Chronic Relapsing Inflammatory Optic Neuropathy: a Systematic Review of 122 cases reported

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Abstract

Chronic relapsing inflammatory optic neuropathy (CRION) is an entity described in 2003. Early recognition of patients suffering from CRION is relevant because of the associated risk for blindness if treated inappropriately. It seems timely to have a clinical review on this recently defined entity.

A systematic literature review, irrespective of language, retrieved 22 case series and single reports describing 122 patients with CRION between 2003 and 2013. We review the epidemiology, diagnostic workup, differential diagnosis and treatment (acute, intermediate, long–term) in view of the collective data.

These data suggest that CRION is a distinct nosological entity, which is seronegative for anti-aquaporin 4 auto–antibodies and recognised by and managed through its dependency on immuno–suppression. Revised diagnostic criteria are proposed in light of the data compromising a critical discussion of relevant limitations.

Keywords: optic neuritis, steroid dependent optic neuritis, relapse, ON, CRION

1. Introduction

The last decade witnessed important discoveries in immune–mediated diseases of the optic nerve (Figure 1). At the turn of the century, optic neuritis (ON) was discussed, described and studied as the presenting symptom of or a relapse in multiple sclerosis (MS). Progressive visual loss after an episode of ON was not necessarily recognised. A decade ago two observations were made almost simultaneously: Desmond Kidd *et al* described Chronic Relapsing Inflammatory Optic Neuropathy (CRION) [1] and Vanda Lennon *et al* discovered a specific auto–antibody (NMO-IgG) for NMO [2]. Recognition of these two entities is relevant for patient management targeted at preservation of their vision, because in contrast to MS there is a considerable risk of blindness.

Patients with ON who were seropositive for NMO-IgG were at increased risk for a spontaneous later relapse and conversion to NMO [3]. Naturally, the question arose if CRION was part of NMO spectrum disease. This hypothesis was rejected by prospective study demonstrating that 95% of patients with CRION were seronegative for NMO-IgG [4]. These findings are consistent with a subsequent multi–center study with 94% of patients with ON being seronegative cases for NMO-IgG [5]. Likewise, another multi–center study found the majority of cases with bilateral onset of optic neuritis to be NMO-IgG seronegative [6].

A limitation of the test for NMO-IgG was that about 20-40% of patients with clinical definite NMO remained seronegative. In this context the description of complement activation leading to astrocytic necrosis [7, 8] paved the way for another discovery. Glial fibrillary acidic protein (GFAP) is a highly sensitive biomarker for astrocytic damage [9, 10] and was found to be elevated in over 98% of patients with acute NMO [11, 12]. Using this biomarker the hypothesis was tested whether patients with CRION would also exhibit the glial damage so characteristic for NMO. Again, the hypothesis was rejected, both in a single center [13] and multi–center setting [14]. Taken together no link could be made between CRION and NMO using either highly *specific* [2] or highly *sensitive* [13, 14] laboratory tests.

Based on the accumulating evidence that CRION is a nosological distinct entity this systematic review was performed. The aim was to carefully describe the clinical phenotype, provide advise on diagnostic work–up and treatment. As will become clear there was a need to revise the diagnostic criteria for CRION in light of these data.

Methods

Search strategy and selection criteria. A systematic review of the literature was conducted on all publications on CRION since the original description by Kidd *et al*

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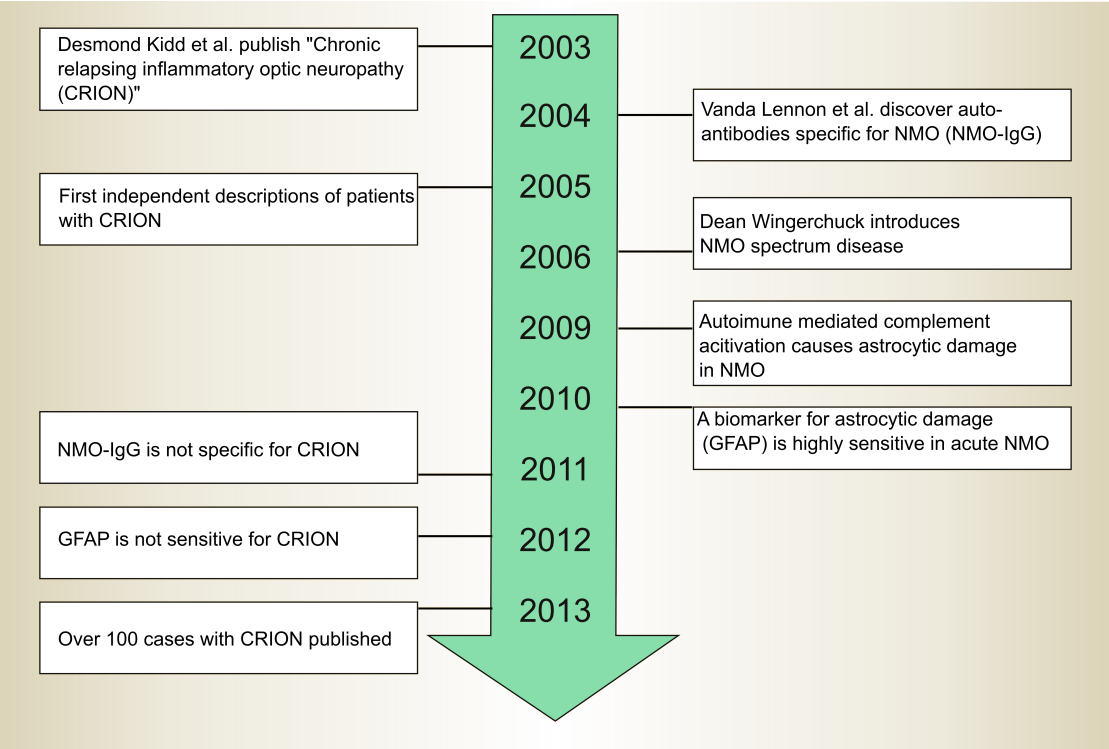

Figure 1: *10 years of separating CRION as a nosological entity from NMO.*

in 2003 [1]. The following databases were searched irrespective of language: Pubmed, EMBASE, Medline, Web of Science and Google Scholar. The search terms used were "chronic relapsing inflammatory optic neuritis", "CRION", "optic neuritis and steroid and dependence" and "steroid dependent optic neuritis". All articles and abstracts were screened for further references. Finally Google Scholar was used to trace citations of the original description of CRION [1]. This combined search strategy revealed 22 publications [1, 4, 15–34]. Subsequently, corresponding authors were contacted by email in an attempt to complete the published data.

In total we identified 126 published cases. Of the 19 CRION patients from one London publication [4], 4 overlapped with the 15 original cases [1]. For discussion of these cases the last follow-up data were used [4]. Therefore the total number of cases published in the last decade (2003–2013) are 122.

There were other reports on corticosteroid dependent optic neuritis, but either CRION was not mentioned specifically or review of the clinical information suggested an alternative diagnosis (see reference [35] and references therein).

Data analyses. Descriptive statistics were performed using SAS software (V9.3). Normally distributed data were presented as mean±standard deviation. Non-Gaussian data wer presented as median and interquartile range (IQR). The weighted mean was used to calculate the overall average for those data where group statistics were available from some publications and detailed individual data from others. Visual acuity values were converted into decimal notation. Count finger (CF), hand movement (HM), light perception (LP) and no light perception (NPL) were all rated as zero. Graphs of summary statistics were prepared with SAS including the choro statement for a standardised world-map on the epidemiological data.

Epidemiology

The youngest reported case was 14 years at presentation [22] and the oldest 69 years [4]. The distribution per decade live is presented in Figure 2. Taken together the weighted mean of the published age was 35.7 years [1, 4, 15–24, 26, 31]. There was a female predominance of 59 cases (48%) over males 25 cases (20%), with no gender information on the remaining 39 cases (32%).

CRION is a world-wide disease with publications from every continent with the exception of Africa and Australia (Figure 3). Patients from these two continents have been seen by us [4]. Most cases come from the UK [1, 4, 19, 24, 34] (n=35, 28%, red shaded area in Figure 3), followed by France [31] (n=20, 16%), Brazil [33] (n=18, 14%), India [28] (n=13, 11%), Turkey [29] (n=11, 9%), USA [17, 26, 27] (n=11, 9%), with small case series or single case reports from the remaining countries (black shades areas in Figure 3). The overall distribution suggests a reporting bias in the literature. Therefore the data available are unlikely to be definite. It is likely that the condition is under-reported. Taken together prevalence and incidence data cannot reliably be calculated at present.

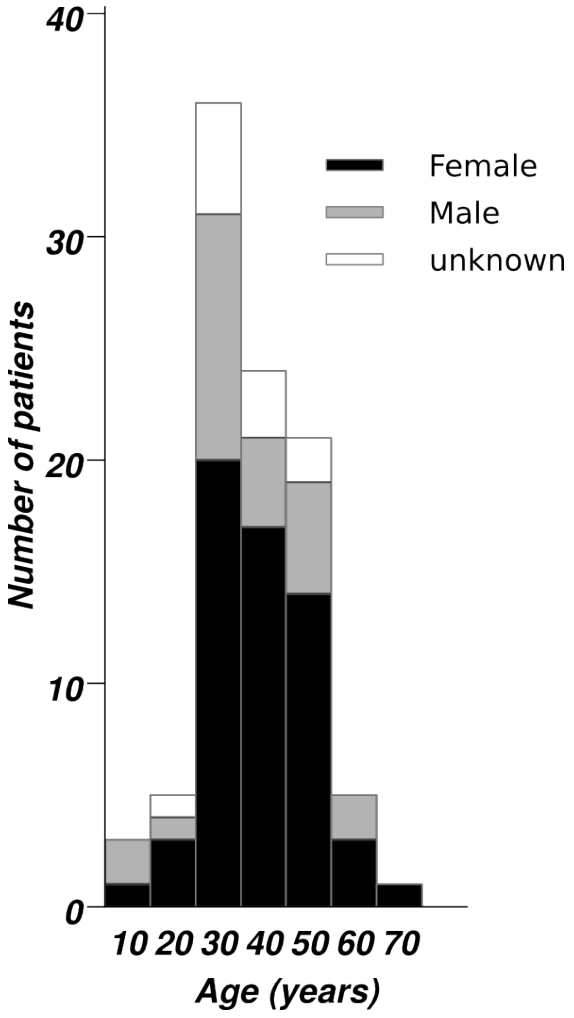

Figure 2: *Age of onset in CRION. The total number of women (black bars), men (grey bars) and those patients were gender was not reported (empty bars) are shown.*

Data from the ethnically diverse London population suggested that the risk for CRION may be higher in patients of African or African-Caribbean heritage [36]. From those CRION cases were ethnicity was published 20 (16%) where Caucasian and 16 (13%) non-Caucasian (3 African, 5 Afrocaribean, 1 Arab, 4 Asian, 1 Australian, 1 Moroccan, 1 Pakistan) with ethnicity data non-available in the majority of cases (n=87, 71%).

Aetiology

The aetiology remains unknown [1]. For this reason it was suggested to name the condition Chronic Relapsing Inflammatory Optic Neuropathy instead of using more restrictive terms such as optic neuritis. The strong response to immuno-suppressive treatment, see further down, suggests the aetiology to be at least in part immune-mediated. However the term "auto-immune optic neuritis" which had been used in a previous publication describing cases of non-MSON was not used as an autoimmune basis could not be established with certainty in the patients described, only that there was a dependence on immune suppression which might also be seen in, for example, a restricted form of a granulomatous disease.

Semiology

Visual loss. Bilateral visual loss either simultaneous or sequential has been observed in 36 patients (59%) [1, 4, 15, 19, 21, 24–27, 29, 34]. Not in all cases the time lag of visual loss between the eyes were noted, but true simultaneous loss of vision was present in 8 cases [1, 15, 24, 26, 32]. In 12 cases visual loss was only on the left [4, 16–18, 26, 27] and in 11 cases only on the right [4, 20, 22, 23, 26, 27]. In another 2 cases visual loss was monocular without further data [32] and information was not published in the remaining cases.

Frequency of episodes. As the diagnosis can only be made following at least one relapse all patients experienced more than one episode. The number of episodes was not always detailed. Eighteen episodes were reported in one case [23], 17 in another [22], 16 in one of the original CRION cases [1, 4]. There were 11 cases with 5-10 episodes [1, 4, 18, 20, 26, 28, 29]. Thirty-four patients had less then 5 episodes [1, 4, 15, 16, 19, 21, 24–26, 28, 29]. Others were reported to have experienced "several" episodes [17] or more than two episodes [29].

Presenting visual acuity. Visual loss in the affected eye was severe in most cases. Summary statistics were performed on the published visual acuity (VA) at presentation using the decimal notation [1, 4, 15, 16, 18, 20–27, 34]. The median VA in the affected eye was 0.02 (IQR 0-0.25). A pooled analysis of the affected eyes illustrated that the data were severely skewed to the left (Figure 4). Therefore the use of logMAR visual acuities would be more useful for

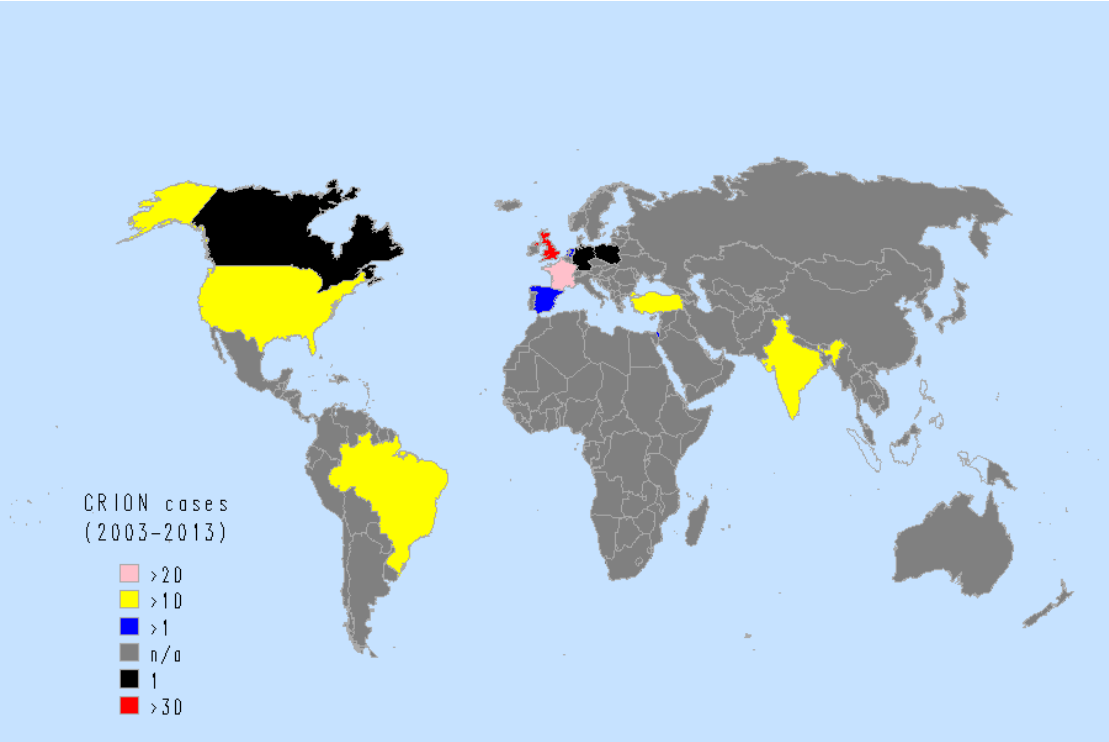

Figure 3: *CRION cases published per country between 2003 and 2013.*

future studies. In fact 68% of CRION patients had a presenting VA of 0.1 or less compared to 36% in the Optic Neuritis Treatment Trial (ONTT) [37]. Of the CRION patients only 12% had a VA better than 0.5 compared to 35% in the ONTT [37].

Outcome visual acuity. Following the same approach the median outcome VA was 0.33 (IQR 0.1–1.0) in the affected eye [1, 4, 15, 17–27, 29, 29, 34]. Outcome VA was less than 0.1 in 33% of CRION patients compared to only 1% of patients from the ONTT [38]. Another 30% of CRION patients had an outcome VA of less than 0.5 compared to only 2% from the ONTT [38].

This comparison should be interpreted with caution because of the heterogeneity in follow-up time, clinical assessment and data reporting for the CRION cases in contrast to the rigorous study protocol applied in the ONTT which permitted for long-term follow up data on 65% of the original ONTT cohort. It is also very likely that the timing and duration of corticosteroid treatment in the acute setting is critical in determining the visual outcome. The mean delay between onset of visual symptoms and inclusion into the ONTT was 5.0±1.6 days. Hyperacute treatment prevented loss of vision during a relapse in three cases with CRION [19].

Pain. Pain at onset was present in 43 cases [1, 4, 16, 17, 19–23, 32, 34], absent on direct questioning in only 3 cases [1, 15, 21] and not reported in the remaining patients.

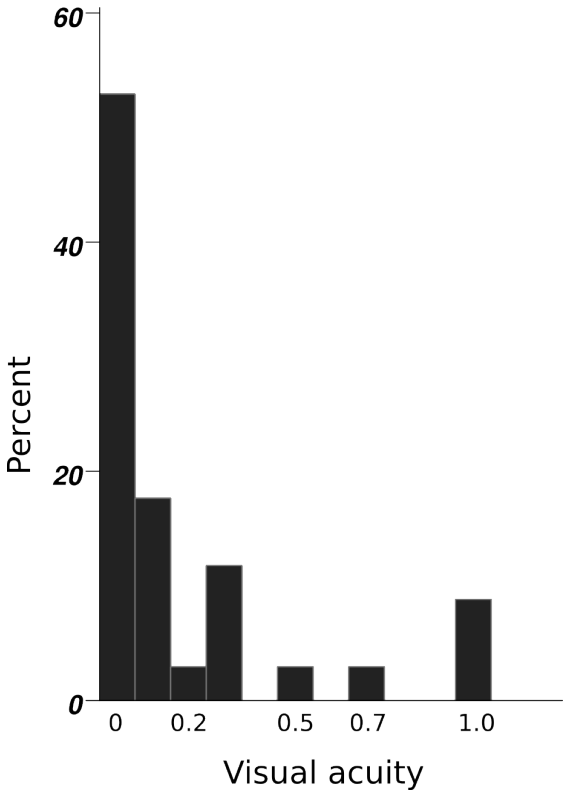

Figure 4: *Onset visual acuity in CRION. The pooled data of the affected eyes show a trend for severe loss of vision (>0.01) in a majority of cases.*

Absence of pain occurs in a small proportion of patients with CRION. Pain, like in other types of optic neuritis/neuropathy, be associated with intra-orbital rather than intra- cranial pathology of the optic nerve/chiasm [39].

Uveitis. Concomitant uveitis was reported in 9/122 (7%) of the CRION cases [22, 27]. This is more than the about 0.7% reported in MSON ([40] and references therein).

Chronicity. The average published follow-up time was 56±54 months (4.6 years) with a median of 36 months (3 years) and a range of 4 to 204 months [1, 4, 15, 17, 19–28]. The heterogeneity of these data severely limits any estimate of long-term chronicity of CRION. In our own experience disease activity can settle over a decade.

Diagnostic workup

A diagnosis of CRION requires exclusion of other neurological, ophthalmological and systemic conditions as discussed [1, 4, 15–34].

History taking. A careful eye history should include pattern and speed of onset of visual loss and associated positive visual symptoms such as photopsias, scintillations. It is important to ask whether the visual symptoms were bilateral which suggests involvement of the optic chiasm. It is not always easy to clearly distinguish simultaneous bilateral loss from sequential visual loss because symptoms in one eye may be so severe that more subtle symptoms in the other eye were missed.

A pertinent history question is with regard to pain on eye movement or ocular discomfort [39] as has been discussed above. If present, pain severity should be rated on a visual analogue scale (VAS) ranging from 0-10. Pain of sufficient severity to interfere with sleep is very unusual in MSON. Other forms of pain than those associated with eye-movements have been reported and range from headache to dull ache of the peri-orbital region.

Rapid resolution of pain, if present, and improvement in vision when treatment with corticosteroids is given should be carefully asked for. In general, resolution of pain is entirely non-specific, but recurrence of pain after reducing or stopping steroids is a red flag. If there is return of pain or deterioration in vision then a non-MSON such as NMO, sarcoidosis associated optic neuropathy or CRION should be suspected.

Clinical examination. We recommend a routine neurological and ophthalmological examination in order to exclude other conditions.

The routine examination should include testing of visual function (visual acuities (high and low contrast), colour vision, visual fields). In cases with unilateral presentation a relative afferent pupillary deficit (RAPD) is present in all cases in our experience. Retinal examination should be performed in each patient by direct and indirect ophthalmoscopy.

If indicated by the clinical examination additional tests may be required such as automated perimetry and electrophysiology.

Paraclinical tests

Overall the imaging, CSF and serological testing at present are helpful mostly in a negative sense. CRION should be suspected when the paraclinical tests discussed below do not provide strong evidence for an alternative diagnosis.

Laboratory investigations. From the literature review the laboratory tests to be considered include: haematology, electrolytes, GT, ACE, ASAT, ALAT, ANA, anti-aquaporin 4 antibodies (AQP4-IgG), Vit B12, folate, thyroid function and appropriate serology [1, 4, 15–34].

If an autoimmune pathology is suspected our own, resource saving approach is to first check for ANA. If the ANA are positive, particular in young patients, more extensive immunological work-up may be required because SLE and other systemic autoimmune disease remain high in the differential diagnosis [35].

Of note, a prospective study showed that NMO-IgG was only present in about 5% of patients with CRION [4] which is comparable to the overlap with other immune-mediated optic neuropathies and auto-immune diseases [5, 6]. Five more NMO-IgG positive cases have been reported from Brazil [33]. In NMO there is a literature on low titre ANA titres, acetylcholine receptor antibodies and other auto-antibodies [5, 6]. There are no such associations so far emerging in the CRION reports [4, 33]. Testing for NMO-IgG was done in some studies [16, 18–20, 24, 25, 28, 29, 32]. Not all studies specified which test was used to test for NMO-IgG. Therefore we have not conducted a meta-analysis on these data. Testing for NMO-IgG using state-of-the-art assays is recommended, because of analytical sensitivity and high clinical specificity for NMO [41].

There is no diagnostic blood biomarker for CRION [13, 14]. Possibly blood neurofilament levels may be of some prognostic value, because they indicate more substantial axonal damage at onset [42].

In our practise we do not routinely perform a LP, but in selected cases this may be necessary and should comprise a comprehensive cerebrospinal fluid (CSF) analyses [43].

Research recommendations: there is no consensus protocol on how to process and store patient samples with optic neuropathies in an area of biomarker discovery. Patient samples are valuable, particularly if taken during an acute episode. Storage of such samples can be necessary either if analysis for specific antibodies or protein biomarkers is planned in another laboratory or for future research. In our own practise we aim to spin blood samples within 1 hour from sampling at 2,000 g for 10 minutes at room temperature and to store multiple aliquots of 500 μL in 1.5 mL polypropylene tubes at -80°C. A longer sample

processing time increases the risk for haemolysis and proteolysis. Storage at higher temperatures may invalidate future tests on unstable compounds.

Imaging. A **chest X-ray** or **CT** of the thorax is recommended in patients with suspected sarcoidosis, which is an important differential diagnosis [35].

An **MRI** of the orbits, brain and spinal cord should be performed at first presentation for diagnostic and prognostic purposes. A repeat MRI scan of the orbits may be deemed necessary during the follow-up if clinical reasoning suggests progressive orbital pathology which may have been missed on the first scan. Coronal scans of the orbits with fat suppression are particularly useful. A normal MRI scan of the brain was reported in 49 patients [1, 4, 16, 18–21, 23, 24, 26, 28, 32]. In two cases a single hyperintense lesion on T2 weighted images was seen either in the periventricular white matter [1] or posterior parietal lobe [32]. Another case showed multiple hyperintense T2 lesions of the deep white matter of unknown significance [15]. Revision of the MRI of our own case did not fulfil the radiological criteria for MS [44]. We were not able to personally revise the two other images, but the phrasing of the text suggests an "incidental" finding [15, 32] rather than radiological dissemination in time and space as typical for MS [44]. Because of the challenges of distinguishing non-specific from relevant lesions on MRI a multi-site consortium with expert MRI neuro-radiologists would be desirable to definitely describe the role of this important imaging modality for CRION.

Optical coherence tomography (OCT) is valuable for quantitative and qualitative assessment of retinal layers. Because the sensitivity of current spectral-domain OCT devices is such that known artefacts can mask longitudinal changes of retinal layer thickness adherence to quality control criteria is advised [45]. As yet, there are no systematic OCT data available in CRION patients. In our own (unpublished) experience there is severe atrophy of the retinal nerve fibre layer (RNFL), ganglion cell layer (GCL) as well as presence of microcystic macular oedema (MMO) [46–48] in the inner nuclear layer (INL, see Figure 5).

Differential diagnosis

The most frequent differential diagnosis remains optic neuritis due to multiple sclerosis (MSON). There are clear diagnostic guidelines for this entity which is labelled as a clinically isolated syndrome (CIS) at first presentation and MS if dissemination in time and space can be demonstrated as outlined by International Panel criteria [44].

Those patients without MRI evidence for demyelination elsewhere in the CNS have experienced an episode of isolated ON (ION). In such patients there is a chance for a future relapse. If such a relapse occurs spontaneous, they are described as relapsing isolated ON (RION).

Next, there is a list of systemic diseases which can be associated with optic neuritis such as ideopathic granulomatous optic neuropathy, diabetic papilloedema, toxic and nutritional (Vit B12 deficiency, tobacco-alcohol, methanol, ethanol), infectious optic neuropathies (syphilis, tuberculosis, Lyme, viral aetiology). Whilst Lyme disease remains endemic in certain areas, syphilis and tuberculosis are on a world-wide increase.

Ischaemic optic neuropathies can sometimes be difficult to distinguish. They embrace anterior and posterior ischaemic optic neuropathy (AION, PION) and giant cell arteritis (GCA). Presence of vascular risk factors, laboratory investigations and biopsy of the superficial temporal artery may be necessary. Likewise, primary ocular causes will need to be excluded such as posterior scleritis, maculopathies and retinopathies.

There is a large list of hereditary optic atrophies which may be suggested by an appropriate family history. The two most frequent conditions here are Leber's hereditary optic neuropathy (LHON) and dominant optical atrophy (OPA). Rare are endemic cases of optic neuropathy such as described in Cuba or Tanzania.

The differential diagnosis further embraces compressive pathologies such as primary tumours, metastases, tuberculoma, thyroid ophthalmopathy, aneurysms and sinus mucoceles. The relevance for appropriate imaging in these cases cannot be overestimated.

Finally, there are conditions only described in the last couple of decades which may not be generally recognised due to their low frequency such as the big blind spot syndromes [26, 27, 49–51].

Treatment

Treatment and response to treatment was published for 92 CRION cases [1, 4, 16, 18–24, 26–29, 31, 32, 34]. The treatment consisted of three phases: (1) restoring visual function in the acute phase, (2) finding a strategy to stabilise vision on the interim and (3) preserving vision on the long-term with minimal treatment side-effects.

1. Acute phase: intravenous steroids (methylprednisolone, 1 mg/kg) for 3-5 days or plasmapheresis. The use of IVMP was reported in 79 CRION cases, all of whom responded [1, 4, 15–26, 28, 31]. A relapse occurred after stopping IVMP, but the time lag was not noted systematically.
2. Intermediate phase: the use of oral steroids (prednisone and in two cases also deflacort) was documented for 69 CRION cases [1, 4, 15–29, 32, 34]. We give oral steroids (prednisone) at a starting dose of 1 mg/kg. These can be gradually reduced to identify an individually variable minimal effective doses. During the oral taper rigorous follow-up of the visual function is advised. A relapse after stopping steroids was reported in 67 CRION cases [1, 4, 15–17, 19–29, 32]. Interestingly, one study mentioned 7 cases in

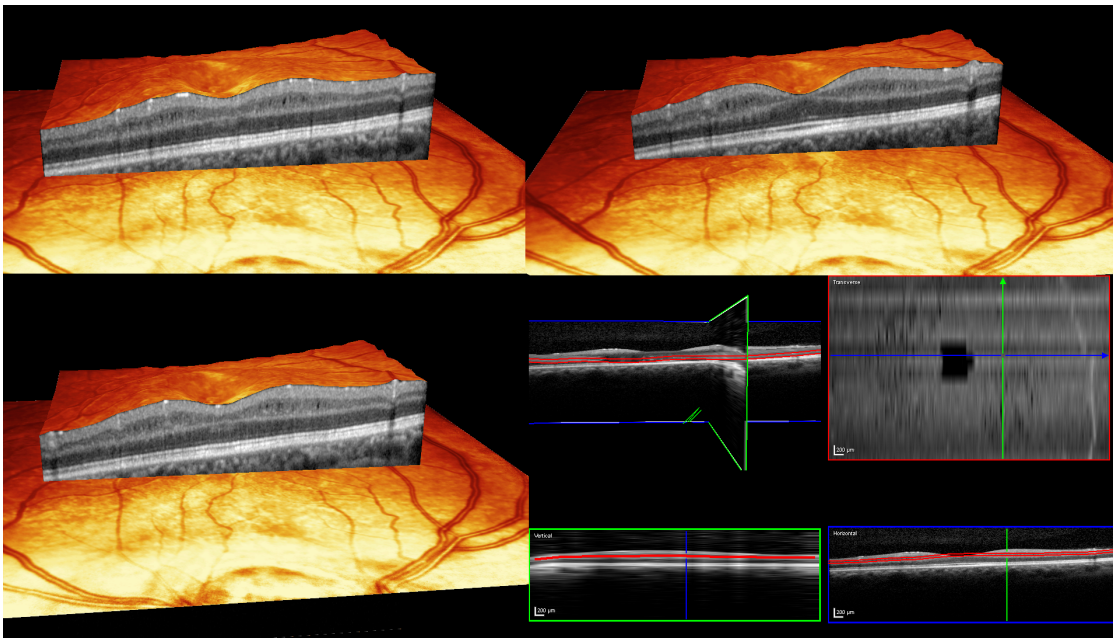

Figure 5: *Microcystic macular oedema (MMO) on serial B-scans in a own (unpublished) case with CRION. A transverse section of the inner nuclear layer (INL) showing MMO as multiple black slits is shown in the inset (bottom right). For this composite image all A-scan data between the two red lines were combined. Note, that the transverse section cuts just above the macula, leaving a black hole in the middle.*

whom no further relapses occurred after withdrawal of steroids [28].

3. Long term: add on of a steroid sparing medication such as for example azathioprine [1, 4, 16, 19, 21, 26–28], methotrexate [1, 17, 18, 22, 26, 27], cyclophosphamide [17, 27] or mycophenylate [19, 21, 25, 27, 28]. Some authors also recommend the use of intravenous immunoglobulin (IVIG) [26, 35]. Five of the six CRION patients treated with IVIG remained stable for an average of four years following cessation of steroids, one relapsed [26].
   Other long-term treatment options include cyclosporine [21] or plasma exchange (PE) [4, 15, 25]. One study reported success with six-weekly infusions of infliximab [21]. Infliximab is a tumour necrosis factor (TNF)-α blocker. One needs to be aware that there is a risk for patients with demyelinating disease to get worse under treatment with (TNF)-α blockers [21].

In all patients who require long-term steroids, osteoporosis prophylaxis is recommended on the basis of the national or locally established guidelines. The long-term use of steroids remains challenging for patient management [52].

Discussion and diagnostic criteria

Over the past decade CRION as a distinct entity [1] remained in the shadow of NMO [2]. The description of specific auto-antibodies in NMO by the Mayo group in 2004 provided for the first time a highly specific diagnostic test so much needed in the field [2]. In contrast, the description of CRION one year earlier was mainly clinical [1]. Additionally, the epidemiological data summarised in this review suggest that CRION is much less frequent than NMO. Nevertheless the number of publications on CRION has constantly risen from one in 2003 [1], two in 2005 [15, 17] to 7 in 2012 [24, 25, 28, 31–34] with a total of 122 reported CRION patients over the past decade [1, 4, 15–34].

There is prospective data showing that the two entities are separate [4]. Stringent use of the clinical criterion by Kidd *et al* resulted in a diagnostic specificity of 95% for separating patients with CRION from NMO. Only one patient (5%) of prospectively collected CRION cases was NMO-IgG seropositive [4]. These data are further supported by this review, only one study reported presence of NMO-IgG in 5 more cases with suspected CRION [33]. A critical reappraisal of these cases suggests a more likely diagnosis for high risk CIS or NMO-spectrum disease. We recommend testing for presence of NMO-IgG in all cases with suspected CRION using highly sensitive assays [41]. A diagnosis of CRION should be reconsidered in any NMO-IgG seropositive patient as NMO is much more likely. Likewise we cannot comment whether or not a critical reappraisal of the MRI lesions from two further patients may not suggest an alternative diagnosis [15, 32].

Could CRION be part of a "seronegative" NMO spectrum disorder? We would oppose such a concept, because it creates a poorly defined umbrella term which lumps almost any optic neuropathy of unknown aetiology together. Borrowing from van Gijn on a related issue [53] we would like to ask back if "seronegative NMO spectrum disorder" will stand the test of time as a nosological entity?

In contrast to the original report, bilateral (sequential) loss of vision and pain are not consistently present in CRION. Likewise, brain imaging did show isolated, subtle or unspecific abnormalities outside the optic nerves and chiasm in 3 cases [1, 15, 32]. Because we were not able to critically reappraise all of these scans it does not seem possible to be too dogmatic about the necessity of a completely normal brain MRI in all cases with CRION at present.

Importantly, this review suggests that not all groups apply the same criteria for making a diagnosis of CRION. For example steroid dependence was not considered a mandatory criterium in 7 patients [28]. We content and side with Morrow and Wingerchuck who consider steroid dependence to be a key diagnostic criterium for CRION [54]. We therefore propose the following five *diagnostic criteria:*

1. History: optic neuritis and at least one relapse
2. Clinical: objective evidence for loss of visual function
3. Labor: NMO-IgG seronegative
4. Imaging: contrast enhancement of the acutely inflamed optic nerves[1].
5. Treatment: response to immunosuppresive treatment and relapse on withdrawal or dose-reduction of immunosuppresive treatment

Outlook

The risk of a relapse on withdraw of steroids is so strong that this is considered as a core diagnostic feature. Therefore an immune-mediated pathology is, at least in part, very likely. With the discovery of new auto-antibodies such as anti-AQP4 or anti-KIR4.1 antibodies we anticipate similar developments for CRION. The availability of a specific auto-antibody for CRION would help to identify patients as early as possible as well as greatly facilitating further refinement of the diagnostic criteria. Retinal OCT permits to reveal structural changes with high resolution. Future prospective studies are required to investigate if there are structural changes within the retina which permit to distinguish CRION from other forms of optic neuritis.

Conclusion

CRION represents a severe optic neuropathy. CRION should be recognised early, because there is a considerable risk of severe, potentially blinding loss of vision for the patient. Lastly, it is essential that the diagnosis of CRION (with NMO and sarcoidosis associated optic neuritis) are considered in any patient presenting with *de novo* optic neuritis as the consequences of following standard protocols developed in the context of MSON can have disastrous consequences. The authors have seen numerous patients who, when their vision has crashed after a short course of corticosteroids have been told that they have had the appropriate treatment for optic neuritis and no further sight saving treatment has been considered. Many of these patients were sent to us when the second eye became involved because of the extremely poor visual outcome in the first eye and it has been possible to save that eye by following the protocols for the management of CRION outlined in this article.

List of abbreviations

AION = anterior ischaemic optic neuropathy, AQP4 = aquaporin-4, CF = count fingers, CRION = chronic relapsing inflammatory optic neuropathy, CSF = cerebrospinal fluid, CT = computed tomography, GCA = giant cell arteritis, GCL = ganglion cell layer, GFAP = glial fibrillary acidic protein, HM = hand movement, INL = inner nuclear layer, ION = isolated optic neuritis, IVIG = intravenous immunoglobulin, IVMP = intravenous methylprednisolon, LHON = Lebers heriditary optic neuropathy, LP = lumbar puncture, MMO = microcystic macular oedema, MRI = magnetic resonance imaging, MS = multiple sclerosis, MSON = Multiple Sclerosis optic neuritis, NMO = neuromyelitis optica, NPL = no light perception OCT = optical coherence tomography, ON = optic neuritis, ONTT = Optic Neuritis Treatment Trial, OPA = dominant optical atrophy, PE = plasma exchange, PION = posterior ischaemic optic neuropathy, RION = relapsing isolated optic neuritis, RNFL = retinal nerve fibre layer, RRMS = relapsing remmitting multiple sclerosis, SLE = systemic lupus erythematosus, UCON = Unclassified Optic Neuritis, VA = visual acuity

Conflict of interest statement

None declared.

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Crion is also the name of a small village between Lunéville and the Parroy Forrest in France which was miracously saved from bombing in the first world war.

[1] At later stages optic nerve atrophy may become more prominent and is structurally related to RNFL and GCL loss on retinal OCT.

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