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Atypical forms of optic neuritis

Formes atypiques de névrites optiques

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ABSTRACT

Inflammatory optic neuritis (ON) represents a frequent clinical situation in neurology and ophthalmology. The most current etiology is multiple sclerosis (MS) but, when MRI and Cerebrospinal fluid (CSF) analyses are normal, ON is usually considered as “idiopathic” with a suspected viral etiology. In rare cases, a systemic disease such as sarcoidosis, lupus or Sjögren syndrome may be diagnosed. In several cases either a recurrence or a myelitis may occur without any argument for MS. In the first case, it corresponds to relapsing inflammatory optic neuritis (RION) and in the second case to neuromyelitis optica (NMO). In the present paper, the author successively presents the various clinical situations and complementary findings (infectious, vasculitis, NMO or idiopathic) that can lead to a differential diagnosis of MS in a context of ON.

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RÉSUMÉ

La neuropathie optique (NO) est une situation fréquente en neurologie et en ophtalmologie. L’étiologie la plus courante est la sclérose en plaques (SEP) mais quand l’IRM et l’analyse du liquide céphalorachidien sont normales, la NO est habituellement considérée comme idiopathique, potentiellement d’origine virale. Dans de rares cas une maladie systémique (lupus, sarcoïdose, Sjögren) est retrouvée. Dans d’autres cas, une récidive de NO homo-ou controlatérale correspondant à une recurrent optic neuritis (RON), voire l’apparition d’une myélite peut être observée. Dans cet article, l’auteur propose d’aborder successivement ces différents cas de figure (infection, vascularite, NMO ou RON) qui constituent les principaux diagnostics différents de la SEP dans le domaine de la NO.

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1. Introduction

Optic neuritis (ON) is an acute inflammatory demyelinating syndrome of the central nervous system and represents a frequent clinical situation in neurology and ophthalmology. In acute demyelinating ON, patients typically present with a short progressive unilateral vision loss with quite variable intensity. A perioocular and retro-orbital pain is observed in more than 90% of cases and most patients show reduced contrast sensitivity, dyschromatopsia and defect on visual field (Beck et al., 1992). The most frequent etiology is multiple...
sclerosis (MS) and the optic neuritis treatment trial (ONTT) study showed that 50% of ON patients converted to clinically definite MS after a 15 years follow-up period (ONTT group, 2008). When MRI, biological and Cerebrospinal fluid (CSF) analysis are normal, ON is usually considered as idiopathic with a suspected viral etiology. However, the first step on the field of ON diagnosis is to be sure that the origin is inflammatory. Before confirming the diagnosis of ON, there are several differential diagnose that should be suggested, especially if there is some red flags (lack of pain, age > 50, vascular risk factors, abnormalities in fundus...). The two more frequent etiologies on this field are meningioma, especially in women older than 45–50 years old (Ref) and anterior ischemic ON (AION), especially in case of very acute visual loss frequently associated with altitudinal visual field defect. In these two cases, patients are frequently older than in inflammatory ON and pain is lacking.

2. Inflammatory optic neuritis in multiple sclerosis

The main etiology suspected during a first ON episode is the inaugural manifestation of MS but ON may also occur in the setting of other pathologies such as neuromyelitis optica (NMO), infectious diseases, or autoimmunity diseases. The 15 years follow-up report from the ONTT had previously considered a conversion rate of 50% (72% with an abnormal baseline brain MRI, 25% with a normal MRI) to MS after isolated ON in adults (ONTT group, 2008). With another look, this result also means that about 50% of patients will never developed MS after a first episode of ON. In several cases, we never found any etiologies of the ON event and we use the term of idiopathic ON, which is probably a heterogeneous group of patients with “unknown” or “yet not known” diagnosis. Long term follow-up studies have shown that patients may be diagnosed as MS, neuromyelitis optica (NMO) or other diseases even after a very long time (15/20 years or more) but after a so long term period the number of patients who converted remains very low.

3. Optic neuritis secondary to infection

Typical ON due to infectious is rare. More frequently, infectious ocular diseases are neuroretinitis rather than ON. Ophthalmologist frequently observes a macular star, which is pathognomonic of infection, especially Bartonella. However, in several situations (high risk population for sexual transmissible diseases, high risk region for Lyme disease, immunodepression...) clinician may be careful to particular infectious or parainfectious ON. For example, although relatively rare compared to the high number of ON, we recently report typical cases of ON secondary to Lyme disease (Blanc et al., 2010). Cerebrospinal analysis frequently shows lymphocytic meningitis and high intrathecal index for Borrelia, which is a very highly specific, but only 70% sensitive test for “neurolyme” (Blanc et al., 2007). Recently, we observed in our department an increase number of cases with syphilis or human immunodeficiency virus (HIV) ON but a majority of cases were neuroretinitis mimicking ON rather than typical ON (especially without signs of ON on MRI or VEP). The other feature that can be observed is a postinfectious ON, isolated after various infection or vaccination, or in a larger syndrome as acute disseminated encephalomyelitis (ADEM). On these cases, ON is frequently a mild symptom in a larger neurological feature including severe deficit and consciousness alteration (de Seze et al., 2007). In cases of postinfectious ON, intravenous corticosteroid treatment may be used as for other ON but clinician has to be sure that infection is eradicated before using this drug.

Fig. 1 – Typical extended T2-weighted hypersignal in the spinal cord of a neuromyelitis optica (NMO) patient. A. Sagittal plane. B. Axial plane.
4. **Optic neuritis due to neuromyelitis optica**

From a clinical point of view, ON of MS and NMO may be significantly different. The initial presentation may be similar but NMO is believed to cause very severe and often bilateral, visual disability and optic nerve damage. In MS, attacks tend to be less severe and have a better visual and retinal prognosis (de Seze et al., 2008a; Ratchford et al., 2009). These data suggesting that a greater retinal nerve fiber layer (RNFL) thickness reduction (<15 μm) measured by optical coherence tomography (OCT) can be helpful in distinguishing MS from NMO. This differentiation is actually essential for the therapeutic and management strategies. However, an important overlap is observed between the two diseases. Brain MRI is frequently normal in NMO but can show brainstem or periventricular (especially periependymal) lesions, especially in young patients. Spinal cord MRI may show extended T2 hypersignal (Fig. 1), which can occur many years after one or more ON episodes. The most interesting test for distinguishing MS and NMO, excepted brain and spinal cord MRI, is the dosage of anti-aquaporine 4 (AQP-4) antibodies discovered in 2004 (Lennon et al., 2004). This test is very specific of NMO but sensitivity is between 50 to 80% depending to techniques and populations (Jarius and Wildemann, 2010b). Because of the high frequency of ON, it seems difficult to test all ON for this antibody (problem of cost and also possible false positive). In a first line check-up for ON we propose to test severe, recurrent or bilateral ON only. Making differences between NMO and MS is of importance because treatments are quite different. In 2006, new diagnostic criteria for NMO were proposed including ON and myelitis plus two of the three following criteria: normal brain MRI, positive AQP-4 antibodies and extended lesion on spinal cord MRI (Wingerchuk et al., 2006). It was demonstrated that immunosuppressor rather than immunomodulator especially interferon Beta are more effective in NMO (Papeix et al., 2007; Collongues and de Seze, 2011). In several cases it was demonstrated that interferon Beta might increase disease activity (Shimizu et al., 2010). Rituximab seems to be one of the most promising drug in NMO (Cree et al., 2005) and this treatment may be also discuss in severe ON associated with positive AQP-4 antibodies.

![Fig. 2 - Bilateral optic neuritis in a patient with neurosarcoïdosis. A. Shows a bilateral perineuritis hypersignal in post Gadolinium injection T1-weighted image (left) and in T2-weighted image (right). B. Shows a chiasma granuloma in post Gadolinium injection T1-weighted image.](image)
5. **Optic neuritis due to systemic diseases**

ON may also be a part of a systemic disease such as systemic lupus erythematosus, sarcoidosis or Sjögren syndrome. However, in our experience, and when a large screening of the literature is made, the frequency of these pathologies is very rare. The most frequent findings may be Sjögren syndrome (Tesar et al., 1992; Govoni et al., 2001; Delalande et al., 2004), sometimes associated with myelitis conducting to a diagnosis of NMO, this association being also observed with lupus (Pittock et al., 2008). Another possible diagnosis, in the field of systemic disease, is sarcoidosis. In this case, we frequently observed perineuritis with granuloma or infiltration of the perioptic or chiasmal region (Fig. 2). Salivary gland biopsy may be of major interest for these two last diagnose (Sjögren and sarcoidosis).

6. **Recurrent optic neuritis**

Although ON is frequently limited to a single episode, 3 to 5% of patients experience recurrent episodes (affecting either or both eyes, sequentially or simultaneously) with a negative workup for MS, NMO or other causes (Lucchinetti et al., 1997; Pirko et al., 2004). That disorder named relapsing ON (RON) is poorly described in view of the lack of large cohorts (Arndt et al., 2008; de Seze and Arndt, 2010). Medical literature shows two forms of RON: chronic relapsing inflammatory ON (Kidd et al., 2003), named CRION, which is a progressive ON relapsing after steroids withdrawal and recurrent idiopathic ON (Arndt et al., 2008; Matiello et al., 2008; Petzold et al., 2011), named RION, which is a non-progressive relapsing ON without steroids dependence. As for isolated ON, RON may progress to demyelinating central nervous system (CNS) diseases, as MS, NMO or systemic diseases. Their natural history study demonstrated a global risk of progression to MS lower than in the ONNT study. In a previous study, the combined conversion rate to MS or NMO was 27% at five years and 42% at 10 years (Pirko et al., 2004). The discovery of AQP-4 antibodies, specific for patients with NMO, has also changed our understanding of RON (Lennon et al., 2004). This antibody is a valuable tool to define an extended spectrum of NMO disorder, distinguishing, among inflammatory demyelinating diseases of the CNS, several features corresponding to NMO spectrum with similar epidemiology, immunopathology, disease course and prognosis than NMO (Lennon et al., 2004; Jarius and Wildemann, 2010b). Recent studies report that about 20 to 25% of the patients with RON converted to NMO within five years, with a higher rate (50%) in positive AQP-4 antibodies group, than in the seronegative group (10%) (de Seze et al., 2008b; Matiello et al., 2008). Although the above RON epidemiologic studies provide useful data, they have several limitations: to date, only six clinical studies have been published. The first two were processed before the identification of AQP-4 antibodies making difficult any interpretation regarding NMO diagnosis (Kidd et al., 2003; Pirko et al., 2004). The other four studies mainly explored the association between RON and the frequency of AQP-4 antibodies without focusing on clinical and paraclinical data (Matiello et al., 2008; de Seze et al., 2008b; Jarius et al., 2010a; Petzold et al., 2011). In addition, description of RON by these studies expressed a disagreement about several features. There is no consensus on the existence of two forms of RON, recurrent (RION) and chronic and corticodependent (CRION), nor is there a clear RON nosology (expanding spectrum of NMO, atypical MS or a new autoimmune disease). We recently performed a study on 62 RON patients and we showed that about 70% corresponds to RION and 30% to CRION (unpublished data). After eight years of follow-up we distinguished three groups: 20% of patients with a high risk of MS (few MRI lesions not fulfilling MS criteria and/or oligoclonal bands), 10% with a high risk of NMO (positive anti-AQP4 antibodies), and 10% associated with a systemic disease. The 60% remaining patients seems to correspond to a subgroup of “idiopathic” RON which could be classified as a separated auto-immune entity but we cannot exclude that several patients will converted to one of the three other subgroups during a longer follow-up. In this study, we also individualized two groups of patients with a poor prognosis (high risk of NMO and CRION patients) that may be treated early with immunosuppressant treatments.

7. **Conclusion**

ON is a frequent symptom, mainly (50%) associated with MS but there are also many other conditions that may be evoked especially when red flag are present. In a number of cases of ON, etiology remains “unknown” or “not yet known” and follow-up of patients is of importance regarding the possible evolution to MS, NMO or vasculitis. However, in other cases ON remains idiopathic even after a large work-up and a long follow-up and a viral cause is suggested but usually without serological proof. Finally, several ON are recurrent, corresponding to RION or CRION, two new entities recently identified in the literature that seem to be an autoimmune entity possibly distinct from other etiologies.

**Disclosure of interest**

The author declares that he has no conflicts of interest concerning this article.

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