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Pediatric Neuromyelitis Optica Spectrum Disorders: Three case Report and Review of Literature

Running title: Pediatric Neuromyelitis Optica…

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Abstract

Introduction: Neuromyelitis optica spectrum disease (NMOSD) is a rare autoimmune inflammatory astrocytopathic demyelinating disease of the CNS. In the majority of patients, an autoantibody to the water channel protein aquaporin-4 (AQP4) would cause humoral inflammatory demyelination and axonal damage. The disease defined as clinical syndromes of optic nerve, area postrema, spinal cord, diencephalon, or cerebrum or MRI finding related to involvement of these regions. According to recent consensus diagnostic criteria, NMOSD categorized as NMOSD with AQP4 Ab, Also NMOSD without AQP4 Ab. Early onset is defined as the disease presentation before 17 years old. According to the pediatric NMOSD working group most clinical, laboratory characteristics and neuroimaging of this disease are the same as adult onset, and same criteria could be used for pediatric NMOSD. Differentiation of NMO from MS and acute disseminated encephalomyelitis (ADEM) are matters of importance in decision making in order to choose an appropriate therapy. It has also been reported that some MS therapies could aggravate NMO exacerbations and lead to permanent disability.

Case Presentations: Three patients under the age of 17 years old were present in neurology clinic, due to their recurrent optic neuritis and cervical myelopathy. AQP4 Ab was positive in two patients, and the other patient was seronegative for AQP4 Ab. according to the recent international consensus definition. All of the patients went under treatment with corticosteroid pulse therapy in acute relapses, and two of them were getting azathioprine as a disease modifying therapy, and the other patient went under rituximab, because of new relapses in spite of azathioprine therapy. Azathioprine and rituximab were safe and tolerated well without any significant side effects in all of them.

Conclusions: Pediatric NMOSD is a rare but life threatening disease, which pediatrician and pediatric neurologists must be aware of its presentations and treatment.

Keywords: Pediatric, Neuromyelitis Optica Spectrum Disorders, NMO

1. Introduction

Neuromyelitis optica spectrum disease (NMOSD) is a rare autoimmune inflammatory demyelinating disease of the CNS (1). NMOSD with AQP4-IgG is defined as clinical syndromes of optic nerve, area postrema, spinal cord, brainstem, cerebral, or diencephalic presentations, or MRI finding related to involvement of these regions (1). Additional MRI findings are required to enhance specificity of criteria for diagnosis in NMOSD without AQP4-IgG, while the lack of seropositivity for AQP4-IgG exists. The Pediatric Working Group members noted that adult consensus criteria are applicable in pediatric patients (1). In the majority of cases, an autoantibody to the astrocytic water channel protein aquaporin-4 (AQP4) causes humoral inflammatory demyelination, and leads to axonal damage (2). High relapse rate and disability gathering in neuromyelitis optica may cause severe neurological disabilities, like permanent blindness and paralysis, which could be partly prevented by using proper attack prevention. (2).

NMOSD median age onset is 39 years old (3, 4). Early onset is defined as the disease presents under the age of 17 years old (5). The mean age of child NMOSD is 12-14 years old, and it was reported that the youngest case was at the age of two years old. (6).

Difference of NMO from MS and acute disseminated encephalomyelitis (ADEM) is a matter of importance in decision making for choosing an appropriate therapy. It has also been reported that some MS therapies could aggravate NMOSD, and lead to permanent disability (7, 8 and 9). The aim of this study to present rare cases of pediatric NMOSD, to review the other reports and emphasize that this rare disabling life threaten disorder could be modified with disease modifying therapies.

2. Case Presentations

- **Case 1**

A 16-year-old female patient was referred to Sina hospital MS clinic because of two distinct episodes of painful blurred vision with 3 months apart in 2017. Both episodes were diagnosed as optic neuritis. and were recovered by pulse therapy. Neurologic examination showed bilateral mild optic atrophy, generalized hyperreflexia and bilateral Babinski sign. AQP4 Ab and MOG (Myeline associated glycoprotein), both were negative. Vasculitis tests were normal. Brain MRI showed posterior corpus callosum involvement and cervical MRI showed LETM (longitudinally extensive transverse myelitis). According to criteria, NMOSD without AQP4 Ab was diagnosed for her. Azathioprine has been started and her neurologic state has been stable now (Fig1).

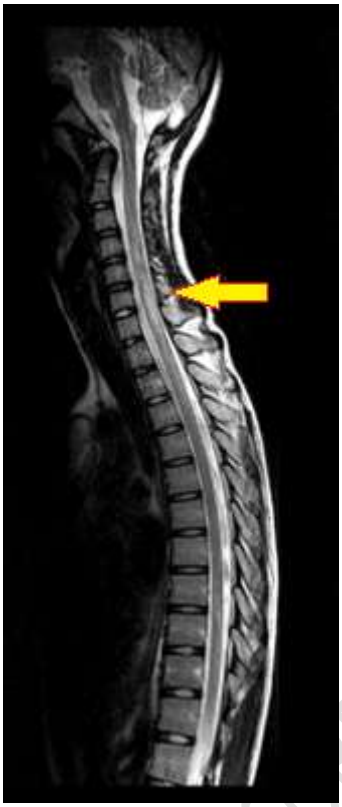

Fig1. Cervical longitudinal extensive transverse myelitis (LETM)

- **Case 2**

An 11-year-old female patient was presented to Sina hospital MS clinic with severe right painful ON in 2016. The visual acuity reduced to two-meter finger count and right Marcus Gunn pupil. Brain MRI showed nonspecific T2 hyperintense deep white matter abnormality. AQP4 Ab was positive. She did not respond to IV steroids well, and plasma exchange was performed with acceptable recovery. NMOSD with AQP4 Ab was diagnosed for her. Azathioprine started. She experienced left severe optic neuritis 3 months later. This new attack also recovered with pulse and plasmapheresis. According to new attack in spite of azathioprine therapy, rituximab was started. Her neurologic state was still stable.

- **Case 3**

A 13-year-old female patient was consulted with a history of cervical pain, and urinary retention ended to quadriparesis, which has been improved by pulse therapy in 2017. She had also another relapse with ataxia and upper limbs pain, which was recovered by pulse therapy. Neurological examination showed signs of upper motor neuron lesions. Vasculitis test were normal, and high titer AQP4 Ab was reported. Azathioprine has been administered, and she experienced no relapses since now. Cervical MRI showed LETM but brain MRI didn't show any abnormality.

3. Discussion and review of the literature

According to recent consensus diagnostic criteria, NMOSD is categorized into NMOSD with AQP4 Ab, and also NMOSD without AQP4 Ab (10). In this criteria 6 core clinical characteristic have defined each implicate 6 CNS areas, including Optic nerve, spinal cord, postrema area of dorsal medulla, diencephalon, brainstem, and cerebral hemispheres. One core criteria with positive AQP4 Ab means NMOSD with AQP4 Ab, but in negative AQP4 Ab patients must present 2 or more different core clinical characteristics and at least 1 core criteria must be considered as one of the optic neuritis, transverse myelitis, or an area postrema clinical syndrome in case of NMOSD without AQP4 Ab (10). Consensus criteria recommended NMO Ab detection with cell base assay, due to high sensitivity (76.7%) and low false positivity (0.1%) in adult patients, but cell-based assay id not available widely, up to now. However, sensitivity of indirect immunofluorescence and ELISAS assay are not low (mean sensitivity is 63%–64% for each) in adult patients (11).

Longitudinally extended transverse myelitis (LETM) in a spinal cord MRI of a patient with transverse myelitis is the most specific and highly suggested neuroimaging finding in NMOSD. This lesion involved cord central gray matter associated with cord expansion more than 2/3 cord axial section, and also more than 3 vertebral body lengths, which enhanced with gadolinium. Nevertheless, acute myelitis in NMOSD isn't always associated with LETM, and in some cases 7%-14% NMOSD presents with short myelitis, initially. (12).

Normal brain MRI is a key supportive finding in NMOSD. 60% of NMOSD patients showed nonspecific asymptomatic white matter lesions, and up to 16% of them showed fulfill Barkhof MS criteria. (13)

Gender does not seem to predict the frequency of attacks once relapsing disease has been presented (14). On the other hand, ADEM like presentation isn't uncommon in pediatric NMOSD (5, 15).

Most clinical, laboratory and neuroimaging characteristics of pediatric NMOSD aren't different to those of adult NMOSD and according to the pediatric NMOSD working group same criteria could be used for pediatric NMOSD. Recent diagnostic criteria for neuromyelitis optica spectrum disease resolved diagnosis challenge markedly, in seronegative NMO Ab circumstances especially. (16).

Pediatric onset of NMOSD includes 4% of NMOSD seropositive cases. Female/male sex ratio is reported as 9:1 in NMOSD compare to 3:1 in MS. In North America, African American children dominate 33-34% of pediatric NMOSD cases, after them are Caucasians, Latin American white non-Caucasian, and after them Asians are placed (17).

38 cases of pediatric NMOSD based on US Network of Pediatric MS Centers shows some demographic and seropositivity characteristics. In this report, mean age of onset (years) reported 10.2 ± 4.7 in NMOSD, and 65% of NMOSD cohort was reported seropositive for

AQP4 Ab, which is close to reports about adults, but series 32% of patients was male in this case, and F/M ratio for patients with NMOSD who were under the11 years old was 1.5:1(18).

19.3 years studying about 12 pediatric NMO patients showed that there is no difference in the number of brain MRI lesions, between the adult NMO and pediatric NMO patients (19).

In a study of 58 cases of pediatric NMOSD, Median age at symptom onset was reported 12 years old (range 4–18), and 98% presented attacks of either optic neuritis (83%) or transverse myelitis (78%) or both, 45% had frequent cerebral symptoms (encephalopathy, ataxia, ophthalmoparesis, intractable vomiting, seizures, or hiccups), 68% had brain MRI abnormalities, also the other autoantibodies were appeared in 76%, and 42% had a coexisting autoimmune disorder, The frequency of AQP4 Ab in children with inflammatory disorders of the CNS was 78% for relapsing NMOSD, and 20% for partial forms of NMOSD, and 66% fulfilled 2006 NMOSD diagnostic criteria. . Azathioprine was administered as monotherapy for six patients, and also eight patients received rituximab, and from these all only one patient was reported as relapse-free after starting rituximab (5).

In a study evaluating 118 pediatric patients, only 6 patients fulfilled diagnostic criteria of NMOSD, and just one of them was seropositive for AQP4 Ab. Authors concluded that NMOSD appears to be rare in white European pediatric population (20).

Follow up of 29 pediatric NMOSD patient's series with average age of 13 years old, with 3/1 female/male ratio and 92% anti-aquaporin-4 seropositivity at disease onset showed that early-onset of NMO morbidity is higher than MS, so NMOSD may have a negative influence on schooling. Authors emphasized that the most important interferer factor in the pediatric NMOSD diagnosis is pediatric MS, and INF treatment may aggravate disease status in NMOSD patients (21).

In a follow up 17 pediatric NMOSD patients, only eight of them (47%) was AQP4 Ab seropositive, and 78% were relapsing NMOSD, it means that 31% of relapsing NMOSD were seronegative, and according to this perhaps we could explain why NMOSD could present as relapsing disease without AQP4 Ab. In this study, relapsing NMOSD in seropositive patients is more common than monophasic NMOSD. But there was no difference amongst the seropositive and seronegative patients according to their sex and ethnicity. 53% of these patients similar to adult NMOSD patients had brain MRI abnormality, and the most common lesions were brainstem lesions extending from medulla to the spinal cord (22).

In a six pediatric NMOSD patients' evaluation, the median age was 11 years old at the time of the study, and F/M was 5/1, also all the cases presented bilateral optic neuritis, 66% of the patients had abnormal brain MRI from the onset, and 50% of patients had symptoms associated to brain lesions during the course of their disease. AQP4 Ab seropositivity was reported 80%. Optic neuropathy was the most impaired feature. TM was presented in all the patients during the course of the disorder (23). This Latin American case series emphasized that race might be considered as a noticeable demographic variable for NMOSD in child (23).

In a cohort belongs to UK national pediatric onset of NMOSD, 20 pediatric NMO with median age of 10.5 years old (2.9–16.8) met inclusion criteria. 90% of them were female,

60% of them have AQP4-Ab positive, 12% CSF OCB positive, 90% Relapsing course, 75% MRI brain abnormalities, 20% Barkhof space involvement, and 100% LETM has reported. The most common brain MRI lesion location was Centrum semiovale/deep white matter (53%). Unilateral optic neuritis was the most first common presentation (40%). This study has emphasized that pediatric NMO first presentation might be similar to others acquired demyelinating syndromes, and careful attention to distinct MRI brain lesion features is very helpful to minimize risk of incorrect diagnosis, and also prevent early recurrence and visual disability of pediatric NMO (24).

In a study about Korean pediatric population, three out of 21 patients met the international NMO criteria. The first case was a 7 years old female, who showed bilateral optic neuritis. Brain MRI showed involvement of corpus callosum, thalamus, and periventricular area. Spinal MRI revealed LETM of thoracic area. She died at the age of 14 years old because of pneumonia. The second patient was a 7 years old male child presented with isolated transverse myelitis, which bilateral optic neuritis added to his clinical presentation 3 months later. His brain MRI showed subcortical T2-weighted hyperintensity in temporo–occipital lobes. And the last case was an 11.7 years old female patient presented with transverse myelitis accompanied by sensory signs and the left eye visual impairment followed by four clinical relapses of transverse myelitis and optic neuritis (25).

In a Brazilian study, 11 pediatric NMOSD patients were under studying. F/M ratio was 2.6/1, AQP4-IgG were positive in 72.7% of patients, and mean age of onset was reported as 14 years old. MRI showed cervical LETM in all patients, and also brain lesions in 45.5% of patients. All of the patients tolerated azathioprine (26).

Current approach in treatment with rituximab is a step – up approach, which reserve rituximab for refractory cases (27). Due to this, some studies suggest rituximab as a first line maintenance therapy in pediatric NMOSDs (28, 29). In a longitudinal follow up of 114 adult NMOSD patients, 10 pediatric NMOSD patients were defined retrospectively, which, therapy escalated to rituximab from azathioprine, because of severe and recurrent new relapses in half of them (29).

Current practice in rituximab administration is a repeated fixed time infusion in every 6-12 months, but recently proposed approach suggests personalized treatment according to regular B-cell depletion and reconstitution monitoring (27, 30). In conclusion, pediatric NMOSD is a rare but life threatening disease, which pediatrician and pediatric neurologists must be aware of its presentations and treatment.

Ethical consideration: the study was conducted upon agreement of the ethic committee of Tehran University of Medical Sciences and the inform consent of the patients is available upon request.

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Conflict of interest: Authors have nothing to disclose.

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References

1. Wingerchuk DM, Weinshenker BG. Neuromyelitis optica (Devic's syndrome). Handb Clin Neurol 2014; 122:581– 599.
2. Wegner C. Recent insights into the pathology of multiple sclerosis and neuromyelitis optica. Clin Neurol Neurosurg 2013; 115: S38–S41.
3. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999; 53:1107–1114.
4. Kantarci OH, Weinshenker BG. Natural history of multiple sclerosis. Neurol Clin 2005; 23:17–38.
5. McKeon A1, Lennon VA, Lotze T, Tenenbaum S, Ness JM, Rensel M, et al. CNS aquaporin-4 autoimmunity in children. Neurology. 2008 Jul 8;71(2):93-100. doi: 10.1212/01.wnl.0000314832.24682.c6. Epub 2008 May 28.
6. Yuksel D, Senbil N, Yilmaz D, Yavuz Gurer YK. Devic's neuromyelitis optica in an infant case. J Child Neurol 2007; 22:1143–1146.
7. Kim SH, Kim W, Li XF, Jung IJ, Kim HJ. Does interferon beta treatment exacerbate neuromyelitis optica spectrum disorder? Mult Scler 2012; 18:1480.
8. Kleiter I, Hellwig K, Berthele A, Kümpfel T, Linker RA, Hartung HP, et al. Failure of natalizumab to prevent relapses in neuromyelitis optica. Arch Neurol. 2012 Feb;69(2):239-45. doi: 10.1001/archneurol.2011.216.
9. Min JH, Kim BJ, Lee KH. Development of extensive brain lesions following fingolimod (FTY720) treatment in a patient with neuromyelitis optica spectrum disorder. Mult Scler 2012; 18:113–115.
10. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International Panel for NMO Diagnosis. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015 Jul 14; 85(2):177-89.
11. Jarius S, Wildemann B. Aquaporin-4 antibodies (NMOIgG) as a serological marker of neuromyelitis optica: a critical review of the literature. Brain Pathol 2013; 23:661–683.
12. Flanagan EP, Weinshenker BG, Krecke KN, Lennon VA, Lucchinetti CF, McKeon A, et al. Short myelitis lesions in aquaporin-4-IgG–positive neuromyelitis optica spectrum disorders. JAMA Neurol. 2015 Jan;72(1):81-7. doi: 10.1001/jamaneurol.2014.2137.
13. Kim W1, Park MS, Lee SH, Kim SH, Jung IJ, Takahashi T, et al. Characteristic brain magnetic resonance imaging abnormalities in central nervous system aquaporin-4 autoimmunity. Mult Scler. 2010 Oct;16(10):1229-36. doi: 10.1177/1352458510376640. Epub 2010 Aug 4.
14. Zare-Shahabadi A, Langroodi HG, Azimi AR, Sahraian MA, Harirchian MH, Baghbanian SM. Neuromyelitis optica and pregnancy. Acta Neurol Belg. 2016, 18: 1-8.

15. Krupp LB1, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler. 2013 Sep;19(10):1261-7. doi: 10.1177/1352458513484547. Epub 2013 Apr 9.
16. Hyun JW, Jeong IH, Joung A, Kim SH, Kim HJ. Evaluation of the 2015 diagnostic criteria for neuromyelitis optica spectrum disorder. Neurology. 2016 May 10;86(19):1772-9.
17. Lotze TE1, Northrop JL, Hutton GJ, Ross B, Schiffman JS, Hunter JV. Pediatrics. 2008 Nov;122(5):e1039-47. doi: 10.1542/peds.2007-2758. Epub 2008 Oct 6.
18. Chitnis T, Ness J, Krupp L, Waubant E, Hunt T, Olsen CS, et al. Clinical features of neuromyelitis optica in children: US Network of Pediatric MS Centers report. Neurology. 2016 Jan 19;86(3):245-52.
19. Collongues N, Marignier R, Zéphir H, Papeix C, Fontaine B, Blanc F, et al. Long-term follow-up of neuromyelitis optica with a pediatric onset. Neurology. 2010 Sep 21;75(12):1084-8
20. Huppke P, Blüthner M, Bauer O, Stark W, Reinhardt K, Huppke B, et al. Neuromyelitis optica and NMO-IgG in European pediatric patients, Neurology. 2010 Nov 9;75(19):1740-4
21. Fragoso YD, Ferreira ML, Oliveira EM, Domingues RB, Ribeiro TA, Brooks JB, et al. Neuromyelitis optica with onset in childhood and adolescence. Pediatr Neurol. 2014 Jan;50(1):66-8.
22. Banwell B, Tenembaum S, Lennon VA, Ursell E, Kennedy J, Bar-Or A, et al. Neuromyelitis optica-IgG in childhood inflammatory demyelinating CNS disorders, Neurology. 2008 Jan 29;70(5):344-52
23. Peña JA1, Ravelo ME, Mora-La Cruz E, Montiel-Nava C. NMO in pediatric patients: brain involvement and clinical expression. Arq Neuropsiquiatr. 2011 Feb;69(1):34-8.
24. Absoud M, Lim MJ, Appleton R, Jacob A, Kitley J, Leite MI, et al. Paediatric neuromyelitis optica: clinical, MRI of the brain and prognostic features. J Neurol Neurosurg Psychiatry. 2015 Apr;86(4):470-2. doi: 10.1136/jnnp-2014-308550. Epub 2014 Aug 4.
25. Lim BC1, Hwang H, Kim KJ, Hwang YS, Cheon JE, Kim IO, et al. Relapsing demyelinating CNS disease in a Korean pediatric population: multiple sclerosis versus neuromyelitis optica. Mult Scler. 2011 Jan;17(1):67-73.
26. Fragomeni MO, Bichuetti DB, Oliveira EML. Pediatric-onset multiple sclerosis in Brazilian patients: Clinical features, treatment response and comparison to pediatric neuromyelitis optica spectrum disorders. Mult Scler Relat Disord. 2018 Oct; 25:138-142
27. Baghbanian SM, Asgari N, Sahraian MA, Moghadasi AN. A comparison of pediatric and adult neuromyelitis optica spectrum disorders: A review of clinical manifestation, diagnosis, and treatment. J Neurol Sci. 2018 May 15; 388:222-231.

28. Olivieri G, Nociti V, Iorio R, Stefanini MC, Losavio FA, Mirabella M, et al. Rituximab as a first-line treatment in pediatric neuromyelitis optica spectrum disorder. Neurol Sci. 2015 Dec;36(12):2301-2.
29. Baghbanian SM, Sahraian MA, Moghadasi AN, Asgari N. Disability and Therapeutic Response in Paediatric Neuromyelitis Optica Spectrum Disorder: A Case Series from Iran. Iran J Child Neurol. Summer 2019; 13(3): 99-104
30. Nosadini M, Alper G, Riney CJ, Benson LA, Mohammad SS, Ramanathan S, et al. Rituximab monitoring and redosing in pediatric neuromyelitis optica spectrum disorder. Neurol Neuroimmunol Neuroinflamm. 2016 Jan 21;3(1): e188.