Neuroimaging in Pediatric Optic Neuritis: A Narrative Review

Running Title: Pediatric Optic Neuritis

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Abstract

**Context:** Pediatric optic neuritis can occur in isolation or in association with neuroinflammatory disorders. Abnormal orbital and cranial Magnetic Resonance Imaging were reviewed in literature diagnosed as Pediatric Optic Neuritis primarily presented with visual problems.

**Evidence Acquisition:** A PubMed literature search was accomplished using the following search terms; Neuroimaging, Pediatric, Optic Neuritis, Multiple Sclerosis, and Magnetic Resonance Imaging.

**Results:** Poorly demarcated changes in white and/or gray matter, well-demarcated white matter changes, confluent lesions in white matter, and nonspecific small lesions or nothing in certain regions of the brain are the most common patterns of children with optic neuritis. Optic nerve lesions can be revealed by the thin fat suppression imaging technique. Contrast-enhanced sequences, especially by short tau inversion recovery, allow differentiation of particular high-signal intensity foci in the optic nerve and newly formed active lesions from inactive lesions.

**Conclusion:** Brain imaging should be performed in all patients, if possible, during the following two weeks after the initial diagnosis. The cranial neuroimaging can predict multiple sclerosis development in pediatric patients with demyelinating brain lesions.

**Keywords:** Pediatric, Optic Neuritis, Neuroimaging, Magnetic Resonance Imaging
1. Context

Pediatric Optic Neuritis (PON) is commonly presented as a spectrum of neuroinflammatory disorders such as Monophasic Optic Neuritis (MON), Isolated Recurrent Optic Neuritis (IRON), Neuromyelitis Optica (NO), and Acute Disseminated Encephalomyelitis (ADEM) as well as in chronic diseases such as Multiple Sclerosis (MS).

Optic neuritis is an inflammation of the optic nerve clinically specified by decreased visual acuity, field defects, diminished color vision, and positive Marcus Gun if unilateral (1). Neuroimaging enhancement and latency of conduction on Visual Evoked Potentials are important findings to confirm the diagnosis. Despite the assignation of the identical name, children are not little adults; suffering children are different from those affecting adults. Children might present with bilateral painless optic nerve head swelling and more severe visual impairment after a prodromal viral illness. Visual recovery in children is more expectable. Most pediatric patients with PON are older than 12 years. However, the correlation between puberty and risk associations is unknown. Children are less likely to develop MS compared to adults, but it is more likely to be a preliminary representation of ADEM (2). Optic neuritis in children with its peculiar clinical features has a better prognosis than in adulthood. The main concern for therapeutics is the relationship of optic neuritis with multiple sclerosis. (3) PON encounters more difficulty in diagnosis, including; unilateral, subclinical, spontaneously resolving, and poor history presentation, also a tendency for children to simulate vision loss to obtain glasses being diagnosed as spurious, delaying diagnosis and treatment. In a child with PON, a guided medical workup helps to differentiate the various metabolic, infectious, autoimmune causes and treatable space-occupying lesions. Generally, the patients are treated with intravenous methylprednisolone, although the decision to treat varies between practitioners (4).

Among the newly developed neuroimaging techniques, magnetic resonance imaging (MRI) is considered a reliable noninvasive, reproducible approach for the diagnosis and management of PON. Brain MRI is more sensitive to the white matter than the grey matter lesions. MRI with high sensitivity serves as an important component of subclinical disease activity and diagnostic criteria especially for MS and NMO spectrum disorders (5, 6).

However, the disadvantages of MRI are a limitation to detect the inherent of demyelinating lesions and being an expensive modality. MRI helps to rule out the other differential diagnoses such as brain tumors that may appear similar to demyelinating lesions, without the necessity to use invasive procedures. Furthermore, it is particularly useful to detect the evolution of clinically silent lesions (7).

In this study, we only present and discuss the findings of recent investigations in which the impact on PON was assessed. However, little surveys exist about this association in children growing up.

2. Evidence Acquisition

A PubMed literature search limited to the English language from 1995 to 2019 was accomplished using the following search terms; Neuroimaging, Pediatric Optic Neuritis,
Multiple Sclerosis, and Magnetic Resonance Imaging. Herein, qualitative results get from research studies are explained. The articles were then reviewed to exclude those related primarily to brain disease (such as raised intracranial pressure), adult cases and studies in healthy subjects as these were not the aim of this review. For the meaning of this review, case control, randomized controlled trials, cohort studies, evidence from meta-analyses, and systematic reviews were included. Case reports or case series were included only if there were specified evidence by two or more articles in order to merge unusual finding as an index of future investigation. We excluded articles considering skillful viewpoint and letters to the editor. A total of 325 potentially relevant records were identified. Following the exclusion of 239 citations, 86 full text papers were retrieved for detailed examination. A total of 27 articles matched the eligibility criteria.

3. Results
Neuroimaging can disclose the cranial MRI sequences with axial T2, axial FLAIR, sagittal T2, and contrast-enhanced axial T1.
Generally, the brain MRI of demyelination in children has one of the following four patterns: poorly demarcated changes in white and/or gray matter, well-demarcated white matter changes, confluent lesions in white matter, nonspecific small (< 0.3 cm) lesions or nothing. These lesions more commonly involve certain regions of juxtacortical and cortical gray matter, deep and periventricular white matter, thalamus, corpus callosum, basal ganglia, cerebellum, and brainstem (8).
In orbital MRI, optic nerve lesions can be found by thin (2-3mm) fat suppression imaging, that can be achieved with fat-saturated fast-spin echo technique or fat-saturated T1-weighted imaging following contrast enhancement (9-12).
Optic nerve imaging by Short Tau Inversion Recovery (STIR) sequences, may display particular high-signal intensity foci in the optic nerve. Contrast administration can enhance these lesions, but that does not occur in a healthy optic nerve. Certain MR findings of optic nerve lesions with greater length involvement or lesion within the optic canal may predict a poor visual outcome, although this is still controversial among some investigators.
The Signal Intensity Ratio (SIR) of the optic nerve to the white matter on STIR is a distinctive measure for acute optic neuritis. Patients with acute optic neuritis have higher SIRave and SIRmax than in control patients (13).
NO lesions have different types of MRI findings; they are longitudinally extensive, and involve several optic nerve segments. Contrary, MS lesions are often localized focally in one optic nerve segment (14).
Diffusion-Weighted and Diffusion-Tensor imaging may yield more pathologic information about optic nerve than conventional anatomic imaging, such as T2 signal intensity, and enhancement. However, the application of these advanced technologies is too time-consuming and laborious for customary clinical application.
Three-Dimensional Double Inversion Recovery (3D DIR) is preferred over 2-dimensional STIR for the detection of optic nerve signal abnormalities. Multiplanar DIR sequences have the foremost efficiency for the diagnosis of PON (9).

In the pediatric population, MS may be expressed initially as PON. However limited data are available about the rate of progression of isolated optic neuritis to MS. Table 1 shows the results of some relevant studies concentrated on the clinical and radio-imaging features of PON. Most of these investigations were case series or longitudinal observation. The greatest rate of MS development was 36%, reported by Wilejto et al in Canadian children with PON (30).

Diagnosis of MS was proposed by McDonald criteria, which could also assist the early diagnosis of MS in teenagers (5, 15).

Brain MRI is considered as sensitive modality for the detection of white matter’s lesions. The MRI in MS agreement suggests essential sequences for brain MRI include: 2D or 3D contrast-enhanced T1-weighted, axial proton density and/or T2-Fluid-Attenuated Inversion Recovery (FLAIR)/T2weighted, sagittal 2D or 3D T2FLAIR (16).

Diffusion Tensor Imaging and Magnetization Transfer Ratio are two modern non-conventional MR imaging techniques that were demonstrated to be sensitive to optic nerve damage; especially in patients with prior episodes of PON. Axial diffusion-weighted imaging able to differentiate an acute gadolinium-enhanced MS lesion from an acute restricted ischemic lesion (17, 18).

Although spinal MRI is highly sensitive to detect silent lesion, it is not recommended routinely in patients without spinal cord symptoms (19). In the absence of spinal cord signs, spine imaging can probably be postponed unless an antibody against aquaporin 4 testing is positive. (20)

The diagnosis of PON and MS is supported by the contrast agent administration to detect active lesions specified by the Blood-Brain Barrier breakdown. Repeated use of contrast agent in serial MRI in a young population may have some concern regarding the deposition of considerable gadolinium amounts in the brain (21).

The MRI can predict MS in pediatric patients with demyelinating brain lesions. A recent prospective study in Canadian pediatric patients suggests that the presence of at least one black hole (a persistent hypointensity for more than 3 months on T1weighted imaging) and at least one periventricular lesion (Dawson's finger) were predictive parameters of MS in pediatric patients (22).

Commonly, brain lesions of MS become visible as well-defined, high signal ovoid-shaped areas on T2-weighted and T2FLAIR images extend throughout the white matter, generally in the areas of juxtacortical and periventricular, corpus callosum, cerebellum, and brainstem.

T2-weighted imaging is the technique suitable for the detection of supratentorial, infratentorial and spinal cord lesions, however, T2FLAIR imaging offers better sequence for cortical, juxtacortical, and periventricular lesions (23, 24).

Proton Density-Weighted Imaging approaches better detection of periventricular lesions with lesion-tissue contrast. This sequence is especially helpful in patients with an incomplete myelinated brain as in young children.
Delicate spinal cord lesions can be identified by STIR imaging technique. STIR scans also give fat suppression, so properly gain sensitivity for the optic nerve and spinal cord imaging (24). Contrast-enhanced T1-weighted sequences allow differentiation of newly formed active lesions from inactive lesions with displaying different schemas of contrast enhancement. This lesion enhancement lasts for about 3 weeks and may be changed base on the treatment modalities (25). Brain MR imaging of MS children is different from adults: they have a higher lesion loading on their initial scans; lesions are larger, confluent, with indistinct borders, and deeper in grey matter; more easily decrease in T2-bright lesions; and tumefactive lesions (lesions of >2 cm, with surrounding edema) are more common in younger children with MS (26, 27).

<table>
<thead>
<tr>
<th>Study design</th>
<th>NO. patient’s analysis</th>
<th>Average age, years</th>
<th>FU, years (range)</th>
<th>Clinical features</th>
<th>MRI data</th>
<th>Author, location (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort</td>
<td>25</td>
<td>9.9</td>
<td>1.1</td>
<td>Bilateral in 56%, recovery in 76% of affected eyes.</td>
<td>Normal MRI in 24%</td>
<td>Brady et al, USA, 1999 (28)</td>
</tr>
<tr>
<td>Case Series</td>
<td>15</td>
<td>9.1</td>
<td>1.5</td>
<td>Papillitis in 64%, Bilateral in 66%, MS progression to 26%.</td>
<td>Abnormal MRI; optic nerve in 63%, Brain lesions in 33%</td>
<td>Morales et al, USA, 2000 (29)</td>
</tr>
<tr>
<td>Case Series</td>
<td>27</td>
<td>10.9</td>
<td>1.1</td>
<td>Optic disc change in 81%, Bilateral in 37%, lead to MS in one patient.</td>
<td>No patient level data available</td>
<td>Lana-Peixoto, de Andrade, Brazil, 2001(30)</td>
</tr>
<tr>
<td>Cohort</td>
<td>36</td>
<td>12.8</td>
<td>2.4</td>
<td>Bilateral in 42%, recovery in 83% of affected eyes, MS development in 36%.</td>
<td>Abnormal MRI; optic nerve in 55%, Brain lesions in 54%</td>
<td>Wilejto et al, Canada, 2006 (31)</td>
</tr>
<tr>
<td>Cohort</td>
<td>30</td>
<td>11.9</td>
<td>5.4</td>
<td>Monophasic in 77%, 60% of them had isolated optic neuritis. 23% lead to MS</td>
<td>Abnormal brain MRI seen in 40%</td>
<td>Alper, Wang, USA. 2009 (32)</td>
</tr>
<tr>
<td>Case Series</td>
<td>31</td>
<td>10.1</td>
<td>2.2</td>
<td>Monophasic bilateral optic neuritis in 45%,</td>
<td>Abnormal MRI observed in</td>
<td>Cakmakli et al, Turkey, 2009 (33)</td>
</tr>
</tbody>
</table>
MS development in 26%.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>29</th>
<th>9.7</th>
<th>4.2</th>
<th>In children with idiopathic optic neuritis, MS developed in 17%</th>
<th>Brain lesions in 38% in T2/FLAIR.</th>
<th>Bonhomme et al, USA, 2009 (34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Series</td>
<td>34</td>
<td>9.8</td>
<td>4.8</td>
<td>In children with optic neuritis and positive oligoclonal bands in spinal fluid had a predictive factor for MS development.</td>
<td>Abnormal brain MRI increases the risk of MS development.</td>
<td>Heussinger et al. Netherlands, 2013 (11)</td>
</tr>
<tr>
<td>Case Series</td>
<td>40</td>
<td>11.2</td>
<td>1.1</td>
<td>55% had bilateral optic neuritis, 10% of children were diagnosed as MS.</td>
<td>Abnormal brain MRI brain 65%, 35% children showed only optic nerve enhancement.</td>
<td>Khadse et al, India, 2017 (35)</td>
</tr>
<tr>
<td>cohort</td>
<td>69</td>
<td>7.2</td>
<td>2.75</td>
<td>Isolated optic neuritis in 23%, 4% lead to MS, acute disseminated encephalomyelitis in 52% or neuromyelitis optica in 7%.</td>
<td>Cerebral MRI with poorly demarcated lesions in 71%.</td>
<td>Baumann et al, USA 2018 (36)</td>
</tr>
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MRI; magnetic resonance imaging, MS; multiple sclerosis

### 4. Conclusions

Brain MRI should be performed in all patients, if possible, during the following two weeks after the initial diagnosis of PON.

Fat suppression MR imaging can detect optic nerve lesions, attained either with fast spin-echo technique or contrast-enhanced T1-weighted imaging. Although the abnormal gadolinium-enhanced MRI is not diagnostic for demyelinating optic neuritis -since these findings can be seen in other conditions such as neoplastic infiltrative, cytomegalovirus, rheumatic optic neuropathy-, contrast enhancement and STIR may be helpful to distinguish an acute inflammatory lesion.
from an acute restricted ischemic lesion. The implication of modern orbital MRI sequences in standard clinical practice assesses the patient for compressive lesions, meningeal enhancement, and inflammatory or demyelinating lesions elsewhere in the brain to obtain relevant information for assessment, treatment, and prognosis of PON.

The presence of lesions, commonly oval-shaped and located in the region of periventricular white matter is an ominous prognostic factor for the increase in the possibility of future development of MS.

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**Conflicts of interest**
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