

Pediatric Optic Neuritis Post Vaccination: A Literature Review

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Abstract

Pediatric optic neuritis (PON) tend to have their differences with adult optic neuritis (ON). It might happen due to several etiologies such as neuromyelitis optica disorder, acute disseminated encephalomyelitis, multiple sclerosis and many more. While cases of post infectious and post vaccination rarely happened in adults compared to other etiologies, it works differently on pediatric cases. Pediatric ON caused a lot by post infectious and post vaccinations episode, and may or may not associated with other etiology. Vaccines are a must have thing to do in childhood period, therefore it is crucial to know more about post vaccinations PON. This article aims to review previous studies discussing pediatric optic neuritis especially the ones due to post vaccination.

Keywords: pediatric optic neuritis, post vaccination, literature review

1. Introduction

Pediatric optic neuritis is defined as primary inflammation of the optic nerve, with visual loss both acute or subacute, periocular pain, visual field defect and dyschromatopsia as the frequent clinical manifestation^{1,2}.

PON have incidence rate that thought to be small compared to adult optic neuritis. It's prevalence rate during a 7-year study in South Korea was 7.68 per 100.000 people whereas for the adult is 19.01 per 100.000 people³. A study in United States showed higher number for the adult's incidence rate at 1.66 per 100,000 person per year, while children sat at 0.51 per 100,000 per year⁴. For PON, mainly cases majorly spread in adolescents, with female sat at the higher predominance, while prepubertal age showed equal incidence between male and female⁵.

While the etiology of optic neuritis might vary most of the time, it is said to be closely related with multiple sclerosis (MS). According to the etiology, ON is divided into typical ON and atypical ON. Clinically isolated syndrome (CIS) and MS are categorized into typical, whereas neuromyelitis optica spectrum disorders (NMOSD), myelin oligodendrocyte glycoprotein-associated diseases (MOGAD), infectious and post vaccination causes as atypical⁶.

While infectious case and vaccination case happened a lot more less in adult, it is a different case in children. While adults tends to experienced MS, children tends to have a varied etiology, and higher number of infectious and post vaccination associated ON. Children are in the age where they get the most vaccine throughout their life. Starting from basic immunization until add-up. Immunization itself is a form of inserting a non-active virus to your body, with the hope of the human bodies will respond accordingly to the expectation of producing antibodies, so in future it

will strengthen a person's immunity. But there's always side effect, and one of it is optic neuritis. Thus, this review will review several studies discussing post vaccination PON in details.

2. Overview of Pediatric Optic Neuritis

ON is an inflammation of the optic nerve, happened unilateral or bilateral. It might and might be not correlated with infection, parainfectious process or demyelinating of the central nervous system (CNS). It involves the peripheral activation of T-cell, that might cross the blood brain barrier, resulting in delayed type IV hypersensitivity. This hypersensitivity leads to demyelination that can be confirmed by the optical coherence tomography (OCT)⁷.

2.1. Epidemiology

During a population-based study in South Korea of optic neuritis, it is shown that PON have a total incidence of 381 during 2012-2016. While the incidence rate showed among the rate of 1.00-1.56 per 100,000⁸. Study in Canada estimated annual incidence of 0.2 per 100,000⁹.

PON predominantly acquired by adolescents, with the mean age of 9-11 years old⁸. A research in United States and Canada showed a mean age of 10.3 years old⁹. Most of the research concluded the mean age ranged between 9-11 years old¹⁰.

Prevalence in PON showed a similar result in adolescent age group when compared to adults, with the ratio of woman to man is 2 : 1⁸. Prepubertal age showed an equal number of both genders⁸. PON showed rather predominantly in adolescent numbers compared to younger children.

While PON have adequate numbers of research when it comes to age and gender, ethnicity is not well studied. A study in southern California stated the numbers of racial background in an affected individual were similar to the ethnic background of general pediatric population in health system¹.

2.2. Etiology

Based on the etiology, PON often happened due to idiopathic cases, clinically isolated, autoimmune response, or manifestation of demyelinating disorder¹. It is stated that younger children who experienced PON were more likely to be associated with acute disseminated encephalomyelitis (ADEM) as much as 80% in prepubertal age. While adolescents are more prone to MS findings¹.

ON associated with MS

As stated before, MS are thought to be often linked with ON. The incidence of the pediatric MS itself in the US is 0.51 per 100,000 person per years¹. Multiple sclerosis is said to be more prevalent in female sex with a ration of 2:1, which can be a cause of sex hormones that surge throughout puberty⁹. According to a meta-analysis by Waldman, every 1 year of increase in age will result an increased risk of MS too¹².

Specific features could be used to help diagnose the MS related PON, there is usually no optic disc swelling to be found, and there are findings of cerebrospinal fluid (CSF) oligoclonal bands (OCB). Magnetic resonance imaging (MRI) tends to show white matter lesions on the periventricular^{13,14,15,16}.

For younger children, ADEM is more frequent compared with MS, so McDonald criteria applied to children 12 years old and below without encephalopathy¹².

Pediatric MS known to have higher recurrences rates^{17,18}, cognitive impairment (19) and late growth of the brain²⁰. Children are more prone to relapse 2-3 times than the adults. While the acute treatment is basically using the same as the other etiology which is IV or oral steroids, it is important to include interferon- β and glatiramer acetate for first line, with second-line including natalizumab or rituximab¹.

Myelin oligodendrocyte glycoprotein-associated disease (MOGAD) optic neuritis

It is usually placed on the surface of the myelin sheath. Some studies recently reported increasing role of MOG antibody in inflammatory resulted in demyelinating diseases focused on CNS³. The mean age found in a study conducted at South Korea, showed the predominant at prepuberty age which was 7.7 ± 3.1 years. Optic disk swelling is quite often to find compared to ocular pain when the eye moves in pediatric patients than in adult^{21,22,23}.

Several studies have come with good visual outcomes, even better in pediatric patients than adult patients even though the VA was similar^{22,24}. It has fewer relapses compared with Aquaporin 4 Immunoglobulin G (AQP4-IgG) associated ON. But relapses in MOG-ON are highly steroid-responsive and steroid-dependent^{25,26,27}.

Neuromyelitis Optica Spectrum Disorder (NMOSD) Optic Neuritis

NMO is specified as an acute type of ON, showed severe episodes and transverse myelitis. It is closely related with antibodies for aquaporin-4²⁸. The diagnostic criteria for NMOSD was released and stated that patients have to fit in the clinical and imaging criteria, but for the AQP4-IgG wasn't needed to be seropositive²⁹. During 2015, the criteria divided into NMOSD with AQP4-Ab and without²⁹. Originally it is thought as a disease that occurred when someone is in their fourth or fifth decades of their life. The pediatric cases summed up to be 3%-5% of the total cases. Age of the onset is 10 to 12, it rarely happened to infants aged less than 16 months³⁰.

The biomarker for NMOSD itself it is yet to be found. Using the recognition of AQP4-IgG, NMOSD approached with a more specialized strategy of treatment²⁹. However, 1 out of 4 patients of NMOSD showed negativity for AQP4-IgG, suggesting a new biomarker to be recognized³¹. Children with positive MOG-Ab positive and negative AQP4-Ab negative have relatively better chance to full recovery compared to children with positive AQP4-Ab test³². It is thought to involve long segments of optic nerve, but predilection for the optic chiasm and posterior optic pathways during ON demyelinating episodes^{22,33,34}.

60% of children with NMOSD suffered PON as well^{35,36}. PON associated with NMOSD showed severe and sometimes permanent visual loss. The median of the time to vision loss less than 20/200 is 1.3 years. NMOSD associated ON usually presented in both eye or bilateral involvement, showed MRI hyperintense at posterior optic nerve, optic chiasm, optic tract or lesion cover more than half of the optic nerve length³⁷. Another sign that needed to be put attention to is the poor recovery of the VA even after administration of the high dose steroids³⁸.

Another findings specified in NMOSD related ON, optical coherence tomography (OCT) found thinning of the peripapillary in the retinal nerve fiber layer (pRNFL) seems to be more persistent compared with MS-ON^{39,40}.

Acute Disseminated Encephalomyelitis (ADEM)

ADEM is an CNS disorder mediated by the immune system, causing inflammatory that predominantly occurred in children⁴¹. ADEM can affect people of any age, but commonly found in children, a study showing median of age presentation of 5-8 years old⁴². It usually happened post

-infectious at the CNS, triggering 50-85% of cases^{43,44}. It is thought that MOG-Abs detected in a group of children with ADS^{14,16,45}.

ADEM ON specifically, showed recurrences and persistent MOG-Ab. ADEM ON usually appeared as unilateral ON, happened from one to 9 episodes².

During a study in 2018, two-third of the cases left with impaired cognitive and visual impairment². MRI findings on ADEM didn't show periventricular and T1 hypointense lesions when compared to MS³². Instead it shows T2 and fluid-attenuated inversion recovery (FLAIR) hyperintense white matter lesion on cerebrum, cerebellum. Differences aside, MS and ADEM often occurred overlapped, observing the whole mechanism of the case might be the only way to distinguished the two of them⁴⁶.

Post Infectious

Post infectious ON, happened in children more than in adults, as much as two-thirds of younger children were infected with antecedent virus. Many infections cases correlated with ON such as varicella zoster virus, cytomegalovirus, syphilis, human immunodeficiency virus, tuberculosis, Lyme disease, brucellosis, mycoplasma pneumonia, toxocara, adenovirus, mononucleosis, cytomegalovirus⁸. These diseases have something in common which include inflammatory, degenerative and vascular processes.

Post infectious PON is often presented with bilateral papilitis and it also may associate with ADEM. It is thought to involve systemic demyelinating process, caused by the virus stimulation not the direct infiltration.

2.3. Clinical Manifestations

ON occurred with pain alongside eye movement, headaches, defect of afferent pupil, and abnormality of the optic nerve such as acute papilitis and pale colored in chronic cases. PON showed differences with adult presentation of ON, bilateral presentation and swelling of the optic nerve are commonly found in over half of the total cases⁵. Children might have difficulty describing symptoms, so they came only with central vision that decreased for several hours to days. VA and color vision loss both have varied presentation⁸. Data from various study showed most of the patients had VA of 20/200 or worse⁴⁶. 70% of PON appeared as bilateral cases for younger children and 70% unilateral cases for adolescents¹¹. Report says in pediatric cases 33%-77% patients suffered pain alongside eye movement. Another point made, was 53% experienced headaches. Papilitis were presented between 46%-69% of the total case of PON¹.

2.4. Treatment

The current treatment of acute optic neuritis, focused on assessing the outcome of VA using high doses of intravenous corticosteroids. After the optic neuritis treatment trial (ONTT) in 1992, high-dose IV methylprednisolone became the mainstay of therapy for acute optic neuritis. IVMP is given as much as 1000 mg every day for 3 days, then followed by oral prednisone of 1 mg/kg per day for 11 days to accelerate the recovery of visual function and improve short-term function (6). In a 2021 study, it was proven that treatment with high-dose methylprednisolone followed by oral prednisone had better VA results⁴⁷.

IV methylprednisolone could be replaced by IV immunoglobulin or PLEX. It can be used for patients who's not responsive toward corticosteroids, especially children with NMO. There are side effects for IV immunoglobulin such as headache, myalgia, fever and allergic reaction. PLEX itself

is a more invasive procedure, and have higher risk of infection⁸. PLEX considered as less tolerated than IVIG. But it shows excellent outcome in patients who's not improving given any steroids medications alone⁴⁹.

3. Post Vaccination Pediatric Optic Neuritis

Causes of PON is considered to be a little bit different compared to adults. Post infectious and post vaccinations ON in children happened more often compared to the adults. Vaccines throughout the childhood such as measles, mumps, rubella, pertussis are reported to have affected PON in past cases ⁸.

ON was reported after a MR vaccine, alongside with ADEM. 11-year-old female, experience high-grade fever, alongside with headache, drowsiness. The MRI showed hyperintensity in entire spinal cord and brain stem. Later on, the patient came with complete loss of visual ability, with relative afferent papillary defect (RAPD), papilitis confirming ON without another neuro deficit. Patient was tested positive for anti-MOG and showed negative for NMO antibodies. The patient fully recovered after 7 days, using intravenous immunoglobulin and intravenous methylprednisolone⁵⁰.

Ryu reported a case of optic neuritis post vaccination of MMR, that started after stopping the steroids treatment, causing optic neuritis to occur. The patient who was a 6-year-old girl had unilateral presentation with NMO test being negative. She received IV methyl prednisolone for 3 days ⁵¹.

A case report in Dr. Soetomo Teaching Hospital stated pre-pubescent age female to complain about sudden blurred vision in one eye, after receiving MR vaccination. Patient showed multiple hyperintense lesion in the right and left subcortical temporo-parietal, rising accusation of ADEM. The symptoms were accompanied by high fever and pain with eye movements ⁵².

As investigation went along, ADEM is known as a result to the vaccine adjuvants and mimicry of the molecule in the viral proteins that being used for vaccinations. Usually aluminum used as vaccine adjuvant, which known to interfere with lysosome function, and have the ability to stimulate the production and secretion of cytokines. Molecular mimicry in the vaccine components is similar to myelin in the CNS, and happened to induce major immunopathogenic mechanism. It triggered immunological reactions including ADEM, myelitis, neuromyelitis, and many more (52). According to Jarius, it might be affected by the immune physiology, especially the molecular mimicry, causing activation of the presenting cell, increased antigens caused over processing, leading to autoimmune process using the B lymphocytes polyclonal activation that increased cytokine production, giving the effect of T-cell being autoreactive ⁵⁰.

More post vaccinations cases showed after MR vaccine, two patients aged 15-years-old boy with mild vasovagal shock immediately after administration of the vaccine. Optic neuritis appeared with acute and complete visual loss, alongside with headaches. Another case of 17-years-old male patient presented with decreasing VA 7 hours after MR vaccination. A retrobulbar optic neuritis diagnosis was made⁵³.

Lately, reports post COVID-19 vaccine stated cases potential for CNS inflammatory syndrome post vaccine administration. Before there was a case report about influenza vaccination associated ON, but it was not a pediatric case. The same thing happened to COVID-19 vaccine, there no cases about PON have been released⁵³.

4. Conclusion

Pediatric optic neuritis is rare compared to adult optic neuritis. Not only the prevalence, but some of the etiologies may differ. ADEM are more prone to children than adults, while post infectious and post vaccination associated optic neuritis tend to occur in higher number in children. There have been several cases reported of optic neuritis in children associated with post vaccinations reaction. Most of the cases reported, occurred post MR vaccinations, followed by ADEM associated ON, and as the effect of stopping steroids treatment abruptly. Therefore, ON could be predicted as one of the side effects of the vaccine. Also steroids treatment should be put into attention before putting it into a stop. No studies were found regarding optic neuritis occurring in children post COVID-19 vaccination.

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