

Review Paper:

Neuroimaging in Pediatric Optic Neuritis: A Narrative Review



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ABSTRACT

Context: Pediatric optic neuritis can occur in isolation or association with neuroinflammatory disorders. We reviewed the abnormal orbital and cranial magnetic resonance imaging in literature diagnosed as pediatric optic neuritis, which was primarily presented with visual problems.

Evidence Acquisition: A PubMed literature search was accomplished using the following key 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 small nonspecific lesions or nothing in some areas of the brain are the most common patterns of children with optic neuritis. The thin, fat suppression imaging technique can reveal optic nerve lesions. 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.

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

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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 (NMO), 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 characterized by decreased visual acuity, field defects, diminished color vision, and positive Marcus Gunn in unilateral cases (1). Neuroimaging enhancement and latency of conduction on visual evoked potentials are essential findings to confirm the diagnosis. Despite the identical name, children are not little adults. Children suffer differently from adults regarding this disease. 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 with PON are less likely to develop MS compared to adults, but they are prone to experience a preliminary representation of ADEM (2). Opticneuritisin children with its peculiar clinical features has a better prognosis than in adulthood. The main concern for therapeutics is the relationship of opticneuritiswith multiple sclerosis (3). Diagnosis of PON is more difficult as there are unilateral, subclinical, spontaneous resolving, and poor history presentation. Also, children's desire to pretend vision loss in order to obtain glasses is being misdiagnosed as spurious, and subsequently delays diagnosis and treatment. In a child with PON, a guided medical workup helps to differentiate the various metabolic, infectious, autoimmune, 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, and reproducible approach for the diagnosis and management of PON. Brain MRI is more sensitive to white matter lesions than the grey matter ones. MRI with high sensitivity serves as an essential component of subclinical disease activity and diagnostic criteria, especially for MS and Neuromyelitis Optica (NMO) spectrum disorders (5, 6). However, the

disadvantages of MRI make it hard to detect the nature of demyelinating lesions and is 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 just present and discuss the findings of recent investigations in which the impact on PON was assessed. However, few studies 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". In this step, qualitative results from research studies were obtained. The articles were then reviewed to exclude those related to brain diseases (such as raised intracranial pressure), adult cases, and studies in healthy subjects as these were not the aim of this review.

For the significance 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 only included if there was specified evidence by two or more articles to merge unusual findings as an index of future investigation. We excluded articles considering the expert viewpoints 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. Finally, 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 periven-

tricular white matter, thalamus, corpus callosum, basal ganglia, cerebellum, and brainstem (8).

In orbital MRI, optic nerve lesions can be found by thin (2-3 mm) fat suppression imaging. This imaging 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 it does not occur in a healthy optic nerve. Specific 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 SIR_{ave} and SIR_{max} than in control patients (13). NMO lesions have different types of MRI findings. They are longitudinally extensive and involve several optic nerve segments. On the 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 everyday clinical use.

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 initially be expressed as PON. However, limited data are available about the rate of progression of isolated optic neuritis to MS. Table 1 lists 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 observations. The highest rate of MS development was 36%, as 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 a sensitive modality for the detection of white matter 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)/T2-weighted, sagittal 2D, or 3D T2-FLAIR (16).

Diffusion tensor imaging and magnetization transfer ratio are two modern non-conventional MRI imaging techniques that were sensitive to optic nerve damage, especially in patients with prior episodes of PON. Axial diffusion-weighted imaging can differentiate an acute gadolinium-enhanced MS lesion from an acute restricted ischemic lesion (17, 18).

Although spinal MRI is highly sensitive in detecting silent lesions, it is not routinely recommended 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 agents in serial MRI in a young population may bring some concerns regarding the deposition of considerable gadolinium amount 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 T1-weighted imaging) and at least one periventricular lesion (Dawson's finger) were predictive parameters of MS in pediatric patients (22).

Generally, MS brain lesions become visible as well-defined, high signal ovoid-shaped areas on T2-weighted and T2-FLAIR images extend throughout the white matter, usually in the juxtacortical and periventricular regions, corpus callosum, cerebellum, and brainstem. T2-weighted imaging is a suitable technique for the detection of supratentorial, infratentorial, and spinal cord lesions; however, T2-FLAIR imaging offers a better sequence for cortical, juxtacortical, and periventricular lesions (23, 24).

Proton density-weighted imaging approaches better detect periventricular lesions with lesion-tissue contrast. This sequence is especially helpful in patients with an incomplete myelinated brain as in young children. The STIR imaging technique can identify delicate spinal cord lesions. STIR scans also give fat suppression, so properly gain sensitivity for the optic nerve and spinal cord imaging (24). Contrast-enhanced T1-weighted sequences al-

Table 1. Clinical studies in PON according to MRI imaging

Author, Location (y) (Reference)	MRI Data	Clinical Features	FU (y) (Range)	Average Age (y)	NO. of Patient's Analysis	Study Design
Brady et al., USA, 1999 (28)	Normal MRI in 24%	Bilateral in 56%, recovery in 76% of affected eyes	1.1	9.9	25	Cohort
Morales et al., USA, 2000 (29)	Abnormal MRI; optic nerve in 63%, Brain lesions in 33%	Papillitis in 64%, Bilateral in 66%, MS progression to 26%	1.5	9.1	15	Case series
Lana-Peixoto, de Andrade, Brazil, 2001 (30)	No patient level data available	Optic disc change in 81%, bilateral in 37%, lead to MS in one patient	1.1	10.9	27	Case series
Wilejto et al., Canada, 2006 (31)	Abnormal MRI; optic nerve in 55%, Brain lesions in 54%	Bilateral in 42%, recovery in 83% of affected eyes, MS development in 36%	2.4	12.8	36	Cohort
Alper, Wang, USA, 2009 (32)	Abnormal brain MRI seen in 40%	Monophasic in 77% of cases, 60% of them had isolated optic neuritis, 23% lead to MS	5.4	11.9	30	Cohort
Cakmakli et al., Turkey, 2009 (33)	Abnormal MRI observed in 39% of patients	Monophasic bilateral optic neuritis in 45%, MS development in 26%	2.2	10.1	31	Case series
Bonhomme et al., USA, 2009 (34)	Brain lesions in 38% in T2-FLAIR	In children with idiopathic optic neuritis, MS developed in 17%	4.2	9.7	29	Cohort
Heussinger et al., Netherlands, 2013 (11)	Abnormal brain MRI increases the risk of MS development	In children with optic neuritis and positive oligoclonal bands in spinal fluid had a predictive factor for MS development	4.8	9.8	34	Case series
Khadse et al., India, 2017 (35)	Abnormal brain MRI brain 65%, 35% of children showed only optic nerve enhancement	55% had bilateral optic neuritis, 10% of children were diagnosed as MS	1.1	11.2	40	Case series
Baumann et al., USA, 2018 (36)	Cerebral MRI with poorly demarcated lesions in 71%	Isolated optic neuritis in 23%, 4% lead to MS, acute disseminated encephalomyelitis in 52%, or neuromyelitis optica in 7%	2.75	7.2	69	Cohort

MRI: Magnetic Resonance Imaging; MS: Multiple Sclerosis.

Journal of Pediatrics Review

low 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 change depending 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 the tumefactive lesions (lesions

of >2 cm, with surrounding edema) are more common in younger children with MS (26, 27).

4. Conclusions

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

Fat suppression MRI 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—these findings can be seen in other conditions such as neoplastic infiltrative, cytomegalovirus, rheumatic optic neuropathy—contrast enhancement and STIR may help 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 possibility of future development of MS.

Ethical Considerations

Compliance with ethical guidelines

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Authors contributions

All three authors equally contributed to the literature search, compiling, and approving the final manuscript.

Conflict of interest

The authors have no financial or personal relations that could create a conflict of interest.

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