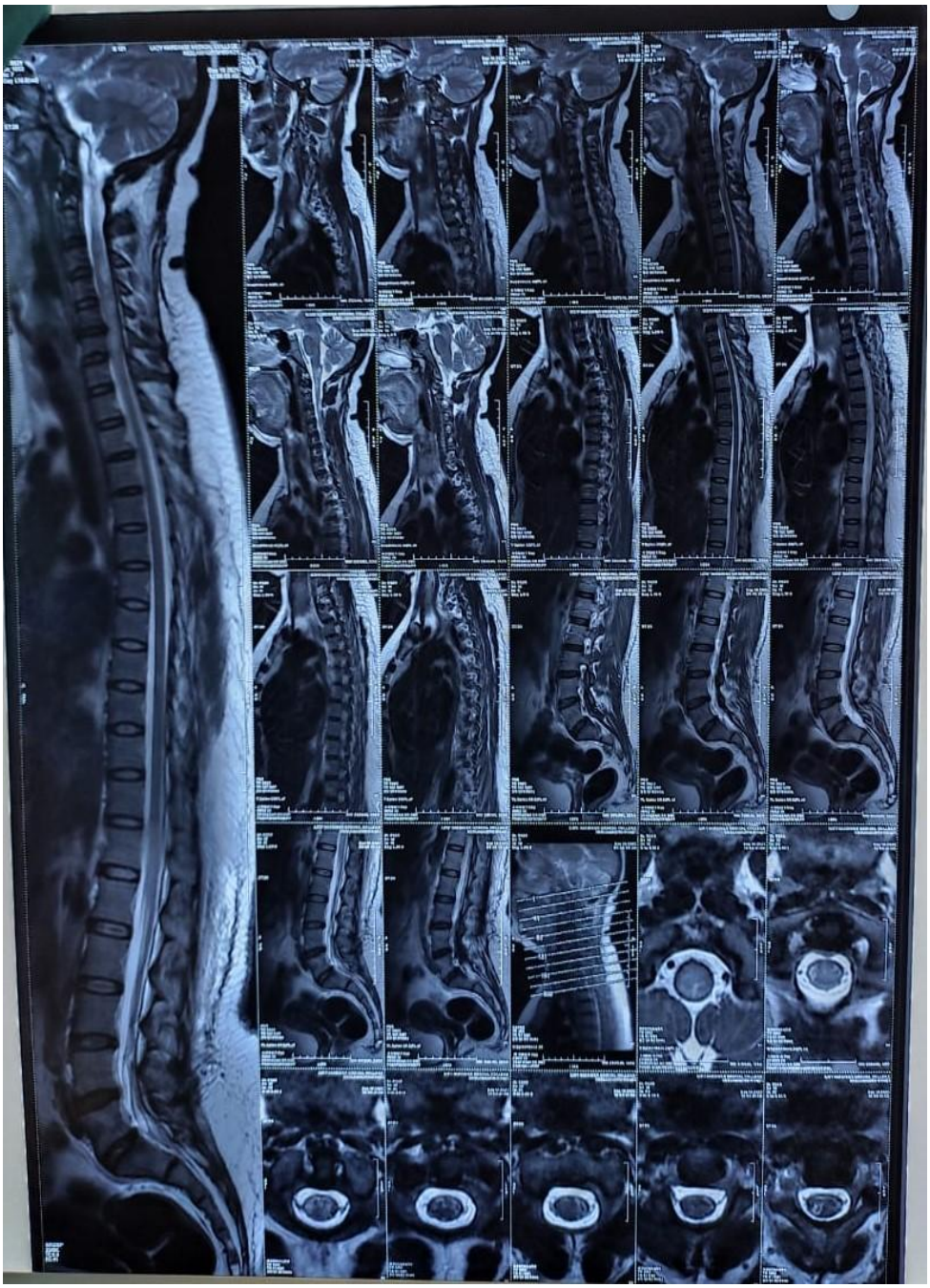

Figure: Contrast enhanced MRI whole spine showing diffusely bulky cervical portion of the spinal cord which shows non enhancing patchy as well as diffuse areas of increased T2/STIR signal intensity: >75% involvement(circumferential) at C2 and C3 and fewer discrete hyperintense lesions at lower levels till C7 level.