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Optic neuritis – general overview with particular emphasis on differential diagnosis

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ABSTRACT

Introduction and purpose

Optic neuritis (ON), especially retrobulbar, is a common inflammatory neuropathy of the optic nerve occurring typically in young adults. This neuro-ophthalmological condition is involved in the clinical picture of multiple diseases and may be frequently a heralding symptom of them [1,2,3,4,5,7,13].

The main aim of this review is to provide clinicians with thorough information on the possible etiologies of ON, its differentiation and management.

Review Methods

For this report, we conducted a research of the available, most recent literature in Pubmed and medical books using the keywords (below). As a result, we included over 30 articles and chapters as a benchmark of our analysis.

A brief description of the State of Knowledge

Optic neuritis is a frequent manifestation of many diseases, with a particular focus on demyelinating processes [1,2,3,4,5,7,13]. Its incidence in central Europe is about 5 per 100 000 people per year [26]. Although the symptoms may be very severe including even abrupt vision loss or intense pain on ocular movement, the prognosis regarding future visual acuity is generally good [1,2,9]. In contrast, the spectrum of diseases underlying optic neuritis is much more diverse [9,10,13,25].

Summary

Although a definite diagnosis is not always possible when looking for the cause of ON, it is crucial to know the possible etiologies and to differentiate them as much as we can by means of commonly used tools. In this way, a correct diagnosis will lead to earlier, more personalized treatment and a better overall prognosis [1,5,9,10,11,15,25].

Keywords: Atypical optic neuritis, typical optic neuritis, retrobulbar optic neuritis, multiple sclerosis, MOGAD, ON, NMO, NMOSD

REVIEW

Introduction

Optic neuritis (ON) is an inflammation of the optic nerve which is triggered by a broad spectrum of conditions. It can also occur sporadically, but it is a diagnosis of exclusion. Finding the exact cause of the inflammation is crucial, as it determines our further management, including the length and type of treatment, and prognosis. As for the course of ON, it can be either monophasic, relapsing or progressive [1,3,4,5,9,10,11,17,21]. When we refer to the time interval, the neuritis may develop in less than 7 days (acute ON), between 7 days and 3 months (subacute ON) or more than 3 months corresponding to chronic ON [21]. The disease occurs mostly in women at the age of 20-40 years. Moreover, obesity, smoking, the Caucasian race, multiple sclerosis (MS) and living in geographically higher latitudes are the factors rendering specific population more susceptible to higher morbidity.

Optic neuritis may occur in every part of the optic nerve. Based on the location of inflammation, ON can be categorized as intrabulbar (with papillits and/or macular edema and star shaped exudates) or retrobulbar (with normal optic nerve head appearance) [9,10,14].

In the review, we will put a paramount emphasis on subacute extraocular inflammation which is often a sign of a neurological or, in some cases, a systemic disorder [1]. Furthermore, it is not uncommon for the ophthalmologist to be the first person to identify or suspect the

presence of a serious general disease in a patient at the time of the ON diagnosis. It is therefore prominent that ophthalmologists keep their knowledge in terms of the differential diagnoses up to date and work effectively in a multidisciplinary team comprising at least a neurologist and a rheumatologist [12,13].

Clinical manifestations of ON

According to its clinical presentation, optic neuritis may be classified as atypical or typical and may occur as a clinically isolated syndrome (CIS) or in association with MS [26].

On admission, a patient with typical ON complains primarily of an acute or subacute decrease in visual acuity (or even blindness), reduced contrast sensitivity, loss of color discrimination, visual field changes and severe retrobulbar pain that is typically aggravated by eye movements [4,5,7,9,10,12,13,14,16,21,24,25]. In some cases there are also positive visual phenomena (phosphenes) in the form of flashes in front of the eyes or headaches in the frontal area [12,14,18]. Appearance of the optic nerve head is typically normal, but in 35% cases it might be swollen [6]. Ipsilateral relative afferent pupillary defect (RADP) is present but might be absent in preexisting or concurrent ON in the fellow eye [18,21,22]. With the natural course of ON, visual acuity (VA) gradually deteriorates for a few days to 2 weeks, followed usually by improvement. In most cases VA gradually improves over months (92% patient has VA >20/40). Despite good clinical outcome, symptoms of reduced contrast and light sensitivity or mild RAPD and other visual functions may persist [1,10,12,13,14,17,25,26]. Another clinical feature of ON can be Uhthoff's phenomenon which is heat or exercise-induced transcient worsening of visual symptoms [5,9,10,22].

Typical vs. atypical ON

On the basis of clinical and neuroimaging findings, a further classification distinguishes two types of inflammation – typical, which includes idiopathic or multiple sclerosis-associated ON (MS-ON), and atypical, which encompasses a range of other diseases, including neuromyelitis optica (NMO/NMOSD), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), chronic relapsing inflammatory optic neuritis (CRION), and many others [1,3,5,11,13,15,16,22,25,26]. In contrast to the typical presentation of ON, atypical neuritis is characterized by a number of distinctive features. These include bilateral involvement, VA impairment which progresses in period > 2 weeks,

early onset (i.e. below the age of 11 years) or late onset (i.e. above the age of 70 years), optic disc edema, poor response to steroids or steroid dependence, worse visual prognosis, tendency to recur, symptoms and changes indicative of an origin other than multiple sclerosis or systemic symptoms [3,5,9,11,15,16,17,22,25,26].

General ON management

Standard treatment of ON is high-dose intravenous methylprednisolone (IVMP; 500-1000 mg/day) for 3-5 days, followed by oral prednisone with gradual dose reduction. In refractory cases (especially in atypical ON associated with NMO/NMOSD), plasmapheresis or IVIG are required as equally effective alternatives [3,5,9,10,13,14,18,21,22,26,38]. As an additional therapy, a proton pump inhibitor is routinely given as a prophylaxis of peptic ulcers [26]. Depending on the etiology of the inflammation, therapy may also be more intensive or longer to achieve optimal results. In fact, the treatment is not always necessary and the decision to initiate it is made on an individual basis [14,26]. The main effect of intensive steroid therapy is the acceleration of the improvement in visual acuity (VA) and relapse prevention, but it does not affect the final outcome. These are largely determined by the prognosis of the underlying disease of ON [3,5,9,12,18,22,26].

Potential diseases underlying ON

The most frequent causes of ON, associated with the CNS and the process of demyelination, include:
multiple sclerosis (MS), neuromyelitis optica/neuromyelitis optica spectrum disorders (NMO/NMOSD) and myelin oligodendrocyte glycoprotein antibody disease (MOGAD) [1,2,3,9,10,12,14,16,22,26].
However, it is also important to consider less common etiologies (listed below), especially if a patient does not meet the criteria of those abovementioned [3,9].

Minor disease entities encompassing nervous system comprise glial fibrillary acidic protein astrocytopathy (GFAP), autoimmune CRMP5 neuropathy, chronic relapsing inflammatory optic neuritis (CRION) or Schidler's disease [3,9,14,22,26].

The rest of the etiologies are categorized into:

- Systemic autoimmune – ON associated with systemic lupus erythematosus (SLE), sarcoidosis, Sjogren's syndrome, polyarteritis nodosa, other vasculitis [9,10,11,12,13,14,18].
- Peri-infectious – ON occurrence following bacterial or, most commonly, viral inflammation, such as COVD-19, measles, mumps, rubella, chickenpox, pertussis, and infectious mononucleosis. Additionally, ON may manifest as a post-vaccination complication [10,12,13,14,16].
- Infectious – ON associated with Lyme disease, syphilis, tuberculosis, sinusitis, cryptococcal meningitis in patients with AIDS, cat scratch disease, herpes zoster or HIV infection [10,12,13,14,16,18,22].
- Toxic – ON induced by toxins/drugs [7,13,16,18]

Diagnosis of ON and the underlying disease

The identification of retrobulbar optic neuritis is usually made by thorough medical history taking and physical examinations which consist of those in front of a slit lamp (to assess the anterior chamber) and ophthalmoscopy (to check the back surface of the eye) [25]. In a typical retrobulbar ON, there are no deviations in those workups, despite subjective symptoms and VA significant reduction assessed by the Snellen charts. If the perimetry is also conducted, it shows most frequently, diffuse reduction in retinal sensitivity within 30 degrees of the central visual field. In rare cases, scotoma or focal visual deficit may be observed, as well [14,26]. The abnormal color vision is usually checked by the Ishihara test, revealing in the majority of patients loss of green (deutranopia) or red (protanopia) vision [4,7,10,18].

To visualize RAPD, a swinging light test in an unlit room with the patient fixating his or her gaze on a distant target is most appropriate, thus preventing accommodation-related pupillary miosis. When light is directed at the affected eye, the pupil dilates as a result of the stimulus of reduced light reaching the midbrain via the involved optic nerve. As the optic nerve regenerates, this symptom becomes less distinctive, but remains in more than 90% of cases [8,18].

In the context of MRI, it is the standard, most important, imaging study that is ordered when optic neuritis is suspected in order to definitively confirm the diagnosis [18,21]. An

orbital MRI subsequently reveals the characteristic enhancement of the optic nerve sheath with 99% sensitivity. In certain instances of atypical ON, the periorbital fat (perineuritis) may also be enhanced [16,21]. An MRI of the brain and spinal cord is required for further diagnosis, as well. Typically, images are evaluated both before and after the administration of gadolinium contrast. A meticulous examination reveals the presence of active lesions, which are indicative of demyelination or may herald the development of some neurological diseases, including i.a. MS and NMO. Their early recognition allows for rapid treatment initiation before the lesions become symptomatic. Thanks to MRI, the actual length, localization and distribution of the lesions in the brain or spinal cord will be made apparently visible [9,10,12,16,18,21,23,26].

Optic coherence tomography (OCT) examination is a valuable diagnostic tool in differentiating the etiologies of optic neuritis, also in distinguishing between MS and NMO/NMOSD [4,7,37]. It allows measurement of the thickness of the retinal nerve fibre layer and a detailed analysis of the optic nerve. In case that a patient exhibits a demyelinating process, the examination will reveal evidence of axonal damage. This will manifest itself in the form of RNFL constriction and retinal ganglion cell-inner plexiform layer (GCIPL) thickening after ON [4,7,8,21,22,25,29,37]. The OCT may also show sub- and intraretinal fluid [14]. Nevertheless, it is not an ideal option as an individual examination in ON, because abnormalities may also occur in healthy patients, or other diseases, such as glaucoma, can influence the results [26].

All in all, one of the most significant benefits of this imaging technique is that it is non-invasive, does not entail any risk of complications, and requires no preparation on the part of the patient [4,8].

Electrophysiological tests, such as the electroretinogram (ERG), a study of changes in the functional potential generated in the eyeball under the influence of light, are also a useful adjunct to diagnostic procedures. Special significance is assigned to this examination particularly if the occult maculopathy or prelaminar optic neuritis is suspected [10,21].

Visual evoked potentials (VEP) are used, as well, but may be preferably interpreted as long as the ERG was conducted. In order to obtain honest and thorough results, the examination should be done within the half of the year after ON because then the sensitivity is highest. The test involves electrodes being attached to the scalp in the occipital region and measuring the patient’s potentials evoked by external visual stimuli. In this way, the visual pathway can be objectively, non-invasively traced without the patient having to be involved.

The results often reflect axonal pathologies or delay in P100 latency, rather characteristic for demyelinating diseases [7,10,21,22,25].

Patients with ON may, as well, benefit from the lumbar puncture (LP) to assess the composition of the cerebrospinal fluid (CSF). Hallmark findings may consist of oligoclonal bands, myelin basic protein or some specific IgG antibodies with its index that can lead to an appropriate diagnosis [7,14,18,26,29].

The following section will examine the characteristics of the most prevalent diseases that may manifest as an episode of optic neuritis.

Multiple sclerosis (MS)

Multiple sclerosis is the most common, autoimmune, demyelinating disease characterized by forming multiple plaques in the CNS system [10,14,20,23,25,29,38]. The background of this process is the focal inflammation dominated by lymphocytes T CD8+ and CD20 positive B-cells, loss of myelin sheaths, axonal injury and loss [24,25]. The myelin is usually afflicted in the regions such as cerebellum, brainstem, spinal cord and optic nerves. At the prime stage, the lesions occur in the white matter, but then they may also involve the grey one. The course of the disease is varied, but usually there are relapses despite treatment, that cause gradual worsening of daily functioning [24]. Thus, the main goal is to decelerate the rate of progression, reduce the frequency of relapses, decrease a number of lesions and reach a "no evidence of disease activity" (VEDA) stage [11,14,20,29]. The patient with MS presents with sensory disturbances in the limbs, face or trunk. Additionally, there is notable weakness of muscle strength, ataxia, impaired sphincters control, chronic fatigue, muscle cramps and visual deficits [10,14,20,24]. In clinical practice, the condition of a patient and the disease progression is assessed periodically in Expanded Disability Status Scale (EDSS) [19,20]. The result usually defines the type and the duration of the therapy and accounts for a basis in terms of its modification. As for the characteristic findings in the examination, the CSF generally reveals oligoclonal bands, leukocytosis, IgG levels >15% total protein, the VEP – P100 latency delay (much more than in NMOSD) with an increased frequency of absent responses and decreased incidence of subclinical alterations [10,20,21,22,29]. One of the most peculiar predictors of long-term disability is the MRI which enables monitoring the patients on subsequent follow-ups. MS lesions are often less extensive than those observed in

NMO/NMOSD, manifesting as ovoid plaques situated in the vicinity of ventricles and the corpus callosum [11,14].

When it comes to the optic neuritis, it affects up to 50% of the MS patients and in 30% of the cases it occurs as a first symptom [14]. Similarly to NMO/NMOSD, such a frequent involvement of these nerves may be explained by a decrease in the blood-brain barrier function [14,25]. Because of such a high importance of ON in the clinical picture of MS, MRI of the brain and spinal cord is a typical procedure performed in patients presenting to the ophthalmologist with symptoms of reduced visual acuity [25,29,38]. The research show that even if there are no lesions found, there is 25% risk of developing multiple sclerosis within 15 years. The statistics dramatically rise to 70% if one or more changes are revealed. That accounts for the overall MS probability in 15 years amounting 50%, which is according to many clinicians an argument for the disease modifying treatment (DMTs) initiation in patients with typical ON, but displaying no abnormalities in the MRI [14,18,26]. However, some data and opinions are conflicting, and the consensus is to weigh the potential benefits of the decision about DMTs administration (i.e. stopping the disease progression) against the risk (i.e. drug-related side effects) [11,18]. Conversely, the decision to treat remains unquestioned if typical lesions are detected on neuroimaging. The basis of the MS recognition, included in McDonalds criteria, is dissemination of the plaques in space and time. That actually means at least two findings, at least 1 of which is contrast-enhancing, in at least two separate imaging studies. For the first-line treatment in definite or subclinical MS, interferon beta and glatiramer acetate are usually prescribed [9,10,11,14,18,20,21,23,24,26,29]. Over the recent years many effective therapies were approved, especially in the form of monoclonal antibodies, which has led to more and more favorable prognosis. However, none of the drugs invented has a remyelinating effect which remains a challenge for future researchers [11].

The MS-associated optic neuritis represents features of the typical neuropathy. The occurrence of the first ON episode is typically at the age of 28-30 years. It manifests itself as a unilateral subacute, painful vision loss [24,25,29,38]. Compared to NMO, the prognosis regarding VA is rather conducive (normally returns to 6/9 or better), with subtle impairments possible. A possible outcome is determined mainly by the presence of white matter lesions in the MRI and oligoclonal bands in the CSF [9,14,20,38].

Neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorders (NMOSD)

Neuromyelitis optica (Devic disease) is a rare demyelinating disorder characterized by the inflammation of the spinal cord and optic nerves. The identification of such a disease

entity has occurred in recent years due to the discovery of specific antibodies against aquaporin 4 (AQP4-Abs) [4,10,13,18,20,21,22,26,27,31,34,36]. This water-channel protein has been found to be expressed in the brain, spinal cord and optic nerves. Those antibodies' positivity combined with typical manifestations allows for a diagnosis of NMO [32,34]. Conversely, in case of seronegativity (about 10-20% patients), more appropriate is the recognition of NMO spectrum disorders which is not as much transparent in its criteria and requires in-depth diagnostics [4,11,16,18,25,26,27,34,36]. The mean age of NMO occurrence is approximately 10 years earlier and female predilection is much more expressed as compared to MS. The pathogenesis of the disease is complex. Many factors are said to induce the demyelination, comprising infections, vaccinations and systemic diseases. Recently, the correlation between myasthenia gravis and coeliac syndrome has been also discovered [27].

The main characteristics of NMO in MRI are the longitudinally extensive lesions in the spinal cord encompassing more than 3 segments and generally, more confluent inflammatory changes and the absence of cortical demyelination [18,20,22,25,26,27,36]. In the CSF examination monocytic or lymphocytic pleocytosis is found and in the majority of cases increased levels of protein are detected. Compared to MS, oligoclonal chains appear in the fluid much less frequently but the VEPs reflect abnormalities more often [18,20,27,36]. Patients with NMO tend to develop loss of sensation, limbs paresis, abnormalities in sphincters control, cognitive dysfunction, an "area postrema" dysfunction, brainstem disturbances or narcolepsy, as well [18,20,22,34,36]. Characteristic peculiarities of the disease involve particularly activation of complement, loss of AQP4 expression, neutrophil accumulation and IgG deposition. The pathological process underlying NMO is the astrocytopathy and necrosis changes rather than neuron deficits and demyelination [4,11,27].

Apart from the transverse myelitis (TM), optic neuritis is a common feature appearing in 1-3% of NMO. It is normally associated with severe vision loss, poor response to treatment and recovery, and the worst prognosis of all possible etiologies [2,11,13,16,20,22,25,26,27,38]. There is a tendency that each subsequent attack of ON causes gradual deterioration of visual functioning. In contrast to MS-ON, it involves more often both optic nerves and causes macular edema. It has been also proved that NMO results in more severe retinal nerve fibre layer (RNFL) and ganglion cell layers thinning visible in OCT [22,26]. The ON management is rather similar regardless of the pathology that caused it. Nevertheless, sometimes it needs to be treated more intensively and for a longer time [4,11,16,27].

In both MS and NMO, immunomodulatory/immunosuppressive therapy to prevent relapse and progression is required soon after the diagnosis. However, some of the medications used in MS are proved to exacerbate the course of NMO, which means that getting to an adequate disease recognition is extremely crucial [11,13,27,34,36]. The final outcomes are in NMO/NMOSD generally much worse and the mortality after 5 years reaches even 25-30% [27].

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is another inflammatory demyelinating disorder involving the CNS. Its distinction has taken place because of the recognition of MOG protein and antibodies directed against them [11,13,22,25,28,30,31,33,35]. This specific molecule is found on the outer membrane of myelin sheaths and it is expressed mostly within the brain, spinal cord and optic nerves, less commonly in the peripheral nervous system (PNS) [22,31]. Its precise function remains unclear, although some data suggests that it may play a role in maintaining the integrity of myelin sheaths as a cell surface [11,31]. As for the course of the disease, it can be monophasic or, more frequently, relapsing-remitting with an overall prognosis being more favorable than in NMO, but it still effects in long-term disability [30,31,35]. Comparing to the abovementioned, the disease is generally more common in Caucasian, has rather a fairly even sex ratio of incidence and occurs at the earlier age [25,28]. Moreover, intracortical demyelinated lesions are more typical than the leukocortical ones [11,33]. Unlike NMO, a particular area of the disease involvement is the lower part of the spinal cord, which also encompasses the medullary cone leading quite often to the inflammation [31]. In patients afflicted MOGAD the brain lesions are larger, more diffused and appear more frequently in the pons, cerebellum, midbrain, gray matter and juxtacortical white matter, as well [25,31]. Although, the disease is not characterized by any pathognomonic clinical or neuroimaging symptoms, some of them manifests with greater frequency. The phenotype in the majority of patients include acute disseminated encephalomyelitis (ADEM), optic neuritis (ON) or transverse myelitis (TM). ADEM is a condition with the highest incidence rate among children [11,30,31]. Its presentation is associated with both systemic symptoms (fever, headache, vomiting, nausea, disturbances in mental status, malaise) and those more specific contingent upon the location in the CNS (difficulties in coordinating movements, visual deficits, sensory loss, hemi-/paresis). Usually, with the natural course of this disorder those

patients develop an “optico-spinal syndrome” as the ON and TM are typical in adulthood [31,35].

A diagnosis of MOGAD can be confirmed by meeting the following criteria: a clinical picture consistent with the disease, distinctive features observed on neuroimaging studies, and the presence of MOG IgG antibodies in the cell-based assay (CBA) test in serum. A key condition is the exclusion of a better diagnosis [30,31,35].

The MOGAD-ON in typical cases affects both optic nerves and is observed to be longitudinally extensive, as well as causing periventricular enhancement on MRI [21,22,25,28,30,31]. Additionally, it is accompanied by moderate to severe disc swelling and sometimes peripapillary hemorrhages [16,22,30,31]. During the ON confirmation, the OCT is able to reflect a more preserved RNFL than is possible with MS or NMO/NMOSD, which is a crucial factor in the differentiation process. The management of ON is largely consistent with that employed for other etiologies. In all cases, the earlier the recognition and treatment, the better vision outcomes. It is widely accepted that treatment should be initiated within a period of 4-7 days following the onset of symptoms. Nevertheless, some patients are suffering from recurrent or steroid-dependent neuritis that requires continuous therapy involving IVIG or tocilizumab. The acute phase results in a severe VA reduction but in general returns within several weeks to the pre-inflammatory state, though, the prognosis is still worse than in typical ON due to the tendency to relapse [11,16,22,25].

When it comes to the long-term relapse prevention for MOGAD patients, no drugs are officially approved. In the current practice, high-dose glucocorticosteroids (GCS; with gradual discontinuation), are commonly used. Sometimes, as maintenance therapy, also IVIG and traditional immunosuppressives (azathioprine, mycophenolate, methotrexate) or rituximab may be helpful as steroid-sparing agents [11,21,22,31,33].

Actually, there exist no tools that would enable to predict and quantify the risk of relapses and further impairments. Nonetheless, it has been delineated which features are connected with better prognosis. Those consist of persisting MOG-IgG (especially in high titres) and a short time to the second attack of the disease [31].

As numerous studies have demonstrated, there are no discernible advantages to testing all patients with ON on admission, primarily due to the inability to assess the sensitivity of the CBA test. Therefore, the greatest conundrum is to when exactly such screening for MOG-Abs should be conducted. The observation of the MOGAD cases has led to the distinction of some characteristics which are indicative of such a diagnosis. Those comprise: onset before the age

of 11, typical MOGAD phenotype, non-specific findings for MS or NMOSD and seronegative NMO [30,31,35].

Glial fibrillary acidic protein (GFAP) astrocytopathy

Glial fibrillary acidic protein (GFAP) astrocytopathy is an autoimmune inflammatory disease affecting the CNS, as well. The disease has in 89% a monophasic course and primarily manifests as meningoencephalitis, although it has the potential to affect nearly every anatomic region. The symptoms may encompass a range of manifestations, including movement dysfunction, seizures, myelitis, and brainstem attacks [16]. The diagnosis is mainly based on the presence of antibodies directed against the glial fibrillary acidic protein (GFAP). In terms of the brain MRI, the presence of distinctive radial perivascular enhancement is typically identified [21]. Typically, the CSF examination reveals features of inflammation and significant pleocytosis [16].

Visual disturbances in GFAP astrocytopathy occur in 25% of the patients and manifest itself by severely decreased VA, but with central field preservation. Optic neuritis is a rare vision-associated phenotype that often means a relapsing disease course. It is usually painless, bilateral and causes prominent optic disc edema (in more than 50% cases asymptomatic). An acute-phase treatment is typically associated with a poor response and prognosis, which closely resembles NMO-ON not only in management but also in prognosis [16].
In conclusion, GFAP-Abs testing should be considered in all cases where the aforementioned characteristics are present.

Collapsin Response Mediator Protein 5 (CRMP5) antibodies-associated neuropathy

The CRMP5 molecule is stated to be the protein responsible for an autoimmune neuropathy and a common marker of a broad spectrum of paraneoplastic syndromes. Cranial neuropathies, polyneuropathies, myelopathy with basal ganglionitis and axonal demyelinating patterns are seen in affected patients. The phenotype involves also ON and retinitis accompanied by moderate to severe optic disc swelling and inflammatory cells in the vitreous body [16,21]. On presentation, the patient, who is usually middle-aged (or older), complains of a subacute painless bilateral reduction in visual acuity, which is in most cases mild to moderate. More distinctive is the MRI of the orbit, which shows no contrast enhancement, and the ERG, which shows some abnormalities due to the retinal inflammation [16].

This neuropathy is known to be particularly associated with small cell lung cancer (SCLC) and, less commonly, thymoma. The data show that as many as two-thirds of patients develop these neurological symptoms before the underlying neoplasm becomes apparent. This is therefore the reason why the diagnosis of this neuropathy is in itself the basis for an active search for the cancer [16,21].

The actual treatment mainly focuses on tumor eradication, while the therapy of the paraneoplastic syndrome itself is ancillary and, as in other cases, implies the inclusion of high-dose steroids, plasmapheresis or IVIG. As a consequence, visual functioning improves in 50% patients, but generally their prognosis also closely depends on the tumor therapy and its effects [16].

Chronic relapsing inflammatory optic neuritis (CRION)

Chronic relapsing inflammatory optic neuritis is, as its name says, characterized by its tendency to recur and GCS dependency, as well. Though, the diagnosis is not as straightforward as it may seem to be, because it requires always a thorough examination and exclusion of at least demyelinating ON. Moreover, the treatment is rather problematic due to the fact that despite rapid response to high-dose GCS, the neuropathy relapses right after (weeks/months) their cessation or dose reduction [11,16,21,22,26]. On the other hand, if the therapy is permanent, the cumulative dose evokes multiple side effects leading to visual dysfunctions [10,11,18]. Therefore, some sort of consensus in ON management is to start the IVMP pulses at a dose of 1mg/kg for 3-5 days (in severe cases with plasmapheresis or IVIG) and to taper the dosage carefully with oral prednisolone [11,16,21]. Some patients will require minimal effective dose of GCS chronically anyway. Other ideas assume early initiation of the steroid-sparing therapy including the use of azathioprine, rituximab, IVIG, cyclophosphamide, methotrexate or mycophenolate [11].

ON associated with systemic diseases

Sarcoidosis

Sarcoidosis is a systemic disease of unknown etiology that causes granulomas, especially (>90%) in lungs [16]. The most specific finding on a chest X-ray is hilar lymphadenopathy. The onset of the disease is accompanied by general symptoms such as fever, weight loss, respiratory symptoms, night sweats or diarrhea. The diagnosis of the

disease is typically made by the recognition of granulomas on bioptic tissue, which are mainly suspected by chest tomography or FDG-PET [16].

The localization of granulomas in other organs is rare but possible. One of the systems involved may be the CNS, which occurs in 5-10% of the cases, with seventh nerve palsy being the most common manifestation. The second frequent symptom is the optic neuritis, described as a subacute to rapidly progressive reduction in VA. The degree of visual impairment is usually severe to complete blindness. Suspicion of sarcoidosis can be based on the presence of concomitant lesions associated with the ocular inflammation, even visible in the anterior chamber [14]. These can be found in up to one third of patients. Furthermore, by the MRI of the orbits the features of perineuritis or optic nerve head granulomas may be detected. ON of such etiology is rather responsive to steroid treatment, however, relapses are common. For this reason, the majority of the patients require low-dose GCS with long-term immunosuppression [14,16].

CONCLUSION

Optic neuritis is a very serious and complex condition to diagnose and treat. It requires a multidisciplinary approach to be properly managed. Differential diagnosis may be a daunting task that demands numerous laboratory and imaging tests.

The prognosis varies depending on the underlying disease and it is difficult to determine the long-time outcome.

The role of an ophthalmologist is to perform a thorough examination and to refer a patient to other specialists such as neurologists or rheumatologists for in-depth diagnostics.

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