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Diagnostic approach in optic neuropathy

Démarche diagnostique devant une neuropathie optique

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ABSTRACT

The diagnostic of optic neuropathy (ON) is a clinical diagnostic, relying on a detailed medical history, and a thorough clinical examination. In some cases, the attribution of the vision loss to a lesion of the optic nerve can be challenging, and further work-up is required to confirm the optic neuropathy. Once the diagnostic of optic neuropathy is stated, the pathophysiological mechanism of the ON has to be determined so that the appropriate therapeutic strategy can be initiated as promptly as possible. The diagnostic work-up must be as targeted as possible, oriented by the clinical examination. The different steps leading to the positive diagnostic of ON, and the etiologic work-up are detailed hereafter in order to achieve the most targeted work-up as possible. Differentials and current pitfalls are being reviewed.

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RÉSUMÉ

Le diagnostic de neuropathie optique est avant tout un diagnostic clinique qui repose sur un interrogatoire policier et un examen clinique détaillé. Dans certains cas, l’attribution de la baisse d’acuité visuelle à une lésion du nerf optique n’est pas évidente et des examens complémentaires peuvent être nécessaires. Lorsque le diagnostic de neuropathie optique est établi, il convient de déterminer le mécanisme physiopathologique en cause afin de proposer le traitement adapté. Le bilan doit être le plus ciblé possible et orienté par les données de l’examen clinique. Les étapes du diagnostic positif et de l’enquête étiologique sont détaillées afin d’obtenir le bilan le plus ciblé possible. Les diagnostics différentiels et les pièges diagnostiques sont également revus.

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1. Introduction

The term of optic neuropathy actually regroups a broad spectrum of ophthalmological or systemic conditions that can affect the optic nerve. The pathophysiological mechanisms of optic neuropathies vary widely including inflammatory, traumatic, ischemic, autoimmune, genetic, or toxic mechanisms. As the prognosis and the therapeutic strategy can dramatically differ according to the mechanism involved, it is crucial to determine as precisely as possible the etiology of the optic neuropathy. There are three important steps in the diagnostic approach of optic neuropathies (Fig. 1): the first step is to identify the optic nerve as the cause of the symptoms...
reported by the patient. This step, although easy in most patients, can be more challenging in certain cases, leading to considerable diagnostic delay. The second step is to narrow the field of possible causes of optic neuropathy with a detailed history and a thorough clinical examination. This second step is essential to target the most appropriate medical work-up (step 3), and to determine precisely the cause of the optic neuropathy.

2. **Step 1: Recognize an optic neuropathy**

Most optic neuropathies will manifest with decreased vision or blurry vision in one or both eyes. In case of an optic neuropathy, visual acuity cannot be improved by a change in the optic correction, and cannot be explained by any opacity in the transparent ocular media (cornea, aqueous humor, lens, vitreous) or any lesion of the retina or its vasculature. According to the etiology, the fundus can disclose evidence of a lesion of the optic nerve (atrophy, swelling, hemorrhage, tumor, infiltration, granuloma...) but in many cases, the fundus appears normal, at least at the beginning. Identifying the ocular signs that point to the optic nerve, as the cause of the vision loss is thus a major challenge in order to progress in the diagnosis.

Beside the vision loss, color vision is usually affected in patients with optic neuropathies. This can be easily tested in clinic using simple tests, such as the Ishihara plates or the HRR plates, or can be further tested using the Farnsworth test. At bedside, color vision can be grossly evaluated by showing to the patient different objects of primary colors (red desaturation is of particularly great value in acquired optic neuropathies). Each object is observed by the patient, eye by eye, in order to detect a desaturation, that the patient usually describes as a paler color when the object is seen through the affected eye. Bilateral slowly progressive optic neuropathy with blue-yellow dyschromatopsia in a child is very evocative of hereditary optic neuropathy such as dominant optic atrophy. In most acquired optic neuropathy, a red-green dyschromatopsia is observed.

Pupil testing is essential for the positive diagnosis of optic neuropathy. The presence of a relative afferent pupillary defect (RAPD) is very evocative of an optic neuropathy, whatever its etiology is. Pupils must be tested in the light and in the dark, with a bright and focused light. Direct and consensual pupillary reflex have to be tested first. Then, the swinging light test will determine if a RAPD is present, by illuminating alternatively the right and the left pupil in the dark. If an RAPD is present, the affected pupil will not constrict as briskly as the fellow one, and will even dilate slowly upon illumination. Even a mild and discrete dilatation, or sometimes just a sluggish pupil compared to the other side, has a diagnostic value for optic neuropathy. The presence of a RAPD demonstrates a lesion of the optic nerve, although it does not bring any information regarding its cause. In case of bilateral and symmetric optic neuropathy, the RAPD will be absent, even though an optic nerve lesion is present.

Usually, clinical evaluation of the patient is sufficient to state the diagnostic of optic neuropathy. Sometimes, clinical features are more confused, and an ophthalmological and electrophysiological work-up may be necessary to confirm the optic neuropathy. In this case, visual evoked potentials (VEP), with or without electro-retinogram (ERG), can help localizing the lesion to the optic nerve. Amplitude and latency of the optic nerve conduction are measured by the VEP, while the ERG will confirm the absence of retinopathy as a differential.

The visual field can also be helpful in doubtful cases, demonstrating all sorts of defects in case of optic neuropathies: the most common of which being an enlarged blind spot, an altitudinal visual field defect, or central or paracentral scotoma. Diffuse visual field defect and fascicular defect can also be observed.

Once the presence of an optic neuropathy has been confirmed, the diagnostic approach will focus on the pathophysiological mechanism of the optic nerve lesion.

3. **Step 2: Identify the pathophysiological mechanism responsible for the optic neuropathy**

3.1. **Medical history: key points**

Many clinical entities are covered by the term optic neuropathy. These causes vary from inflammatory, ischemic, traumatic, infectious, autoimmune, genetic, or toxic conditions. They can reveal either a purely ophthalmological disease, or a systemic disease. It is thus important to gather as much information as possible that could help to narrow the field of possible conditions responsible for the optic neuropathy. The medical history will provide several evidence of the mechanism of the optic neuropathy. It must be very detailed and relies on four major questions that need to be answered as precisely as possible.
3.1.1. Question 1: is the vision loss unilateral or bilateral? Although there are many exceptions to the rule, bilateral optic neuropathy usually suggests a toxic, hereditary or metabolic origin to the optic neuropathy. Sometimes, a bilateral optic neuropathy may begin with a unilateral lesion of the optic nerve, followed shortly after by involvement of the fellow eye (such as in hereditary Leber optic neuropathy). Unilateral optic neuropathy is more evocative of an inflammatory, ischemic, traumatic, or compressive process. This rule has many exceptions of course and many bilateral optic neuropathies can be observed with these conditions as well.

3.1.2. Question 2: was the vision loss progressive or acute? Slowly progressive optic neuropathies are usually due to metabolic, vitamin deficiency, toxic, compressive or infiltrative causes. Some hereditary optic neuropathy can have a slowly progressive course (such as dominant optic atrophy for example). Acute or subacute optic neuropathies are more evocative of an ischemic process (Miller, 1980, 2011) (such as anterior or posterior ischemic optic neuropathy, or radiation-induced optic neuropathy), inflammatory optic neuritis (Voss et al., 2011), traumatic optic neuropathy or infections. If pain on eye movement is associated with a rapid vision loss and a normal fundus, the diagnosis of optic neuritis is evident (Voss et al., 2011). However, pain on eye movement is not always present in case of optic neuritis. The cause of the optic neuritis has to be further investigated.

3.1.3. Question 3: is the vision still decreasing, stable, or improving? Slowly worsening optic neuropathies are highly evocative of a compressive or infiltrative optic neuropathy. If the suspicion of compression is high, the imaging of the optic nerve has to be repeated, even if it was previously reported as normal. Sections focused on the optic nerves, with FAT-SAT and coronal sections have to be performed. Several patients with optic nerve sheath meningoima have suffered from considerable diagnostic delay because of an inappropriate imaging work-up had been performed. The most frequent causes of compression of the optic nerve include meningoima, pituitary adenoma, cranioopharyngioma, orbital hemangioma, or metastasis. However, the compression can sometimes reveal a carotid aneurism requiring emergent diagnosis and treatment. Optic neuropathies due to toxic exposure, vitamin deficiency, metabolic causes and certain hereditary optic neuropathies will be also slowly worsening in the absence of treatment.

On the other hand, ischemic, traumatic or radiation-induced optic neuropathies are usually maximum at setting and do not worsen after the initial few days. Inflammatory optic neuropathy usually worsen over a short period of time (2 to 10 days) and then remains stable or improves slowly.

3.1.4. Question 4: what is the past medical history of the patient and its family? The age of the patient has to be taken into account. In young patients, the diagnosis of inflammatory optic neuropathy is more frequent, when elderly patients usually present with ischemic optic neuropathy. Cardiovascular past medical history, diabetes, overweight or sleep apnea are risks factors for ischemic optic neuropathy. A history of radiation of the brain or neck is evocative of radiation-induced optic neuropathy. Immune-depression is also a risk factor for several causes of infectious optic neuropathies such as syphilis, herpes, CMV, HIV-related optic neuritis, toxoplasmosis, tuberculosis, mucormycosis or cryptococcal meningoencephalitis. Immune-depressed patients are also more at risk for metastasis of a possible malignancy, or lymphoma. Potentially toxic medications have to be looked for such as anti-TNF, antituberculous drugs, or interferon. Ethanol or methanol intoxication has to be evaluated. In elderly patients, the past medical history has to mention the presence or not of any symptoms evocative of giant cell arteritis (GCA) such as fatigue, weight loss, headache, low-grade fever, or proximal joints pain. Any family history of vision loss is evocative of hereditary optic neuropathy. In this case, it is important to determine whether other organs can be affected such as the heart, the kidneys or the ears in certain hereditary optic neuropathies. Finally, the history must determine if the patient has experienced previous signs inflammation of the central nervous system that might be evocative of multiple sclerosis (MS) (Voss et al., 2011).

3.2. Clinical examination: the key points

3.2.1. Data obtained from the ophthalmological examination
The measure of the visual acuity will determine the severity of the optic neuropathy. Although any degree of vision loss can be observed with any type of optic neuropathy (ranging from a blury 20/20 to the absence of light perception), acute severe vision loss in an elderly patient is usually evocative of ischemic optic neuropathy, whereas mild to moderate vision loss in a young adult will be more evocative of an inflammatory optic neuropathy. Radiation-induced optic neuropathies are usually associated with severe vision loss as well (Hudgins et al., 1992; Danesh-Meyer, 2008). All degrees of vision loss can be observed in hereditary optic neuropathy. It is usually admitted that the vision loss is less severe and very slowly progressive in dominant optic atrophy (Baker et al., 2011) compared to Leber optic neuropathy that is usually more profound and rapid.

Associated ophthalmological signs, such as uveitis or scleritis, have to be looked for. Uveitis associated with MS is usually a mild intermediate uveitis, with vasculitis, condensation of cells into the basis of the vitreous (snow-balls), and macular edema. Granulomatous anterior uveitis with anterior synecchia can also be observed. Scleritis, conjunctival granulomas or granulomatous uveitis with retinal vasculitis can be evocative of sarcoidosis (Fig. 2b). The aspect of the optic nerve can also be informative regarding the pathophysiological mechanism of the optic neuropathy. Sectoral or diffuse optic disk swelling is always present in case of an ischemic optic neuropathy, except if the patient is seen weeks from the initial ischemic event. An infiltration of the optic nerve can be evocative of a malignancy (Fig. 2c) (lymphoma, metastasis), or of a sarcoidotic granuloma. In Leber optic neuropathy, during the acute phase, small telangectasia can be observed on the optic nerve edge and surface, sometimes associated with pseudo-optic disk swelling and venous dilatation. The fundus
The optic evolutive inferred evocative neuritis. MRI retinal granuloma hemorrhage optic is associated information is suggestive of retinochoroidal folds is evocative of a compressive origin to the optic neuropathy (Fig. 3).

Finally, oculomotoricity (3rd, 4th and 6th cranial nerves) has to be evaluated, and auscultation of the orbital region has to be performed in order to rule out a bruit related to carotid-cavernous fistula or to an orbital tumor. The lacrimal gland has to be carefully examined (granulomas for sarcoidosis, infiltration for sarcoidosis or lymphoma). Proptosis has to be measured in order to detect any sign of orbital lesion, or Grave disease.

3.2.2. Data obtained from the general examination
All cranial nerves have to be carefully evaluated. Clinical signs of GCA and of Grave disease have to be looked for according to the clinical presentation. Palpation of the neck investigates the presence of cervical adenopathies or thyroid gland enlargement. A complete neurological examination is required in order to detect any sign of central nervous system involvement.

4. Step 3: Determine the appropriate and targeted medical work-up in patients with optic neuropathy

After crossing-over the information obtained both from the medical history and the clinical examination, the field of etiologies of the optic neuropathy is usually narrowed. Cerebral and orbital MRI is not systematic in the work-up of an optic neuropathy.

If the clinical history and the examination are complete and typical of ischemic optic neuropathy (Miller, 2011), the work-up will be limited to an erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) dosage, complete cardiovascular work-up (including an electrocardiogram (EKG), cervical Doppler-ultrasound, cardiac ultrasound, chest X-ray, lipidic work-up), kidney work-up, and polysomnography. Temporal artery biopsy will be discussed according to the patient background and to the clinical signs, if GCA is suspected.

In all other cases, an MRI will usually be necessary. The MRI has to visualize the entire optic pathway, and include coronal T2-weighted images, and FAT-SAT images, with and without gadolinium injection.

If an inflammatory optic neuritis (Atkins et al., 2006; Biousse et al., 2009; Voss et al., 2011) is suspected, the optic nerve appears enlarged with spontaneous hypersignal on

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**Fig. 2 – Fundus aspects of patients with optic neuropathy.** The fundus can be normal in most optic neuritis (2a). Associated signs on fundus examination can give several information regarding the etiology of the optic neuropathy. In patient 2b, occlusive vasculitis with retinal hemorrhage and optic disk swelling with a possible granuloma is evocative of sarcoidosis. In patient 2c, the optic neuropathy is associated with optic disk and sub-retinal space infiltration with yellowish-whitish infiltrates evocative of intraocular lymphoma. Optic disk atrophy (2d) is the final common pathway of all severe optic neuropathy. When the patient is seen at this stage, no information can be obtained regarding the cause of the optic neuropathy and a complete work-up, including an MRI has to be performed.

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**Fig. 3 – Choroidal folds (white arrows) (3a) suggestive of an orbital process, in a patient with a compressive optic neuropathy due to orbital lymphoma with bilateral optic nerve infiltration (arrows’ heads) (3b).**
T2-weighted images, enhancing with gadolinium injection. The MRI also allows the visualization of other hypersignals in the white matter (T2-weighted images), enhanced or not by gadolinium injection, suggestive of demyelination. The MRI will also rule out a possible compression of the optic nerve, or infiltration of the optic nerve or of the orbit. It will also look for any cerebral malformation suggestive of a hereditary syndrome.

Under certain circumstances (severe optic neuritis, bilateral or recurrent optic neuritis, absence of recovery, or associated transverse myelitis), antibodies directed against aquaporin 4 (neuromyelitis optica (NMO) antibodies) have to be tested as well. The positivity of NMO antibodies is suggestive of neuromyelitis optica or Devic disease, requiring an aggressive treatment with steroids, associated with immunosuppressive drugs. However, the absence of NMO antibodies does not rule out the disease. The dosage can be repeated later in the course of the disease, both in the blood and in the CSF, if the clinical presentation is very suggestive of Devic disease (Sellner et al., 2010). Spinal cord MRI is also required if Devic disease is suspected, and can be also useful for the diagnosis of optic neuritis associated with MS, sarcoidosis (Graham et al., 1986), or lymphoma (Lanska et al., 1987; Henchoz et al., 2003; Tavallali et al., 2010).

More rarely, an optic neuropathy can be associated with other systemic diseases such as connective tissues disorders, including systemic lupus erythematosus (SLE) (Siatkowski et al., 2001), periarteritis nodosa, or Sjogren disease. Optic neuropathy can also be associated with Behçet disease (BD). In BD, the optic nerve can be affected either by inflammation (optic neuritis), or by a failure of the vascular supply (ischemic optic neuropathy) (Frigui et al., 2009; Kim et al., 2011). Uveitis or scleritis is frequently observed in patients with BD-associated optic neuropathy. The uveitis is typically non-granulomatous, with or without hypopyon, and usually with occlusive retinal vasculitis leading to ischemic foci of the retina.

In case of bilateral, symmetric, slowly progressive optic neuropathies, the three main etiologies to be investigated are hereditary, metabolic, or toxic. A dosage of B1, B6, B12 and folate vitamins are useful if a vitamin deficiency (Mashima et al., 2000; Chavala et al., 2005) is suspected, especially in alcoholic patients.

Toxic optic neuropathy has to be investigated as well. In patients treated for tuberculosis, the treatment is usually interrupted without further work-up and the visual field is followed. Some acute toxic optic neuropathy such as methanol induced optic neuropathy can be confirmed by blood dosage of methanol. Patients treated with anti-TNF usually present with optic neuritis more than direct toxic optic neuropathy although this latter has been evoked.

In young patients with bilateral optic neuropathy, hereditary optic neuropathy has to be investigated. Leber optic neuropathy (Ji et al., 2012; Mascialino et al., 2012) preferentially affects young male (20–30 years old), although it has been reported at all ages and in women as well. The onset of the optic neuropathy varies from a few hours to a few weeks or months. It is usually asymmetric with bilateralization occurring most of the time within 6 months. The fundus can be normal, or can disclose peripapillary telangiectasia, with pseudo-optic disk swelling and venous dilatation. On visual field, a central scotoma is usually observed. It is maternally inherited through mitochondrial transmission. Three mutations in the mitochondrial DNA are responsible for 95% of cases of Leber optic neuropathy (G 3460 A, G 11778 A, T 14484C) and need to be tested. Other minor mutations are now frequently investigated as well. Another cause of bilateral optic neuropathy is the dominant optic atrophy or Kjer optic neuropathy (Baker et al., 2011; Yu–Wai–Man et al., 2011). It affects children of 4 to 8 years old but can be frequently discovered later in the course of the disease, as the evolution can be very slow. It is usually bilateral but asymmetric. The transmission is dominant autosomal with variable penetrance. On fundus examination, the optic nerve appears pale, mainly on its temporal edge. There is typically a blue-yellow dyschromatopsia, which is very evocative of the diagnosis. A central scotoma can be observed on the visual field. Diagnosis is based on genetic testing for the OPA1 and three mutations testing. If other symptoms are associated with the optic neuropathy, genetic syndromes can be investigated. Wolfram syndrome associates the presence of type 1 diabetes mellitus, insipid diabetes, deafness and optic neuropathy. It usually affects children under the age of 10 years old (Hofmann et al., 1997).

Progressive unilateral optic neuropathy is usually evocative of a compressive or infiltrative optic neuropathy. In children, compression can be due to optic nerve glioma, with or without neurofibromatosis. In adults, most compression is due to meningioma, although other lesions such as hemangioma, metastasis or lymphoma can be observed. Optic disk infiltration can be seen in sarcoidosis, lymphoma, or histiocytosis.

Finally, a thyroid work-up can be included in the etiologic work-up of patients with optic neuropathy, especially if a proptosis or eyelid retraction is present, as apical compression of the optic nerve can occur due to oculomotor muscles enlargement. Ischemic optic neuropathy can also occur in Grave disease in case of an important compression on predisposed patients.

5. **Differentials of optic neuropathy**

If most of the times, the clinical diagnosis of optic neuropathy is easy, it can sometimes be more challenging to determine the cause of the optic neuropathy. Identifying whether the optic nerve is the cause of the vision loss or if it results from retinal, or cerebral dysfunction can also be difficult. Electrophysiology is particularly helpful in such cases. Patients with bilateral symmetric central scotoma can have age-related macular degeneration and it is thus important to carefully study the fundus before starting a work-up for optic neuropathy. Occult maculopathy frequently presents as central or paracentral scotoma with normal fundus, and can thus mimic an optic neuropathy. Accommodative spasms can be responsible for episodes of blurry vision, spontaneously resolutive, mimicking optic neuritis, especially if associated with headache. Some occipital lesions located in the anterior pole of the occipital lobe, can present as lateral homonymous scotoma mimicking a bilateral optic
neuropathy. Transient monocular amaurosis has to be distinguished from optic neuropathy as well.

In addition, even if the diagnosis of optic neuropathy has been appropriately stated, several etiologies can present in similar ways, that do not require the same therapeutic management. For example, Leber hereditary optic neuropathy frequently mimics other optic neuropathies such as neuro-Searching text...