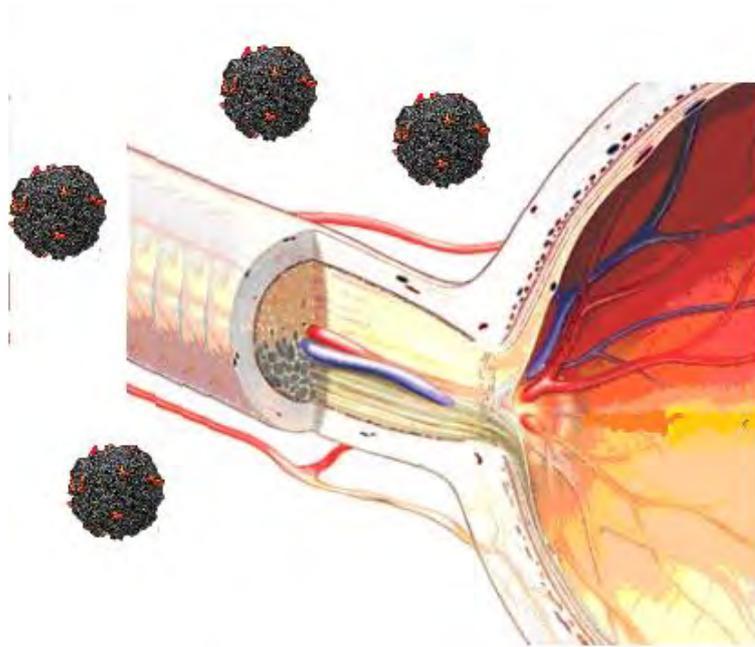


**Clinical profile, causes, and outcomes of optic neuritis at Groote Schuur Hospital**

By

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## DECLARATION

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Dated this \_\_\_\_\_ day of \_\_\_\_\_ 2016.

## ABBREVIATIONS

ADEM	Acute demyelinating encephalomyelitis
CCM	Cryptococcal meningitis
CMV	Cytomegalovirus
HAART	Highly active antiretroviral therapy
MS	Multiple sclerosis
NMO	Neuromyelitisoptica
ON	Optic Neuritis
ONTT	Optic Neuritis Treatment Trial
TB	Tuberculosis
TM	Transverse myelitis
TNF	Tumor necrosis factor
Toxo	Toxoplasmosis
VZV	Varicella zoster

## **ABSTRACT**

### **Objective**

To determine the clinical profile, causes and response to corticosteroid therapy in patients admitted and treated for optic neuritis at a tertiary hospital in Cape Town, South Africa.

### **Methods**

A retrospective case review was conducted of 117 patients admitted to Groote Schuur Hospital and treated for optic neuritis between January 2002 and December 2012. Inclusion criteria were based on clinical findings of acute optic nerve dysfunction with or without optic disc swelling. Demographic information, clinical presentation, course of illness, investigations performed and visual outcomes at discharge and at three month follow up were collected. Data analysis was performed using STATA version 10.0.

### **Results**

60 of 117 patients (51%) had an identifiable secondary cause for optic neuritis. Of the 57 patients with idiopathic optic neuritis only 14 had features of “typical optic neuritis” associated with demyelinating disease. HIV and syphilis accounted for 62% of secondary causes of optic neuritis. Presenting visual acuity of hand movements (HM) or worse and absence of pain with extra ocular movement were associated with poorer final visual outcomes in the idiopathic optic neuritis group.

### **Conclusion**

Optic neuritis in our patients, as elsewhere in Africa, tends to be atypical in presentation, with a high proportion of patients having an identifiable, most commonly infectious, cause. These patients thus require more extensive investigation in order to identify possible causes which may influence management. In settings with a high HIV prevalence, HIV and syphilis testing should form part of the routine first line investigations for patients with optic neuritis. Secondary optic neuritis and idiopathic atypical optic neuritis carry a poorer prognosis than typical demyelinating optic neuritis.

## **Part A - Protocol**

## 1. Introduction

### Problem

Optic neuritis is an inflammatory, infective or demyelinating process affecting the optic nerve.<sup>1</sup>The condition can be classified according to the segment of the optic nerve affected, thus it can be retrobulbar, it can affect the optic nerve head (papillitis), or it can affect the nerve head and retinal nerve fibre layer (neuroretinitis). Aetiologically it can be classified as demyelinating, parainfectious, infectious, non-infectious, or inflammatory.<sup>1</sup>

In the U.S.A, northern Europe and Australasia, demyelinating optic neuritis is the most common cause of painful visual loss in young adults.<sup>2</sup> Furthermore there is a high association in these regions with the systemic demyelinating condition multiple sclerosis. The estimated annual incidence of optic neuritis in the U.S.A is 5 per 100 000 (prevalence 115 per 100 000) which closely follows the epidemiology of multiple sclerosis.<sup>2,3</sup> In contrast multiple sclerosis is rare in Africa.<sup>4</sup> The estimated prevalence in South Africa is 3.5 per 100 000, being recorded predominantly in white people of European descent, though few isolated cases of mixed descent people have been recorded.<sup>4</sup> The landmark prospective Optic Neuritis Treatment Trial (ONTT) followed up 377 cases of optic neuritis over 15years, uncovering valuable information in terms of the clinical risk profile for the development of multiple sclerosis and the response to treatment with high dose corticosteroid therapy.<sup>2,3</sup>

The ONTT identified several clinical features with a high association with demyelinating disease coining the term “typical” features.<sup>2</sup> The main features identified were age (between 15 and 45years), pain on eye movement, no underlying systemic illness, deterioration in vision over a few days to two weeks, thereafter spontaneous improvement within two to three weeks, and unilateral visual loss.<sup>2,5</sup>The ONTT as well as meta-analyses of 12 randomised control trials revealed that corticosteroid therapy significantly improved short term visual acuity but had no statistically significant effect on long term visual outcome.<sup>2,5</sup>

The clinical experience at Groote Schuur Hospital is that the vast majority of our patients do not fit the typical profile of the ONTT. Furthermore the HIV epidemic confounds the clinical picture both due to the neurotrophic nature of the virus and associated opportunistic infections. The basis for the use of corticosteroid therapy stems from the ONTT. Patients thus require admission for three days of intravenous corticosteroids followed by oral therapy as an outpatient (despite there being no evidence for long term visual benefit).<sup>2,3</sup>

Pokroy et al looked at the clinical profile of cases of idiopathic optic neuritis in black Africans and their response to treatment.<sup>6</sup> In contrast to the ONTT they found that of the 10 patients in their study, the majority had bilateral consecutive or simultaneous disease and 15 out of

the 18 eyes had optic disc swelling.<sup>6</sup> They found that black African patients had a poorer visual prognosis compared to the patients in the ONTT.<sup>6</sup> The study however excluded secondary causes of ON in African patients. There is little information as to the causes of optic neuritis in an African population.

Storoni et al reported similar findings of atypical optic neuritis in patients of African or African-Caribbean backgrounds.<sup>7</sup> They further report that this group of patients has a disproportionately higher representation within the neuromyelitis spectrum of disorders than Caucasian patients in the study population.<sup>7</sup> Several studies have further shown a high incidence of aquaporin-4 antibody (a marker for neuromyelitisoptica) amongst patients with isolated atypical optic neuritis, furthermore NMO-seropositivity was shown to be a predictor of poor outcome.<sup>8,9</sup>

This study will look at all cases of optic neuritis admitted to and investigated at Groote Schuur Hospital. Clinical and demographic profiles of patients as well as secondary causes and response to treatment will be reported on.

## **1.2 Justification**

- To describe the clinical and demographic profile of patients with optic neuritis attending Groote Schuur Hospital (urban African community)
- To determine if there are any clinical or demographic features that help predict the course, final outcome and response to therapy
- To determine the causes of optic neuritis in the above population
- To determine the short term and long term visual outcome of patients affected with optic neuritis in the above population
- To determine the response to steroid therapy for optic neuritis in the above population
- To determine whether the above response to treatment justifies admission for and exposure to the side effects of corticosteroid therapy.

## **Objective**

Research questions:

- What are the clinical and demographic features of optic neuritis in patients attending Groote Schuur Hospital?
- What clinical or demographic features help predict the final visual outcome or the response to treatment with corticosteroids?

- What are the underlying causes of optic neuritis in this population?
- What is the short term and long term effect on visual outcome following treatment with corticosteroids?

## **2. Methods**

### **2.1 Study Design**

Type of Study – Descriptive and Analytical Retrospective case series

### **2.2 Sample Collection**

Medical records of patients admitted to Groote Schuur Hospital Department of Ophthalmology with optic neuritis from the period 2002 to 2012 will be collected for analysis.

Patient records for this period will be obtained via the clinicom system using the ICD 10 code H46.0.

### **2.3 Measurement**

Case records will be reviewed and the following data extracted for analysis:

#### **1. Demographic information**

- Age
- Gender
- Race

#### **2. Clinical Information (background and presentation)**

- Known ocular disease
- Known systemic disease
- Unilateral or bilateral involvement
- Pain with eye movement on presentation
- Presenting visual acuity both eyes
- Presenting Ishihara score both eyes
- Brightness and contrast scores both eyes
- Presence of relative afferent defect and grading
- Visual fields (if able to perform)
- Optic disc (swelling present or absent)

### **3. Investigations done and diagnosis if underlying cause present**

- CT scan (positive or negative findings)
- MRI findings (positive or negative for plaques suggestive of multiple sclerosis)
- Blood investigations (autoimmune markers, serum ACE, ESR, FBC, HIV, VDRL& FTA)
- Lumbar puncture (positive or negative findings)
- Secondary diagnosis if applicable

### **4. Follow up & Response to Treatment**

Visual acuity, Ishihara score & brightness appreciation

- at discharge (after three days of intravenous methylprednisilone)
- at first follow-up and time of first follow up (weeks – months)
- at final visit and time of last visit post onset

### **3. Analysis**

Data will be collated on Microsoft Excel spreadsheets and analysed using STATA version 9.0. The data will be collected as both numerical and categorical variables. Variables will be described, where appropriate, using means, medians and proportions. Univariate and multivariate analysis will be performed with appropriate statistical tests of significance (t-test for parametric data, Wilcoxon rank-sum for non-parametric data and Chi square or Fischers exact test for proportions). All statistical tests of significance will be based on a p value < 0.05.

The main analysis will focus on:

1. Clinical and demographic features that predict the course and outcome of optic neuritis in the population sample.
2. The response to treatment with a course of systemic steroids (three days of intravenous methylprednisilone followed by 11 days of oral prednisone) using visual acuity, Ishihara colour plate scores and subjective brightness appreciation as the measures of outcome.
3. The proportion of cases of optic neuritis that can be attributable to a secondary cause and those that are regarded as idiopathic.

## **4. Ethics & Communication**

### **4.1 Ethics**

Ethical approval for this study will be obtained from the University of Cape Town Faculty of Health Sciences Ethics Committee.

### **4.2 Reporting of Data**

A paper reporting the findings of the study will be submitted to a peer reviewed journal for consideration for publication.

## **5. Budget**

Nil required

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## **Part B – Literature review**

## **1. Objectives**

Optic neuritis is an inflammatory disorder of the optic nerve with multiple aetiologies<sup>1,2</sup>. In high income countries demyelinating disease, and more specifically multiple sclerosis, is the leading cause of optic nerve inflammation<sup>1,2</sup>. Multiple sclerosis (MS) predominantly affects female Caucasian patients<sup>1,2</sup>. The aetiology of optic neuritis in Africa, with high endemic rates of HIV infection and other infectious diseases, is poorly described. The objectives of this literature review are:

- To determine the clinical profile of optic neuritis in African patients / population;
- To determine the predominant aetiology of optic neuritis in African patients;
- To determine if HIV is a cause and/or risk factor for the development of optic neuritis;
- To determine the effect of steroid therapy for the treatment of optic neuritis in populations with a low multiple sclerosis incidence;
- To identify gaps in knowledge and the need for further research.

## **2. Literature search strategy**

The PubMed Health database was used to perform a search of relevant literature in peer reviewed journals. The search was conducted with the following keywords:

Optic neuritis + multiple sclerosis, atypical, typical, neuromyelitisoptica, African population, HIV, treatment, ADEM.

## **3. Summary and interpretation of literature**

### **3.1 Introduction**

Optic neuritis (ON) is defined as an inflammatory condition of the optic nerve<sup>1,2,3,4</sup>. The aetiology can be divided into demyelinating, infectious, para-infectious and non-infective inflammatory disorders<sup>1,2,3</sup>. The most common cause of optic neuritis worldwide is demyelinating disease, and in countries where multiple sclerosis is common this accounts for the majority of cases<sup>1,2,3,4</sup>. In the United States the incidence of optic neuritis is approximately 5/100 000, which closely follows the incidence of multiple sclerosis<sup>1,2,3</sup>. Optic neuritis is most commonly unilateral and tends to affect females more than males<sup>1,2,4</sup>.

### **3.2 Optic neuritis and demyelinating disease**

Demyelinating optic neuritis is the most common cause of unilateral, painful visual loss in young adults in the United States<sup>3</sup>. Most cases of optic neuritis are idiopathic but it is the initial manifestation of multiple sclerosis in approximately 20% of patients<sup>1,3</sup>.

MS is a demyelinating disease characterized by episodes of neurological fall out that are divided by both time and space<sup>5</sup>. There is a female preponderance with a male to female ratio of 1:5. Magnetic resonance imaging (MRI) on patients with MS typically shows periventricular plaques<sup>5,6</sup>. The landmark Optic Neuritis Treatment Trial (ONTT) was a multicenter randomized control trial with 15 year follow-up data looking at risk factors and treatment outcomes for MS related optic neuritis<sup>6</sup>. 389 patients were recruited and the study consisted of two components; the ONTT (consisting of three treatment arms) and the Longitudinal Optic Neuritis Study, which was a follow up of the clinical progression. The aims of the study were to describe the natural history of demyelinating ON, assess the benefits and risks of treatment with corticosteroid, and identify risk factors for the development of MS<sup>2,6</sup>. The ONTT identified those features which had a higher association with the development of MS giving rise to the term “typical optic neuritis”. The features of typical optic neuritis are summarized in Table 1<sup>4</sup>. One of the main findings of the study was the predictive value of MRI abnormalities or plaques and the risk of developing MS. The 15 year data shows that the risk of MS with typical optic neuritis and no plaques on MRI is 25%; with one or more plaques this risk increases to approximately 75%<sup>6</sup>.

Neuromyelitisoptica(NMO) is an acute inflammatory demyelinating disease affecting the optic nerves and spinal cord<sup>7</sup>. Episodes of demyelination tend to recur and optic nerve involvement may be unilateral or bilateral<sup>4,7</sup>. ON may precede or follow an episode of transverse myelitis<sup>7,8</sup>. The varied presentation of NMO often leads to its misdiagnosis as possible MS, and thus a new classification of NMO spectrum disorders was devised<sup>7</sup>. In a cohort of 175 patients 87% did not present with simultaneous onset bilateral ON and myelitis. Most presented with isolated unilateral ON, isolated bilateral ON, isolated myelitis or brainstem encephalitis<sup>9</sup>. More recently the serum antibody NMO-IgG has been identified and is found to be present in approximately 70% of cases<sup>9,10</sup>. The NMO antibody targets Aquaporin 4 channels and results in a cascade of events resulting in inflammation<sup>9,10,11</sup>. The NMO study group considers NMO-antibody testing to be the most important test in the work up of patients with suspected NMO<sup>10</sup>(See Table 2. Diagnostic criteria for NMO). Since the initial clinical presentation is varied, NMO-antibody testing helps differentiate these symptoms from possible MS<sup>10,11</sup>. Various groups have suggested the terms AQP4-Ab positive classical NMO (for patients presenting with ON and myelitis) and AQP4-Ab positive ‘high risk syndromes for NMO’ (for isolated ON, myelitis or encephalitis)<sup>10</sup>. Recent advances in retinal imaging using OCT have shown that a single attack of NMO ON causes more damage to the retinal nerve fibre layer (RNFL) than MS<sup>12</sup>. This may account for the poorer visual outcome in NMO<sup>12</sup>.

The pathogenesis of demyelinating conditions is not well understood but is thought to be a result of T cell mediated (MS), or antibody mediated (NMO) inflammation of the central and peripheral nervous system<sup>2</sup>. The release of cytokines and other inflammatory mediators causes neuronal cell death, resulting in demyelination and aberrant nerve conduction<sup>2</sup>. The possible role of molecular mimicry inciting an autoimmune response has also been postulated in particular with NMO and tuberculosis<sup>13,14</sup>. MS and NMO account for most cases of demyelinating disease; however, there are various other described conditions with clinical overlap.

Acute demyelinating encephomyelitis (ADEM) is a monophasic, multifocal demyelinating process which may have associated ON<sup>15</sup>. The ON is more commonly bilateral, severe and tends not to occur in isolation of systemic manifestations<sup>15</sup>. ADEM is often preceded by an immunological trigger such as a recent viral infection or vaccination<sup>15,16</sup>. It occurs more commonly in children and tends to occur in the winter months<sup>15</sup>. Neurological symptoms manifest within days of disease onset and encephalopathy is usually present early in the disease course<sup>15</sup>. The International Paediatric MS study group proposed diagnostic criteria to differentiate ADEM from MS<sup>15</sup>. The criteria include poly symptomatic neurology including encephalopathy, no previous evidence of demyelination and distinct radiological features<sup>15</sup>. There is a postulated link between HIV infection and the development of ADEM<sup>16</sup>. Raychaudhuri et al describe a case of the haemorrhagic variant of ADEM in a patient presenting with acute bilateral blindness as the presenting feature of his illness<sup>16</sup>. ADEM has been described both during seroconversion illness as well as late in the disease process<sup>16</sup>. Table 3 lists some of the differentiating features between ADEM, MS and NMO.

**Table 1. Typical and Atypical features of Optic Neuritis<sup>4</sup>**

Typical Optic Neuritis	Atypical Optic Neuritis
<ul style="list-style-type: none"> <li>• Acute to sub-acute onset – progressive over a few days to two weeks</li> <li>• Young adult patient, typically less than 45 years of age, but may be of any age</li> <li>• Periocular pain (90%), especially with eye movement – preceding or coinciding with visual loss</li> <li>• Unilateral loss of visual acuity – variable severity</li> </ul>	<ul style="list-style-type: none"> <li>• Age &gt;50yrs or &lt;12yrs</li> <li>• Absence of pain or severe pain</li> <li>• Severe visual loss</li> <li>• Systemic illness that can account for symptoms, including immune-suppression</li> <li>• Bilateral involvement</li> <li>• Gross disc swelling associated with haemorrhages</li> </ul>

<ul style="list-style-type: none"> <li>• Normal (65%) or swollen (35%) optic nerve head</li> <li>• Visual field defect – almost any type</li> <li>• Spontaneous visual improvement in &gt;90% starting within two to three weeks regardless of treatment</li> <li>• No deterioration in vision when corticosteroids are withdrawn</li> </ul>	
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**Table 2: Diagnostic criteria for NMO<sup>10</sup>**

<p><b>Definite NMO</b></p> <ul style="list-style-type: none"> <li>• Optic neuritis</li> <li>• Acute Myelitis</li> </ul> <p>+ at least two of the following</p> <ul style="list-style-type: none"> <li>• Contiguous MRI spinal cord lesion involving three or more vertebral segments</li> <li>• Brain MRI non-diagnostic for MS</li> <li>• NMO IgG seropositivity</li> </ul>
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**Table 3. Differentiating features between MS, NMO & ADEM**

	<u>MS</u>	<u>NMO</u>	<u>ADEM</u>
<b>Demographics</b>	<ul style="list-style-type: none"> <li>• Females &gt; males</li> <li>• 2-3<sup>rd</sup> decade</li> <li>• Caucasian</li> </ul>	<ul style="list-style-type: none"> <li>• 2-3<sup>rd</sup> decade</li> <li>• More common in Non-caucasians with atypical ON</li> </ul>	<ul style="list-style-type: none"> <li>• Children</li> </ul>
<b>Clinical Features</b>	<ul style="list-style-type: none"> <li>• Typical ON</li> <li>• Inter-nuclear ophthalmoplegia</li> <li>• Partial myelitis</li> <li>• Brainstem event</li> <li>• Events disseminated in space and time</li> </ul>	<ul style="list-style-type: none"> <li>• Transversemyelitis</li> <li>• Bilateral or unilateral ON</li> <li>• Endocrine disorders</li> </ul>	<ul style="list-style-type: none"> <li>• Encephalopathy</li> <li>• Seizures,</li> <li>• Ataxia</li> <li>• Depressed level of consciousness</li> </ul>
<b>Radiological</b>	<ul style="list-style-type: none"> <li>• Ovoid periventricular lesions perpendicular to axis of ventricle</li> </ul>	<ul style="list-style-type: none"> <li>• Contiguous spinal cord lesions over three or more vertebral segments</li> <li>• Extensive optic nerve and chiasmal lesions</li> </ul>	<ul style="list-style-type: none"> <li>• Multifocal diffuse white matter lesions with poor margins</li> <li>• Bilateral thalamic/basal ganglia involvement</li> <li>• Spraying of periventricular white matter.</li> </ul>

### **3.3 Optic neuritis in African patients**

Limited information is available on the causes and outcomes of ON in African populations. Pokroy et al looked at the clinical profile of cases of idiopathic ON in black Africans and their response to treatment<sup>17</sup>. In contrast to the ONTT they found that of the 10 patients in their study, the majority had bilateral consecutive or simultaneous disease and 15 out of the 18 eyes had optic disc swelling<sup>17</sup>. Black African patients also had a poorer visual prognosis compared to the patients in the ONTT<sup>17</sup>. The review, however, excluded secondary causes of ON in African patients.

Many case reports and series describe secondary causes for ON in African patients. The causes include malaria, syphilis, infectious meningitis and nutritional disorders<sup>18,19,20</sup>. Several reports of endemic optic neuropathy have been described particularly in Eastern and Central African countries and are thought to be a consequence of micronutrient deficiencies.

Plant et al report on an epidemic of optic neuropathy affecting young adults in coastal Tanzania<sup>20</sup>. 47% of cases had associated peripheral neuropathy. No cause was identified but the patients showed some clinical similarity to Strachan's syndrome and, although not confirmed, it was probably due to micronutrient deficiencies<sup>20</sup>. A similar epidemic is described in Somalia with 105 acute cases of optic neuropathy in young adults with evidence of a peripheral neuropathy<sup>21</sup>. Micro-nutrient deficiencies must thus be considered in patients presenting with bilateral optic neuritis with associated peripheral neuropathy. A follow up study in Dar-es-Salaam recruited 57 cases to identify a causal agent in Tanzanian epidemic optic neuropathy<sup>22</sup>. They found associations between low folate status, cooking indoors more than twice a week on coal or wood fired stoves, and an increased risk of developing optic neuropathy<sup>22</sup>.

### **3.4 Multiple sclerosis and neuromyelitisoptica in South African patients**

The global prevalence of MS varies between 2 and 150 / 100 000<sup>23</sup>. There are several studies which have tried to identify the MS rates in South Africa. Dean et al in 1967 reported an incidence of 13/100 000 in English speaking whites with 0 cases reported in black patients<sup>24</sup>. A follow up study in 1994 (using case records dating back to 1947) reported only six cases of possible MS in black South Africans<sup>25</sup>. Bhigjee et al reported on crude prevalence data in the Kwazulu Natal province of South Africa, with a prevalence of 25.63/100 000 in whites, 0.99/100 000 in blacks and 1.94/100 000 in people of mixed descent<sup>26</sup>. All of these studies seem to confirm that MS is uncommon in black and mixed ancestry people.

There is very limited information regarding the epidemiology of NMO in African countries, and there is also little information about global prevalence rates. The estimated prevalence of NMO is between 0.5 and 4.4 / 100 000<sup>27</sup>. Several clinic based studies also suggest that NMO is more common in non-white populations<sup>28,29</sup>. The geographic distribution of NMO may thus oppose that of MS<sup>28</sup>. The available literature is limited to several case reports and case series of the clinical manifestations of NMO.

Storoni et al reported findings of atypical ON in patients of African or African-Caribbean backgrounds<sup>30</sup>. They found that this group of patients has a disproportionately higher representation within the neuromyelitis spectrum of disorders than Caucasian patients in the study population<sup>30</sup>. A high incidence of aquaporin-4 antibody (a marker for NMO) has been found in patients with isolated atypical ON<sup>28,32</sup>. NMO-seropositivity was shown to be a predictor of poor outcome<sup>28</sup>.

Several studies have found a possible causal relationship between tuberculosis infection and NMO<sup>13,14</sup>. A review of 14 patients found an odds ratio of 4.6 for the presence of active TB versus the control group. A separate report also noted a close temporal relationship between pulmonary TB and the development of NMO and postulated that the mechanism was an immune reaction to tuberculosis.

MS is uncommon in African populations with black Africans having the lowest prevalence of the disease. Studies looking at ON in African or Afro-Caribbean populations have found that the clinical presentation is more atypical, that there is a higher association with NMO spectrum disorders, and that these patients thus carry a more guarded visual prognosis compared to MS related ON<sup>28,31</sup>.

Although accepted as distinct clinical entities there is some evidence that MS, NMO and other demyelinating conditions are part of a spectrum of disorders with a common pathogenetic mechanism<sup>31</sup>. Modi et al describe a series of cases of recurrent, remitting and relapsing demyelinating disease affecting black patients, with a female preponderance<sup>31</sup>. The cases showed a predominant clinical picture of NMO but had overlapping features of MS, NMO and ADEM<sup>31</sup>.

### **3.5 Optic neuritis and HIV**

Sub-Saharan Africa carries approximately two thirds of the global burden of HIV infection with an estimated 25 million infected individuals<sup>32</sup>. The overall prevalence of optic nerve disease in HIV ranges between 8% and 33%<sup>33,34,35,36</sup>. The neurotropic nature of the virus has been attributed as a direct cause of optic neuropathy in the absence of opportunistic infection; however, opportunistic infections must first be ruled out as an aetiology. The most

common opportunistic agents are cryptococcus, toxoplasma, varicella, syphilis and cytomegalovirus<sup>37</sup>.

Optic neuropathy can occur in any stage of the disease<sup>38</sup>. Case reports have described optic neuropathy as a primary presentation, and it may be part of the seroconversion illness<sup>37,39,40</sup>. A relapsing form of optic neuropathy similar to demyelinating disease has also been described<sup>41</sup>. There are several postulations about the pathophysiology of HIV optic neuropathy.

HIV infection can cause a microangiopathy<sup>42</sup>. Endothelial cell dysfunction and the unchecked activation of the platelet cascade leads to microvascular occlusive disease<sup>42</sup>. The proposed mechanism is an ischaemic neuropathy. Non-arteritic ischaemic optic neuropathy as a result of HIV infection, has been described in a young patient with no other vascular risk factors<sup>43</sup>.

HIV has been shown to directly invade the optic nerve<sup>44,45</sup>. Post mortem analysis of optic nerves in HIV positive individuals has shown mononuclear cell infiltration with oligodendrocyte and myelin degeneration<sup>45</sup>. The resultant insult is a product of HIV induced macrophage activity with cellular damage occurring as a result of cytokine and tumor necrosis factor (TNF) alpha release rather than by direct invasion by HIV<sup>45</sup>.

The neurotropic nature of HIV is well described<sup>46</sup>. The potential reservoir of virus in neuronal tissue leads to immune system dysfunction<sup>46</sup>. There is an increase in autoimmune markers during the seroconversion stage and then again during HAART therapy<sup>47</sup>. Multiple rheumatological conditions with an autoimmune basis have been described in patients during the above stages of viral infection<sup>47</sup>. There is thus a possible pathogenic role for an autoimmune based optic neuropathy particularly in recurrent or relapsing cases.

Non-nucleoside reverse transcriptase inhibitors are potentially toxic to mitochondria resulting primarily in lactic acidosis<sup>48</sup>. The additional mitochondrial insult may cause optic neuropathy in patients with a predisposition such as Lebers hereditary optic neuropathy<sup>49</sup>. Toxic optic neuropathy is also more commonly seen in patients on ethambutol therapy and HAART<sup>50</sup>. The possible effect of these drugs as an aetiology should be considered, particularly in patients with bilateral disease<sup>50</sup>.

### **3.6 Treatment for Optic Neuritis**

The Optic Neuritis Study Group published the findings of the Final Report of the Optic Neuritis Treatment Trial in 2008<sup>51</sup>. The data were based on a 15 year follow up of 389 patients recruited into the study between 1988 and 1991<sup>51</sup>. The study found that the greatest predictor of the development of ON was the presence of plaques on MRI scan<sup>51</sup>. The role of

corticosteroid therapy raised some important observations. High dose intravenous corticosteroids followed by a ten day oral tapering dose improved visual recovery time but had no effect on long term visual outcome versus placebo controls<sup>51</sup>. The use of oral corticosteroids seemed to increase the risk of a second neurological event in the first two years following treatment<sup>51</sup>. However this risk was not significant after two years<sup>51</sup>. A Cochrane review of the role of corticosteroid therapy has also found that steroids have no statistically proven benefit in terms of final visual outcome<sup>52</sup>. The vast majority of patients with typical ON have complete or near complete visual recovery following the initial episode<sup>51,52</sup>. The decision to treat patients with demyelinating ON with corticosteroids is dependent on the need for rapid visual recovery.

In contrast, there is a higher incidence of atypical ON in African or Afro-Caribbean populations. Pokroy et al reported poorer visual outcomes in 18 eyes treated with steroid therapy with only six eyes achieving a vision of 6/12 or better at three month follow up<sup>17</sup>. A higher association of NMO as well as relapsing optic neuritis was found in patients of African or Caribbean descent<sup>30</sup>. Therefore, ethnicity, needs to be considered in the investigation and management of patients presenting with optic neuritis, particularly with atypical features<sup>30</sup>. Most American and European centres have protocols for the treatment of isolated idiopathic ON based on the ONTT, a policy which has been adapted to other countries with different ethnic profiles. The use of steroids may prove of benefit in cases of atypical ON in preventing retinal nerve fibre layer injury<sup>12</sup>. Although patients with atypical ON have poorer outcomes compared to typical demyelinating ON, steroids may play a role in halting disease progression<sup>9,30</sup>. Furthermore, it will identify patients with poor response to steroids, or relapsing cases who need to be considered for long term steroid sparing immunosuppressive therapy.

Steroids have also been shown to have a benefit in both infectious and non-infectious inflammatory optic neuropathies<sup>53</sup>. Several case reports describe improvement in visual function following ON secondary to systemic lupus erythematosus, sarcoidosis and Wegeners granulomatosis<sup>54,55,56</sup>. These patients, however, required a longer steroid taper than that used in the ONTT and also required long term steroid sparing immunosuppressive therapy<sup>54,55,56</sup>.

Steroids have also been used in conjunction with definitive treatment for infectious ON. Several case reports describe the use of steroid therapy in combination with anti-retroviral therapy for the treatment of HIV associated ON<sup>57,58,59</sup>.

There is no clear consensus on the type and route of administration of steroid therapy. Several series have shown dexamethasone to be as effective as methylprednisone with the

added advantage of lower cost<sup>60</sup>. Omoti et al describe the effective use of sub-tenonsdepo-methylprednisolone acetate, followed by oral prednisolone for the treatment of optic neuritis<sup>61</sup>. In the three reported cases all recovered visual acuity to 6/6<sup>61</sup>.

There is no randomized control trial looking at steroid versus placebo treatment for the treatment of AQP-4 positive isolated or atypical optic neuritis.

### **3.7 Need for further research**

The clinical spectrum of optic neuritis in an African population group is not well described. Several studies mentioned above have confirmed the low prevalence of MS in Sub-Saharan Africa, yet the clinical profile, causes, and outcomes of ON in an African population has not been elucidated. The role of HIV and other infectious diseases impact on the presentation and outcome of optic neuritis is not well understood.

The treatment of ON at Groote Schuur Hospital involves admission for baseline serological and imaging studies and treatment with intravenous methylprednisone, followed by tapering oral prednisone (as described in the ONTT). Patients of African lineage have a higher incidence of atypical ON and the effect of steroid therapy on disease progression has not been well established.

This study aims to describe the clinical profile of ON presenting to the Groote Schuur Hospital ophthalmology unit, to describe the secondary causes of optic nerve inflammation and to determine the outcomes of ON. The findings of this study will allow one to assess the possibility of a treatment based study comparing various treatment arms versus placebo to determine whether steroid therapy is indeed beneficial for the treatment of atypical, idiopathic ON in an African population.

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## **Part C – Publication ready format**

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## **Clinical profile, causes, and outcomes of optic neuritis at Groote Schuur Hospital**

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### **Introduction**

Optic neuritis is defined as an inflammatory condition of the optic nerve<sup>1</sup>. The aetiology can be divided into demyelinating, infectious, para-infectious and non-infective inflammatory disorders<sup>1</sup>. The most common cause of optic neuritis worldwide is demyelinating disease, and in countries where multiple sclerosis is common, this accounts for the majority of cases<sup>1,2,3</sup>. In the United States the incidence of optic neuritis is approximately 5/100 000, which closely follows the incidence of multiple sclerosis<sup>1,2,3</sup>. Optic neuritis is most commonly unilateral and tends to affect females more than males<sup>1,2,3</sup>. The optic neuritis treatment trial identified those features which had a higher association with the development of multiple sclerosis giving rise to the term “typical optic neuritis”<sup>4</sup>. The features of typical optic neuritis include acute vision loss over two weeks with recovery by four to six weeks, pain on extra-ocular movement, age between 15-45 years, unilateral involvement, and no other systemic illness to account for the symptoms<sup>1</sup>.

In contrast African populations tend to have more atypical presentations of optic neuritis and a lower prevalence of multiple sclerosis<sup>5,6</sup>. Limited information is available on the clinical profile, causes and outcomes of optic neuritis in African populations. We describe the clinical profile, causes and outcomes of cases admitted to the Groote Schuur Hospital with optic neuritis.

### **Methods**

A retrospective analysis of 117 case records of patients admitted to Groote Schuur Hospital and treated for optic neuritis between January 2002 and December 2012 was conducted. Inclusion criteria were based on clinical findings of acute optic nerve dysfunction with or without optic disc swelling. Acute optic nerve dysfunction was defined by the following clinical signs; visual loss, presence of an afferent papillary defect, dyschromatopsia (objectively measured using Ishihara test plates edition 7) and decreased light brightness appreciation. All patients admitted with acute optic nerve dysfunction were investigated with serological tests, chest x-rays (to help exclude sarcoid and tuberculosis), imaging in the form of a contrasted CT scan and cerebro-spinal fluid (CSF) analysis if no contra-indication to lumbar puncture were present. Serological tests performed were aimed at excluding

systemic conditions known to be associated with optic neuritis, thus an auto-immune screen (rheumatoid factor, ANA, c and p ANCA, anti ds-DNA and anti-phospholipid antibody), serum angiotensin converting enzyme, HIV serology, serum RPR and FTA, erythrocyte sedimentation rate and full blood count with differential was conducted. All patients admitted for optic neuritis were treated with systemic steroids in the form of 3 days of intravenous methylprednisone (1gm daily), followed by 10 days of 1mg/kg oral prednisone. NMO antibody testing was not available during the study period. Demographic information, clinical presentation, course of illness, investigations performed and visual outcomes at discharge and at three month follow up were collected. Patients who had positive serological tests, chest x-rays, CSF analysis or abnormalities of neuro-imaging suggestive of a possible secondary cause were labeled as having secondary optic neuritis. Treatment for the secondary cause was instituted as appropriate. Patients who had negative serology, chest x-rays, neuro-imaging and CSF analysis were labeled as having idiopathic optic neuritis. The idiopathic groups were then sub-divided as being atypical or typical. Atypical optic neuritis was defined as having any one of the following clinical criteria; profound vision loss (worse than count fingers vision), visual loss of 3 or more weeks with no improvement, bilateral involvement, absence of pain and age >50 years or < 12years. The data was collated in an excel spreadsheet and then analysed using STATA version 10.0. Wilcoxon-Mann Whitney rank-sum test was used to test significance of associations. Logistic regression analysis was also used to test significance in multivariate analysis.

Ethical approval for the study was obtained from the Human research and ethics committee of the University of Cape Town.

## **Results**

Figure one shows the numbers of secondary and idiopathic optic neuritis, and the numbers of idiopathic optic neuritis with typical and atypical features.

Figure two shows the causes of secondary optic neuritis.

Table one shows the demographic and clinical profile of secondary and idiopathic optic neuritis.

Table two shows the outcomes at discharge and 3 month follow up of secondary and idiopathic optic neuritis.

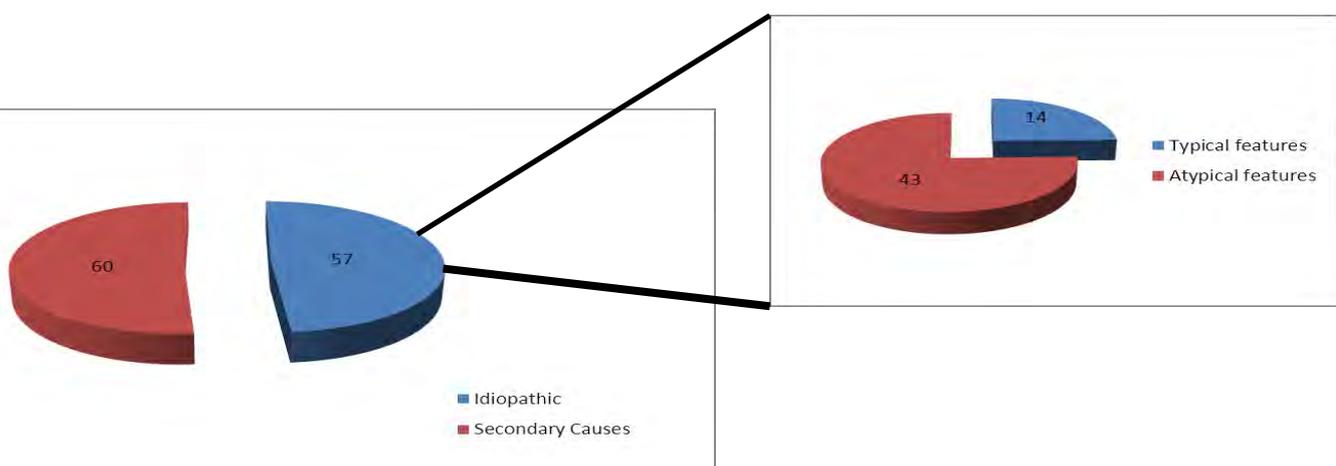
Patients with secondary optic neuritis and idiopathic atypical optic neuritis with a presenting visual acuity (VA) of HM or worse had a poorer outcome at follow up (mean VA =1.53

LogMAR vs 0.81 LogMAR,  $p = 0.015$ ) compared to patients with better than HM presenting vision in the same group.

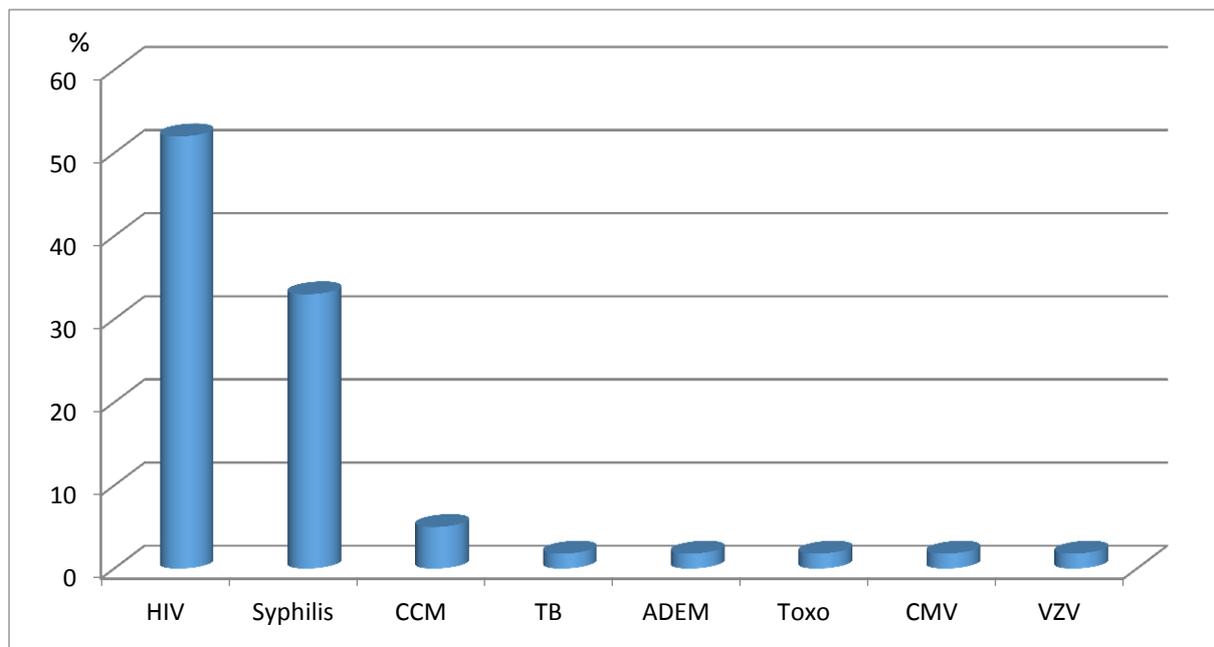
There were four cases (4 of 117) in which the CT scan was abnormal. Two had a pituitary tumour, one had a tuberculous granuloma and one had non-specific cerebral atrophy. MRI was only performed for patients in whom there was a high index of suspicion for demyelination, thus the majority of MRI scans were performed on patients with typical optic neuritis. 13 of 20 MRI scans (11 performed for patients with typical ON and 2 for idiopathic atypical ON) were abnormal, with the predominant finding being areas of non-specific white matter abnormal signal, possibly indicating demyelination. Serum angiotensin converting enzyme, full blood count and erythrocyte sedimentation rate were normal in all cases. The only blood investigations that yielded positive results were the HIV (28 cases) and serum FTA (12 cases). Lumbar puncture was performed in 90 of 117 cases. 70 of the 90 cases yielded normal CSF findings. The predominant finding in abnormal lumbar punctures was a mild leukocytosis with normal total protein (15 cases). Three cases demonstrated cryptococcal meningitis (CCM), one was cytomegalovirus PCR positive and one was varicella zoster PCR positive. In these patients visual loss from optic nerve inflammation was the presenting feature of their disease.

No difference in mean VA at 3 month follow up was demonstrated for unilateral vs bilateral disease or for the presence of disc swelling at presentation in any of the 3 subgroups analysed.

Of the 14 patients with typical optic neuritis four patients went on to develop possible multiple sclerosis (three of mixed descent and one Indian), and one white patient had clinically definite multiple sclerosis. No cases of multiple sclerosis were found in black patients.



**Fure 1. Numbers of secondary and idiopathic optic neuritis, and idiopathic optic neuritis with typical or atypical features**



**Figure 2. Causes of secondary optic neuritis**

(CCM = cryptococcal meningitis, TB = tuberculosis, ADEM = acute demyelinating encephalomyelitis, Toxo = toxoplasmosis, CMV = cytomegalovirus, VZV = varicella zoster)

**Table 1. Demographic & clinical profile of secondary and idiopathic optic neuritis**

	Secondary	Idiopathic atypical	Idiopathic typical
<b>Number</b>	60	43	14
<b>Age</b>			
Mean	36.34	40	35.36
Median	35	39	32
Min	14	20	18

	Max	79	62	52
<b>Gender</b>				
	Male	23	13	11
	Female	37	27	3
<b>Race</b>				
	Black African	40	18	1
	Caucasian	3	2	2
	Mixed ethnic	16	18	10
	Indian / asian	1	5	1
<b>Papillitis</b>		40	23	8
<b>Bilateral</b>		27	12	0
<b>Pain on EOM</b>		18	10	14
<b>Time from onset to presentation (days)</b>				
	Mean	15.06	8.35	10.64
	Median	7	7	7
	Min	1	1	1
	Max	168	28	56
<b>Presenting VA (LogMAR)</b>				
	Mean	2.2	2.35	1.05
	Median	2	2.5	0.9
	Min	0.2	0.2	0.2
	Max	4	4	2
<b>Presenting Ishihara (score out of 14)</b>				
	Mean	1.4	0.5	5
	Median	0	0	1
	Min	0	0	0
	Max	14	12	12

**Table 2. Outcomes of secondary and idiopathic optic neuritis**

	<b>Secondary</b>	<b>Idiopathic atypical</b>	<b>Idiopathic typical</b>
<b>VA at discharge (LogMAR)</b>			
<b>Mean</b>	1.38 (+/- 1.14)	1.44 (+/-1.16)	0.36 (+/-0.51)
<b>Median</b>	0.9	1.4	0.2
<b>Min</b>	0	-0.1	0
<b>Max</b>	4	4	2

<b>VA at 3month follow-up (LogMAR)</b>			
<b>Mean</b>	1.34 (+/- 1.26)	1 (+/- 1.17)	0.23 (+/- 0.52)
<b>Median</b>	1	0.3	0.1
<b>Min</b>	-0.1	-0.1	-0.1
<b>Max</b>	4	4	2
<b>Ishihara at discharge</b>			
<b>Mean</b>	3.06 (+/-4.97)	4 (+/-5.09)	10.5 (+/-3.93)
<b>Median</b>	0	0	12
<b>Min</b>	0	0	0
<b>Max</b>	0	14	14
<b>Ishihara at 3month follow-up</b>			
<b>Mean</b>	4.68(+/-5.8)	6.6(+/-6.09)	12.14(+/-3.7)
<b>Median</b>	0	5	13.5
<b>Min</b>	0	0	0
<b>Max</b>	14	14	14

## **Discussion**

Optic neuritis in the study population differs from that reported in Europe and the United States with the majority of patients either having a secondary cause or having atypical features.

38(69%) of 55 patients with secondary optic neuritis tested for HIV were positive. Absence of pain and optic disc swelling are more common features of optic neuritis in the study group. In the idiopathic atypical group, the absence of pain, profound visual loss and bilateral disease are the main clinical features deviating from the typical features of the optic neuritis treatment trial (ONTT).<sup>4</sup>

Pokroy et al looked at the clinical profile of cases of idiopathic optic neuritis in black patients and their response to treatment.<sup>6</sup> In contrast to the ONTT they found that of the 10 patients in their study, the majority had bilateral consecutive or simultaneous disease and 15 out of the 18 eyes had optic disc swelling.<sup>4,6</sup> Black patients had a poorer visual prognosis compared to the patients in the ONTT.<sup>4,6</sup> The review did not look at secondary causes of optic neuritis in black patients. Idiopathic optic neuritis in our study population is predominantly atypical, in keeping with these findings.

Similar findings of atypical optic neuritis are reported in patients of African or African-Caribbean backgrounds.<sup>5</sup> This group of patients had a disproportionately higher representation within the neuromyelitis spectrum of disorders than caucasian patients in the study population.<sup>5</sup> Several studies have further shown a high incidence of aquaporin-4 antibody (a marker for neuromyelitis optica) amongst patients with isolated atypical optic

neuritis.<sup>5,7,8</sup> Neuromyelitis optica seropositivity was shown to be a predictor of poor outcome.<sup>5,7,8</sup>

There are several studies which have tried to identify the multiple sclerosis rates in South Africa. Dean et al reported an incidence of 13/100 000 in English speaking whites with no cases reported in black patients<sup>9</sup>. In a follow up study in 1994, only six cases of possible multiple sclerosis in black South Africans was found<sup>10</sup>. A study on crude prevalence data in the Kwazulu-Natal province of South Africa found a prevalence of 25.63/100 000 in whites, 0.99/100 000 in blacks, and 1.94/100 000 in people of mixed descent<sup>11</sup>. All of these studies seem to confirm that multiple sclerosis in black and mixed ancestry people is uncommon. Although the study population is small and the time frame not long enough, our study seems to also suggest that demyelinating optic neuritis associated with MS is uncommon in black patients.

The ONTT identified risk factors predicting multiple sclerosis associated optic neuritis<sup>4</sup>. The identification of these features helped to identify cases in which extensive investigation would prove unhelpful and therefore unnecessary<sup>2</sup>. In our study 4 of the CT scans performed revealed unusual causes of acute optic nerve dysfunction. 2 cases revealed a pituitary adenoma (with compressive optic neuropathy), 1 tuberculous granuloma and 1 generalized cerebral atrophy (thought to be part of advanced HIV disease). Both cases of pituitary adenoma and the tuberculous granuloma showed an initial response to steroid treatment. The cases of pituitary adenoma were referred to neurosurgical services and anti-tuberculous therapy was initiated in the patient with a tuberculous granuloma. Our study population has a high proportion of secondary and atypical idiopathic optic neuritis, and thus African patients with optic neuritis require thorough investigation for causes other than demyelinating disease as this may influence treatment.

The ONTT as well as meta-analyses of 12 randomised control trials revealed that corticosteroid therapy significantly improved short term visual acuity recovery but had no statistically significant effect on long term visual outcome.<sup>2,4</sup> Furthermore the natural course of MS related optic neuritis is recovery of visual function even without therapy. The clinical experience at Groote Schuur Hospital is that the majority of patients do not fit the typical profile of the ONTT. Furthermore the HIV epidemic confounds the clinical picture both due to the neurotropic nature of the virus, and associated opportunistic infections. Steroid therapy may play a more important role in treating optic nerve inflammation (in combination with the appropriate treatment for identified secondary causes), and preventing permanent visual loss in African patients with optic neuritis, where the multiple sclerosis incidence is low.

The secondary, idiopathic atypical and idiopathic typical optic neuritis groups all seemed to show some improvement of visual acuity with steroid therapy. Gains in visual acuity were most pronounced in the idiopathic typical group, in keeping with demyelinating optic neuritis.. A small case series describes the use of subtenons steroid for the treatment of optic neuritis in black patients with good clinical response<sup>12</sup>. Studies on the use of dexamethasone in Indian populations have also shown good response to therapy<sup>13</sup>.

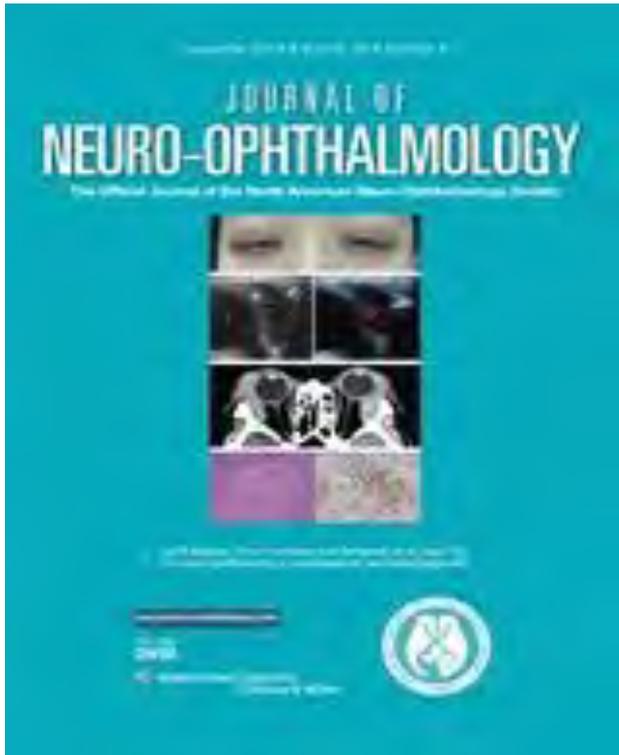
### **Conclusion**

Optic neuritis in African populations, with a low prevalence of multiple sclerosis, tends to be atypical in presentation, with a high proportion of patients having an identifiable secondary, most commonly infectious cause. In settings with a high HIV prevalence, HIV and syphilis testing should form part of the routine first line investigations for patients presenting with optic neuritis. Thorough investigation for possible secondary causes should be undertaken as these may influence management. Secondary optic neuritis and idiopathic atypical optic neuritis carry a poorer prognosis than typical demyelinating optic neuritis.. A weakness of our study is that it is a retrospective case note review. A prospective study to assess various regimens of steroid therapy, and the role of neuromyelitis optica serology in our patients would be helpful.

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1. Manrique RK, Noval S, Aguilar-Amat MJ, Arpa J, Rosa I, Contreras I. Ophthalmic features of spinocerebellar ataxia type 7. *J Neuroophthalmol.* 2009; 29:174-179

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*Online journal*

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## **Appendices**

**Appendix 1.Data Capture Form for patients admitted with Optic Neuritis**

<b>Name</b>		<b>Coding</b>
<b>Folder No.</b>		
<b>Age</b>		
<b>Gender</b>		1= female  2= male
<b>Race</b>		1= Black  2= White  3= Mixed race  4= Indian / asian
<b>Ocular disease</b>		1=Yes  2= No
<b>Systemic disease</b>		1= Yes  2= No
<b>Uni / Bilateral</b>		1= Unilateral  2= Bilateral
<b>Optic disc swelling</b>		1= yes  2= no
<b>Time from onset to presentation (days)</b>		
<b>Presenting visual acuity</b>		

<b>Right</b>		
<b>Presenting visual acuity</b> <b>Left</b>		
<b>Ishihara at presentation</b> <b>Right</b>		
<b>Ishihara at presentation</b> <b>Left</b>		
<b>Pain on eye movement</b>		<b>1 = yes</b> <b>2= no</b>
<b>Brightness score Right</b>		
<b>Brightness score Left</b>		
<b>RAPD and grade</b>		
<b>Visual field defect</b>		<b>1=Centrocaecalscotoma</b> <b>2 = enlarged blind spot</b> <b>3 = total filed loss</b> <b>4 = other</b>
<b>CT findings</b>		<b>1 = Normal</b> <b>2= abnormal</b>
<b>MRI findings</b>		<b>1= normal</b> <b>2= abnormal</b>

<b>Lumbar puncture findings</b>		<b>1= Normal</b> <b>2= abnormal</b>
<b>Blood Investigations:</b> <ul style="list-style-type: none"> <li>• S-ACE</li> <li>• ESR</li> <li>• Autoimmune</li> <li>• VDRL</li> <li>• FTA</li> <li>• HIV</li> <li>• FBC</li> </ul>		<b>1= normal</b> <b>2= abnormal</b>
<b>Secondary diagnosis</b>		
<b>Visual acuity at discharge Right</b>		
<b>Visual acuity at discharge Left</b>		
<b>Ishihara score at discharge Right</b>		
<b>Ishihara score at discharge Left</b>		
<b>Brightness score at discharge Right</b>		
<b>Brightness score at discharge Left</b>		
<b>Visual acuity at 1st follow up &amp; time (weeks)</b>		

<b>Right</b>		
<b>Visual acuity at 1st follow up &amp; time (weeks)</b> <b>Left</b>		
<b>Ishihara score at 1st follow up Right</b>		
<b>Ishihara score at 1st follow up Left</b>		
<b>Brightness score at 1st follow up Right</b>		
<b>Brightness score at 1st follow up Left</b>		
<b>Visual acuity at last follow up &amp; time (weeks)</b> <b>Right</b>		
<b>Visual acuity at last follow up &amp; time (weeks)</b> <b>Left</b>		
<b>Brightness score at last follow up Right</b>		
<b>Brightness score at last follow up Left</b>		
<b>Ishihara score at last</b>		

<b>follow up Right</b>		
<b>Ishihara score at last follow up Left</b>		

## Appendix 2. Department of surgery research committee approval



UNIVERSITY OF CAPE TOWN

### Department of Surgery

Departmental Research Committee  
Professor Anwar Suléman Mall

J-45 Room Old Main Building, Grooté Schuur Hospital,  
Observatory 7925, South Africa

Tel (021) 406 6168/6232/6227 FAX (021) 448 6461  
Email: [Anwar.Mall@uct.ac.za](mailto:Anwar.Mall@uct.ac.za)

6<sup>th</sup> August 2012

Dr H Mustak  
Department of Surgery  
Division of Ophthalmology  
Grooté Schuur Hospital  
University of Cape Town

Dear Dr Mustak,

**RE: PROJECT 2012/088**

**PROJECT TITLE: Clinical profile, causes and outcomes of optic neuritis at Grooté Schuur Hospital**

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

**Signed**

PROFESSOR ANWAR S MALL  
CHAIRMAN: RESEARCH COMMITTEE

### Appendix 3. Human research ethics committee approval

HREC Ref 618/2012 – 23Nov2012

UNIVERSITY OF CAPE TOWN



Faculty of Health Sciences  
Human Research Ethics Committee  
Room E52-24 Groote Schuur Hospital Old Main Building  
Observatory 7925  
Telephone [021] 406 6338 • Facsimile [021] 406 6411  
e-mail: shuretta.thomas@uct.ac.za

23 November 2012

**HREC REF: 618/2012**

**Dr H Mustak**  
Ophthalmology  
D4, NGSH

Dear Dr Mustak

**PROJECT TITLE: CLINICAL PROFILE, CAUSES AND OUTCOMES OF OPTIC NEURITIS AT GROOTE SCHUUR**

Thank you for responding to the issues raised by the Faculty of Health Sciences Human Research Ethics Committee in your letter received 23<sup>rd</sup> November 2012.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**Approval is granted for one year till the 30<sup>th</sup> November 2013**

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: [www.health.uct.ac.za/research/humanethics/forms](http://www.health.uct.ac.za/research/humanethics/forms))

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

**Please quote the HREC. REF in all your correspondence.**

Yours sincerely

A grey rectangular box with the word "Signed" written in a large, black, serif font.

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, FHS HUMAN ETHICS**  
Federal Wide Assurance Number: FWA00001637.

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This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

s.thomas