New Insights on Optic Neuritis in Young People

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Abstract

Objectives: Demonstrate that there is an actual state of knowledge which allows as to make accurate diagnosis of optic neuritis in young people.

Materials and Methods: We have checked three cases of optic neuritis.

The first a 18 years old female with visual loss in the right eye and retro-ocular pain for the last 48 hours with an area of enhancement at the optic nerve and loss of fibers in the unaffected optic nerve.

The second one was 23-year-old male whit acute bilateral visual loss, bilateral disc edema, NMO antibody negative and enhancement of the optic nerves.

The presumed diagnosis was optic neuromyelitis spectrum disease.

The third was a 13 years old male whit acute visual loss, binocular, of three days duration. She had history of nephritis caused by systemic lupus erythematosus. She had AQP-4 positive antibodies.

Conclusions

1- The diagnosis of retrobulbar optic neuritis (the most common demyelinating form) is possible only with the clinical data, however the MRI with gadolinium is necessary to establish if there are demyelinating lesions in other areas and whether they enhance or not with the contrast.

2- With these two data: a) optic neuritis (Clinical Isolated Syndrome CIS) and b) a combination of acute lesions - contrast enhancers and chronic lesions - sustain, according to the new criteria, the diagnosis of MS and justify the immunomodulation treatment.

3- Clinical and MRI data are essential to rule out NMO, although not all cases present AQP P-4 it is a very useful data to confirm the diagnosis and define the treatment, which is different from MS.

Keywords: Optic Neuritis; Young People; AQP-4

Introduction

The Optic Neuritis Treatment Trial (ONTT 1988) provided a clear epidemiologic profile of Optic Neuritis (ON). It was a study of 457 patients with ages from 18 to 46 within 8 days from symptom onset. 77% of the cohort was females and 92% reported ocular pain; 65% had a normal funduscopic examination.

New Insights on Optic Neuritis in Young People

Visual Acuity ranged from 20/20 (10%) to NLP (3%), with an average 20/200 (64%). Surprisingly the most common pattern of visual field deficit was an altitudinal defect. The field defect, therefore, is not helpful in making a diagnosis of ON.

The routine ancillary test of choice is MRI; laboratory testing is generally not helpful. The ONTT concluded that if the clinical picture conforms to the classical picture of ON, no laboratory test is required. Optic Neuritis and AION are occasionally confused because of the overlapping clinical findings.

Must obtain a good history and examination. The idea is to determine if there is evidence of dissemination in time and Space [1].

Case 1: Retrobulbar Optic Neuritis

Female, 18 years old, who had visual loss in the right eye and retro-ocular pain for the last 48 hours.

The figure 1 and 2 demonstrates an area of enhancement affecting the right intracanalicular optic nerve (2 cm enhancement).

Figure 1
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**Figure 1 and 2**: Area of enhancement affecting the right intracanalicular optic nerve.

The patient presented these results in the ocular computed tomography (OCT) (Figure 3):
- 95% Normal Fibers Green
- 5% Normal Fibers Yellow
- 0% Normal Fibers Red

**Figure 3**: Ocular Computed Tomography (OCT).
Four months after an acute optic neuritis there is significant loss of retinal nerve fibers in the right optic nerve. There is also loss of fibers in the unaffected optic nerve.

**Retrobulbar Optic Neuritis. What to do about Multiple sclerosis (MS)?**

What to do then about the risk of MS?

If MRI is abnormal and there is dissemination in space; > 2 lesion: there is evidence in favor of treatment (Figure 4 and 5).

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New Insights on Optic Neuritis in Young People

If initial brain MRI is normal, clinical and MRI monitoring is advisable to detect by either criteria dissemination in time and space. The goal would be to identify the presence of new lesions. It is generally assumed that earlier treatment signifies better prognosis. This is not without controversy. Incorporating MRI Findings in Diagnostic Criteria for Dissemination in space and time (Figures 6 to 10).

Figure 6

Figure 7

Figure 8

Figure 9

Mc Donald’s Criteria (2001): Multiple white matter lesions, perpendicular to the ventricle:

1. Disseminated’s fingers
2. Juxtacortical lesions: U fiber
3. Infratentorial lesions
4. Spinal Cord Lesions

Dissemination in time

1. New T2 lesion/c, comparing two or more serial MRI’s
2. New Gdolinium enhancing lesions
3. Combined non-enhancing lesion and an asymptomatic enhancing lesion

The McDonald’s criteria are MRI criteria used in the diagnosis of multiple sclerosis, were introduced in 2001, revised in 2005 and again recently in 2010. This latest revision improves sensitivity from 46 - 74% with a slight tradeoff in specificity (slight deterioration from 94 - 92%) (Table 1) [2].

Clinical Presentation

<table>
<thead>
<tr>
<th>1 attacka; objective clinical evidence of 1 lesion</th>
<th>Additional Data Needed for MS Diagnosis</th>
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<tbody>
<tr>
<td></td>
<td>None</td>
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<tr>
<td>2 attacksb; objective clinical evidence of 1 lesion</td>
<td>Dissemination in space, demonstrated by: ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord); or Await a further clinical attack implicating a different CNS site</td>
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<tr>
<td>1 attack; objective clinical evidence of 2 lesions</td>
<td>Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack</td>
</tr>
<tr>
<td>1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome)</td>
<td>Dissemination in space and time, demonstrated by: For DIS: ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord); or Await a second clinical attack implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack</td>
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Immunosuppressive actions suggestive of MS (PPMS)

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<th>1 year of disease progression (retrospectively or prospectively determined) plus ≥ 2 of the following criteria:</th>
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<tr>
<td>1. Evidence for DIS in the brain based on ≥ 1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, infratentorial) regions</td>
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<tr>
<td>2. Evidence for DIS in the spinal cord based on ≥ 2 T2 lesions in the cord</td>
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<td>3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)</td>
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Table E. The 2010 McDonald Criteria for Diagnosis of MS.

If the Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is “MS”; if suggestive, but the Criteria are not completely met, the diagnosis is “possible MS”; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is “not MS.”

An attack (relapse; exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings. For DIT:

No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these Criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

MS: Multiple Sclerosis; CNS: Central Nervous System; MRI: Magnetic Resonance Imaging; DIS: Dissemination in Space; DIT: Dissemination in Time; PPMS: Primary Progressive Multiple Sclerosis; CSF: Cerebrospinal Fluid; IgG: Immunoglobulin G.

Case 2: Bilateral Optic Neuritis

23-year-old male with acute bilateral severe visual loss (LP). The patient presented bilateral disc edema (Figure 11) and NMO antibody negative.

The presumed diagnosis was NMO (optic neuromyelitis) spectrum disease. It was evident a significant enhancement of the optic nerves (Figure 12, 13).
The patient made treatment with steroids and Mycophenolate, and got better, whereby the diagnosis was between NMO Spectrum and ADEM (Acute disseminated encephalomyelitis) (Figure 14,15 and Table 2) [3].

Diagnostic criteria for NMOSD with AQP4-IgG
1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnosis*

Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status
1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (2 or more different core clinical characteristics)
   c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnosis*

Core clinical characteristics
1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure 3)
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions (figure 3)

Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status
1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over > 1/2 optic nerve length or involving optic chiasm (figure 1)
2. Acute myelitis: requires associated intramedullary MRI lesion extending over 3 contiguous segments (LETM) OR > 3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis (figure 1)
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions (figure 2)
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions (figure 2)

Table 2: NMOSD diagnostic criteria for adult patients.
Abbreviations: AQP4: Aquaporin-4; IgG: Immunoglobulin G; LETM: Longitudinally Extensive Transverse Myelitis Lesions; NMOSD: Neuromyelitis Optica Spectrum Disorders
New Insights on Optic Neuritis in Young People

NMO Pathogenesis

In 2004 Vanda Lennon, et al. informed in 102 patients with diagnosis of NMO of USA and 12 patients of Japan with clinical compromise of the optic nerve and spinal way.

The presence of a specific antibody IgG that is conjugated to the BHH, micro vessels, ependymal of pial vessels and astrocytes was demonstrated.

It has 73% of specificity; Lennon, et al. demonstrated that the antibody is conjugated to the receiver of AQP-4. There is loss of the AQP-4 receiver immunostaining, which is detectable in early lesions. A monoclonal antibody against the CD-20 lymphocytes receiver (rituximab) is effective in treatment of NMO.

Aquaporin 4 expressing cells staining with anti-Aquaporin IgG from a patient with NMO. In panel C only the cells expressing aquaporin 4 stain (Figure 16) [4].

![Figure 16: Aquaporin 4 expressing cells staining with anti-Aquaporin IgG from a patient with NMO.](image)

NMO Case

13 years old male whit acute visual loss, binocular, of three days duration. She had history of nephritis caused by systemic lupus erythematosus.

In 2008 she had a diagnosis of chiasma neuritis (Figure 17), and made a steroids therapy in high doses and cyclophosphamide, which was successful. She had AQP-4 positive antibodies.

New Insights on Optic Neuritis in Young People


Figure 17: Chiasma neuritis.

Visual Fields (Figure 18).

Figure 18: Visual Fields.
When should we consider a diagnosis of NMO?

- Bilateral optic neuritis
- Compromise of the Optic chiasm
- Simultaneous optic neuritis and spinal cord compromise
- Longitudinally extensive anterior optic pathway compromise (> 4 cm) of enhancement
- Longitudinally extensive myelitis
- The specific diagnosis is important as aggressive immune-suppression is needed.

Discussion and Conclusions

1. The diagnosis of retrobulbar optic neuritis (the most common demyelinating form) is possible only with the clinical data, however the MRI with gadolinium is necessary to establish: a) if there are demyelinating lesions in other areas, b) whether they enhance or not with the contrast.

2. With these two data: a) optic neuritis (Clinical Isolated Syndrome CIS) and b) a combination of acute lesions - contrast enhancers and chronic lesions - sustain, according to the new criteria, the diagnosis of MS and justify the immumodulation treatment.

3. Clinical and MRI data are essential to rule out NMO, although not all cases present AQP P-4 it is a fundamental data to confirm the diagnosis and define the treatment.

Bibliography


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