Accepted Manuscript

Neuroimaging in Pediatric Optic Neuritis: A Narrative Review

Running Title: Pediatric Optic Neuritis

Ali Ahmadzadeh Amiri[1], Abdulrasool Alaee[2], and Ahmad Ahmadzadeh Amiri[3]*

[1]Department of Pediatric, Bahrami Children's Hospital, Tehran University of Medical Sciences, Tehran, IR Iran

[2]Department of Radiology, Mazandaran University of Medical Sciences, Sari, IR Iran, email:

[3*]Department of Ophthalmology, Clinical Research Development Unit of Bu-Ali Sina Hospital, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, IR Iran, email

3*- Corresponding author: Ahmad Ahmadzadeh Amiri, MD., Assistant Professor of Ophthalmology

Postal Address: Department of Ophthalmology, Mazandaran University of Medical Sciences, Bu-Ali Sina Hospital, Pasdaran Boulevard, Sari, IR Iran

Tel& Fax: +98 11 33344506

E-mail: ahmadzdh@yahoo.com

ORCID IDs of all authors (If any):

Ali Ahmadzadeh Amiri: 0000-0001-5605-3521
Abdulrasool Alaee: 0000-0003-0776-8066
Ahmad Ahmadzadeh Amiri: 0000-0002-2700-5480

To appear in: Journal of Pediatrics Review
Received: 2019/06/12
Revised: 2019/08/19
Accepted date: 2019/08/28

Please cite this article as:

Ali Ahmadzadeh Amiri[1], Abdulrasool Alaee[2], and Ahmad Ahmadzadeh Amiri[3]* Neuroimaging in Pediatric Optic Neuritis: A Narrative Review. J. Pediatr. Rev. Forthcoming 2020 April 30.

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 T1wighted 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 1 Clinical studies in PON according to MRI imaging

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

				MS development in 26%.	39% patients.	
Cohort	29	9.7	4.2	In children with idiopathic optic neuritis, MS developed in17%	Brain lesions in 38% in T2/FLAIR.	Bonhomme et al, USA, 2009 (34)
Case Series	34	9.8	4.8	In children with optic neuritis and positive oligoclonal bands in spinal fluid had a predictive factor for MS development.	Abnormal brain MRI increases the risk of MS development.	Heussinger et al. Netherlands, 2013 (11)
Case Series	40	11.2	1.1	55% had bilateral optic neuritis, 10% of children were diagnosed as MS.	Abnormal brain MRI brain 65%, 35% children showed only optic nerve enhancement.	Khadse et al, India, 2017 (35)
cohort	69	7.2	2.75	Isolated optic neuritis in 23%, 4% lead to MS, acute disseminated encephalomyelitis in 52% or neuromyelitis optica in 7%.	Cerebral MRI with poorly demarcated lesions in71%.	Baumann et al, USA 2018 (36)

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, rheumatics 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.

Acknowledgements

The authors would like to thank of Clinical Research Development Unit of Bu-Ali Sina Hospital for cooperation in search strategies.

Ethical Considerations

This research had no ethical consideration.

Funding

There is no specific grant to be received doing this research.

Author's contributions

All three authors contribute to literature searches, compiled and approved the final manuscript.

Conflicts of interest

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

References

1. Hierons R, Lyle TK. Bilateral retrobulbar optic neuritis. Brain 1959; 82:56–67.

2. Rizzo JF III, Lessell S. Risk of developing multiple sclerosis after uncomplicated optic neuritis: a long-term prospective study. Neurology 1988; 38:185–190.

3. Pérez-Cambrodí RJ, Gómez-Hurtado Cubillana A, Merino-Suárez ML, Piñero-Llorens DP, Laria-Ochaita C. Optic neuritis in pediatric population: A review in current tendencies of diagnosis and management. J Optom. 2014 Jul; 7(3): 125–130.

4. Volpe NJ. The optic neuritis treatment trial: a definitive answer and profound impact with unexpected results. Arch Ophthalmol 2008; 126:996–999.

5. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011; 69(2):292-302.

6. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for Neuromyelitis Optica spectrum disorders. Neurology 2015; 85(2): 177-89.

7. Tornatore C, Phillips JT, Khan O, Miller AE, Barnes CJ. Practice patterns of US neurologists in patients with CIS, RRMS, or RIS: a consensus study. Neurol Clin Pract 2012; 2(1):48–57.
8. Verhey LH, Branson HM, Laughlin S, Shrof MM, Benseler SM, Feldman BM, et al. Development of a standardized MRI scoring tool for CNS demyelination in children. AJNR Am J Neuroradiol 2013; 34:1271–1277.
9. Hodel J, Outteryck O, Bocher AL, Zéphir H, Lambert O, Benadjaoud MA, et al. Comparison of 3D double inversion recovery and 2D STIR FLAIR MR sequences for the imaging of optic neuritis: pilot study. Eur Radiol 2014; 24(12):3069-75.
10. Pino-Lopez L, Wenz H, Böhme J, Maros M, Schlichtenbrede F, Groden C, et al. Contrast-enhanced fat-suppressed FLAIR for the characterization of leptomeningeal inflammation in optic neuritis. Mult Scler. 2019 May;25(6):792-800.
11. Heussinger N, Kontopantelis E, Rompel O, Paulides M, Trollmann R. Predicting multiple sclerosis following isolated optic neuritis in children. Eur J Neurol 2013 Sep. 20(9):1292-6.
12. Soelberg K, Skejoe HPB, Grauslund J, Smith TJ, Lillevang ST, Jarius S, et al. Magnetic resonance imaging findings at the first episode of acute optic neuritis. Mult Scler Relat Disord 2018 Feb; 20:30-36.
13. Onodera M, Yama N, Hashimoto M, Shonai T, Aratani K, Takashima H, et al. The signal intensity ratio of the optic nerve to ipsilateral frontal white matter is of value in the diagnosis of acute optic neuritis. Eur Radiol. 2016; 26(8): 2640-5.
14. Mealy MA, Whetstone A, Orman G, Izbudak I, Calabresi PA, Levy M. Longitudinally extensive optic neuritis as an MRI biomarker distinguishes neuromyelitis optica from multiple sclerosis. J Neurol *Sci*. 2015; 15. 355 (1-2):59-63.
15. Sadaka Y, Verhey LH, Shroff MM, Branson HM, Arnold DL, Narayanan S, et al. 2010 McDonald criteria for diagnosing pediatric multiple sclerosis. Ann Neurol. 2012; 72(2):211–23.
16. Rovira A, Wattjes MP, Tintore M, Tur C, Yousry TA, Sormani MP, et al. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis-clinical implementation in the diagnostic process. Nat Rev Neurol 2015; 11(8):471–82.
17. Naismith RT, Xu J, Tutlam NT, Lancia S, Trinkaus K, Song SK, et al. Diffusion tensor imaging in acute optic neuropathies: predictor of clinical outcomes. Arch Neurol 2012; 69: 65–71.
18. Wang Y, van der Walt A, Paine M, Klistorner A, Butzkueven H, Egan GF, et al. Optic nerve magnetization transfer ratio after acute optic neuritis predicts axonal and visual outcomes. PLoS One 2012; 7: e52291.
19. Dalton CM, Brex PA, Miszkiel KA, Fernando K, MacManus DG, Plant GT, et al. Spinal cord MRI in clinically isolated optic neuritis. J Neurol Neurosurg Psychiatry 2003; 74 (11):1577–80.
20. Borchert M, Liu GT, Pineles S, Waldman AT. Pediatric Optic Neuritis: What Is New. J Neuroophthalmol. 2017 Sep;37 Suppl 1:S14-S22.
21. Kanda T, Fukusato T, Matsuda M, Toyoda K, Oba H, Kotoku J, et al. Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction:

evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. Radiology 2015; 276(1):228–32.
22. Verhey LH, Branson HM, Shroff MM, Callen DJ, Sled JG, Narayanan S, et al. MRI parameters for prediction of multiple sclerosis diagnosis in children with acute CNS demyelination: a prospective national cohort study. Lancet Neurol. 2011; 10(12):1065–73.
23. Paty DW, Li DK. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group, IFNB Multiple Sclerosis Study Group. Neurology1993; 43: 662–7.
24. Pirko I. Neuroimaging of demyelinating diseases. Continuum Lifelong Learn Neurol 2008; 14:118–43.
25.Verhey LH, Narayanan S, Banwell B. Standardized magnetic resonance imaging acquisition and reporting in pediatric multiple sclerosis. Neuroimaging Clin N Am 2013; 23:217–26.
26. Waubant E, Chabas D. Pediatric multiple sclerosis. Curr Treat Options Neurol 2009; 11:203–10.
27. Chabas D, Castillo-Trivino T, Mowry EM, Strober JB, Glenn OA, Waubant E. Vanishing MS T2-bright lesions before puberty. A distinct MRI phenotype? Neurology 2008; 71:1090–3.
28. Brady KM, Brar AS, Lee AG, Coats DK, Paysse EA, Steinkuller PG. Optic neuritis in children: clinical features and visual outcome. J AAPOS 1999 Apr; 3(2):98-103.
29. Morales DS, Siatkowski RM, Howard CW, Warman R. Optic neuritis in children. J Pediatr Ophthalmol Strabismus 2000 Sep-Oct; 37(5):254-9.
30. Lana-Peixoto MA, Andrade GC. The clinical profile of children optic neutitis. Arq Neuropsiquiatr 2001 Jun; 59(2-B):311-7.
31. Wilejto M, Shroff M, Buncic JR, Kennedy J, Goia C, Banwell B. The clinical features, MRI findings, and outcome of optic neuritis in children. Neurology 2006; 67:258–62.
32. Alper G, Wang L. Demyelinating optic neuritis in children. J Child Neurol 2009 January; 24(1): 45–48.
33. Cakmakli G, Kurne A, Güven A, Serdaroğlu A, Topaloğlu H, Teber S, et al. Childhood optic neuritis: the pediatric neurologist's perspective. Eur J Paediatr Neurol. 2009 Sep; 13(5):452-7.
34. Bonhomme GR, Waldman AT, Balcer LJ, Daniels AB, Tennekoon GI, Forman S, et al. Pediatric optic neuritis: brain MRI abnormalities and risk of multiple sclerosis. Neurology 2009 Mar 10; 72(10):881-5.
35. Khadse R, Ravindran M, Pawar N, Maharajan P, Rengappa R. Clinical profile and neuroimaging in pediatric optic neuritis in Indian population: A case series. Indian J Ophthalmol 2017 Mar; 65(3): 242–245.
36. Baumann M, Grams A, Djurdjevic T, Wendel TM, Lechner C, Behring B, et al. MRI of the first event in pediatric acquired demyelinating syndromes with antibodies to myelin oligodendrocyte glycoprotein. Journal of Neurology 2018; 265:845–855