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Longitudinally extensive transverse myelitis: a descriptive clinical study

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LONGITUDINALLY EXTENSIVE TRANSVERSE MYELITIS:

A DESCRIPTIVE CLINICAL STUDY

Ismail Moola

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment for the degree of Master of Medicine in the division of Neurology

Johannesburg 2017

I. Declaration

I, Ismail Moola, do hereby declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine in the division of Neurology. This research report is submitted in the publishable format as recognized by the Faculty of Health Sciences. I further declare that this work has not been submitted for any other examination or degree at this or any other University.

……

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FACULTY OF HEALTH SCIENCES

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II. Dedication

To my parents, Iqbal and Munira, for always providing me with unlimited support, guidance, encouragement and love.

To my other parents, Yussuf and Rashida, for your unwaivering patience and support.

To my dearest wife, Farzahna, for your understanding, motivation, unconditional love and being my partner throughout every challenge of life.

To my beloved son, Muhammad Zaydan, for inspiring me.

For my family

III. Presentations originating from this research

- Selected for poster presentation at the congress of Neurological Association of South Africa, Bloemfontein, South Africa, 1st-4th March 2017

- Awarded best poster presentation at the congress of Neurological Association of South Africa, Bloemfontein, South Africa, 1st-4th March 2017

IV. Ethical considerations

Permission for this prospective study was obtained from Professor G. Modi (Head of Division of Neurology, Department of Neurosciences) and the Human Research Ethics Committee of the University of Witwatersrand (clearance number – M150114).

V. Abstract

Background: Transverse myelitis (TM) is a term used to describe inflammation of the spinal cord. A small segment of the spinal cord is usually involved. However, when TM is severe enough to cause T2 weighted hyper-intensities extending across three or more vertebral segments on sagittal spinal magnetic resonance imaging (MRI), it is given the term: longitudinally extensive transverse myelitis (LETM). LETM is an infrequently encountered condition and the incidence of this syndrome is not well described. Recent studies show that the frequency of LETM ranges from 2 to 10% of patients with TM. The causes of LETM can be broadly divided into demyelinating, autoimmune, infectious and miscellaneous. LETM is the most specific radiological finding of the neuromyelitis optica spectrum disorders (NMOSD) and has been extensively described in this condition. NMOSD has been typically found in human immunodeficiency virus (HIV) negative patients. Furthermore, LETM itself is not well described in HIV positive patients.

Aims: Firstly, to describe the clinical characteristics and aetiology of patients with LETM in a South African setting. Secondly, to describe LETM in HIV positive patients.

Methods: 22 Adult patients presenting with LETM to the division of Neurology of the University of the Witwatersrand were included in this prospective study. Patients were recruited from Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Chris Hani Baragwanath Academic Hospital (CHBAH) and Helen Joseph Hospital (HJH). The study population were recruited over approximately 2 years. Results: The aetiology of LETM in this population was as follows: 15 patients were diagnosed as NMOSD, 4 patients had an infective cause, 1 had an ischaemic myelopathy and 2

had an unknown or idiopathic LETM. In terms of HIV status, 15 subjects were HIV negative and 7 were HIV positive. Of those that were HIV positive, 3 patients had tuberculous myelitis causing LETM and 4 met NMOSD diagnostic criteria.

Conclusion: NMOSD is a common cause of LETM and is suggested by cervical involvement compared to a thoracic LETM which suggests non-NMOSD causes. In HIV positive patients with LETM, NMOSD is less likely and alternative diagnoses should be excluded, especially infective causes. Nevertheless, NMOSD occurs in HIV positive patients and may be associated with a high viral load.

VI. Acknowledgements

- I am especially grateful to Professor Modi for guidance as my supervisor and making this research possible

- To my loving family for all their support

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X. Nomenclature

AB	Antibody
ADEM	Acute disseminated encephalomyelitis
ANA	Antinuclear antibody
AQP4	Aquaporin 4
AZA	Azathioprine
CBA	Cell based assay
CD4	Cluster of differentiation 4
CNS	Central nervous system
CRMP-5	Collapsin response-mediator protein-5
CSF	Cerebrospinal fluid
DWI	Diffusion-weighted imaging
EDSS	Extended Disability Status Scale
ELISA	Enzyme-linked immunosorbent assay
ENA	Extractable nuclear antigen
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HTLV1	Human T-lyphotropic virus 1
IgG	Immunoglobulin G
IPND	The International Panel for Neuromyelitis optica Diagnosis
IQR	Interquartile range
IVMP	Intravenous methylprednisolone
IVIG	Intravenous immunoglobulin
LETM	Longitudinally extensive transverse myelitis
MOG	Myelin oligodendrocyte glycoprotein
MRI	Magnetic resonance imaging

MS	Multiple Sclerosis
NMO	Neuromyelitis optica
NMOSD	Neuromyelitis optica spectrum disorders
PLEX	Plasma exchange
SCD	Subacute combined degeneration of the spinal cord
SDAF	Spinal dural arteriovenous fistula
SS	Sjogren’s syndrome
SLE	Systemic lupus erythematosus
T1WI	T1-weighted image
T2WI	T2-weighted image
TB	Tuberculosis
TBA	Tissue-based assay
TM	Transverse myelitis

Chapter 1: Protocol and extended review of the literature

1.1 Introduction

Transverse myelitis (TM) is a term used to describe inflammation of the spinal cord. A small segment of the spinal cord is usually involved. Causes of TM include demyelinating conditions such as Multiple Sclerosis (MS), infections and systemic inflammatory auto-immune disorders. However, when TM is severe enough to cause T2 weighted hyperintensities extending across three or more vertebral segments on sagittal spinal magnetic resonance imaging (MRI), it is given the term: longitudinally extensive transverse myelitis (LETM).[1]

LETM is an infrequently encountered condition and the incidence of this syndrome is not well described. Recent studies show that the frequency of LETM ranges from 2 to 10% of patients with TM.[2] These findings may be inaccurate, as patients with MS or neuromyelitis optica (NMO) were excluded, and the studies were of a small sample size. Furthermore, an accurate reflection of the prevalence of TM in general is also not well known. Thus, a true reflection of the incidence and prevalence of LETM is unknown, but there is a consensus within the literature that it is a condition which is becoming increasingly recognised. The causes of LETM can be broadly divided into demyelinating, infectious, miscellaneous and idiopathic. The miscellaneous category includes neuro-inflammatory, vascular, neoplastic-related and metabolic causes.

In order to guide appropriate and prompt investigations, it is imperative to recognise LETM early. A working diagnosis needs to be formulated quickly as this has major implications on the management and future outcome of the condition. If left undiagnosed and untreated, disastrous consequences may ensue.[2] Thus, one has to be aware of LETM and its common causes.

1.2 Demyelinating diseases and LETM

The demyelinating causes of LETM include neuromyelitis optica spectrum disorders (NMOSD), MS and acute disseminated encephalomyelitis (ADEM). LETM is the most specific radiological finding of NMOSD.[1,3]

1.2.1 Neuromyelitis optica spectrum disorders (NMOSD)

1.2.1.1 Background

NMO or Devic's disease was first described in the late 19th century and is now a well-known cause of LETM. NMO is a severe central nervous system (CNS) demyelinating disorder involving characteristically, as the term neuromyelitis optica suggests, the optic nerves and spinal cord. Traditionally, Devic's disease was used to describe patients with a monophasic illness consisting of acute or subacute bilateral optic neuritis, preceded or followed within days or weeks by a severe myelitis.[1-3] Initially, lesions outside the optic nerves or spinal cord excluded the diagnosis of NMO.[1]

In 2004, Lennon *et al* reported on an NMO antibody (AB), which is more than 90% specific for NMO and is not found in patients with MS.[1,4] The target antigen of this AB was subsequently found to be aquaporin 4 (AQP4), the predominant water channel of the CNS, located in astrocytic foot processes at the blood-brain barrier.[5] The detection of this AB and additional studies revealed that patients with NMO may have cerebral lesion/s, which are often clinically silent, and more importantly are not in keeping with MS.[1] Thus, the 2006 diagnostic criteria for NMO required 1) optic neuritis, 2) myelitis, and 3) at least two of three supportive criteria: a) MRI evidence of a contiguous spinal cord lesion extending over 3 or more segments in length (LETM), b) onset brain MRI non-diagnostic for multiple sclerosis, or c) NMO-antibody seropositivity.[1] This combination of diagnostic criteria were found to be 99% sensitive and 90% specific for NMO.[1]

Since the discovery of the specific NMO AB, patients have been identified with isolated optic neuritis or LETM, with positive AQP4-AB.[6] The 2006 diagnostic criteria for NMO did not include these patients with initial features of NMO or NMO variants. In 2007, these conditions became collectively known as the neuromyelitis optica spectrum disorders (NMOSD).[6] NMOSD included patients with isolated optic neuritis or LETM with AQP4-AB, recurrent myelitis, or recurrent isolated optic neuritis.[1,6] The NMOSD were at that time, unified by the presence of AQP4-AB.[4,5] Further advances in the AQ4-AB allowed detection and improvement on the spectrum of non-opticospinal characteristics of NMO.[3] These findings rendered the 2006 criteria inadequate for current use.[3]

1.2.1.2 Current diagnostic Criteria for NMOSD

Almost a decade later, in 2015, the International Panel for NMO Diagnosis (IPND) proposed updated diagnostic criteria in order to incorporate the NMOSD.[3] Two major points were outlined. Firstly, NMO and its related spectrum disorders would both be incorporated into the umbrella term NMOSD.[3] The reason for this is that the conditions are similar in terms of clinical behaviour, immunopathology and treatment.[3] Furthermore, patients with incomplete forms of NMO may later develop the "classical" syndrome.[3] The historically significant term NMO would be entrenched into the new title NMOSD as most patients, despite non-opticospinal manifestations, eventually develop typical opticospinal disease.[3] Secondly, the international consensus diagnostic criteria would be based on combining clinical, radiological and serological testing.[3]

The criteria divide diagnosis of NMOSD into two groups; NMOSD with AQP4-Immunoglobulin G (IgG) and, NMOSD without AQP4-IgG or where AQ4-IgG status is unknown.[3] In the AQ4-IgG positive group, at least one of six core clinical characteristics needs to be met in order to make the diagnosis.[3] The core clinical characteristics consist of the following CNS regions: 1) optic nerves, 2) spinal cord, 3) area postrema of the dorsal medulla, 4) brainstem, 5) diencephalon, and 6) cerebrum.[3]

Table I: NMOSD diagnostic criteria for adult patients[32]

Diagnostic criteria for NMOSD with AQP4-IgG

1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses[a]

Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (2 or more different core clinical characteristics)
   c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses[a]

Core clinical characteristics

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure 3)
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions (figure 3)

Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status

1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm (figure 1)
2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis (figure 1)
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions (figure 2)
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions (figure 2)

Abbreviations: AQP4 = aquaporin-4; IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis lesions; NMOSD = neuromyelitis optica spectrum disorders.

A few clinical syndromes implicating the optic nerves, spinal cord and area postrema are particularly suggestive of NMOSD.[3] These include; optic neuritis that is simultaneously bilateral, involves the chiasm or more than half of the optic nerve length, causes an altitudinal visual field defect, or causes severe residual visual loss.[3] Other features are a complete (rather than partial) myelopathy, and an area postrema syndrome causing intractable hiccups or nausea and vomiting.[3]

In the AQ4-IgG negative or unknown group, two or more core clinical characteristics need to occur with dissemination in space.[3] At least one of these needs to be one of the three most common NMOSD features: optic neuritis, symptomatic LETM or an area postrema syndrome with associated medullary MRI lesion.[3] Where applicable, additional MRI requirements are also necessary for this diagnostic group (Table 1).[3] The two core features may occur with a single attack or multiple attacks.[3] Thus, making the diagnosis in this AQ4-IgG negative/unknown group is more challenging as more features need to be detected with additional caveats. However, it allows a positive diagnosis of NMOSD to be made in the absence of AQ4-IgG. This is of great benefit in situations where AQ4-Ab is not available or initially negative.

The panel further concluded that a diagnosis of NMOSD cannot be made in patients with isolated asymptomatic AQ4-IgG positivity or asymptomatic compatible MRI lesions, as at least one symptomatic clinical attack is necessary.[3] The clinical course of asymptomatic patients with either positive serology or neuro-imaging is not well known.[3] Also, diagnostic criteria are not met if a single feature is present in the absence of AQ4-IgG as there is no single pathognomonic core characteristic of NMOSD.[3] Similarly, no single feature excludes the diagnosis.[3] However, there are "red flags" that may suggest an alternative diagnosis (Table 2).[3]

Table II: Red flags: Findings atypical for NMOSD[33]

Red flags (clinical/laboratory)
1. Clinical features and laboratory findings
Progressive overall clinical course (neurologic deterioration unrelated to attacks; consider MS)
Atypical time to attack nadir: less than 4 hours (consider cord ischemia/infarction); continual worsening for more than 4 weeks from attack onset (consider sarcoidosis or neoplasm)
Partial transverse myelitis, especially when not associated with LETM MRI lesion (consider MS)
Presence of CSF oligoclonal bands (oligoclonal bands occur in <20% of cases of NMO vs >80% of MS)
2. Comorbidities associated with neurologic syndromes that mimic NMOSD
Sarcoidosis, established or suggestive clinical, radiologic, or laboratory findings thereof (e.g., mediastinal adenopathy, fever and night sweats, elevated serum angiotensin converting enzyme or interleukin-2 receptor levels)
Cancer, established or with suggestive clinical, radiologic, or laboratory findings thereof; consider lymphoma or paraneoplastic disease (e.g., collapsin response mediator protein-5 associated optic neuropathy and myelopathy or anti-Ma-associated diencephalic syndrome)
Chronic infection, established or with suggestive clinical, radiologic, or laboratory findings thereof (e.g., HIV, syphilis)
Red flags (conventional neuroimaging)
1. Brain
a. Imaging features (T2-weighted MRI) suggestive of MS (MS-typical)
Lesions with orientation perpendicular to a lateral ventricular surface (Dawson fingers)
Lesions adjacent to lateral ventricle in the inferior temporal lobe
Juxtacortical lesions involving subcortical U-fibers
Cortical lesions
b. Imaging characteristics suggestive of diseases other than MS and NMOSD
Lesions with persistent (>3 mo) gadolinium enhancement
2. Spinal cord
Characteristics more suggestive of MS than NMOSD
Lesions <3 complete vertebral segments on sagittal T2-weighted sequences
Lesions located predominantly (>70%) in the peripheral cord on axial T2-weighted sequences
Diffuse, indistinct signal change on T2-weighted sequences (as sometimes seen with longstanding or progressive MS)

Abbreviations: LETM = longitudinally extensive transverse myelitis lesions; MS = multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders. These are some common or key findings that should prompt thorough investigation for competing differential diagnoses before making a diagnosis of NMOSD.

1.2.1.3 Epidemiology

A review of population based studies in Europe, South Asia, the Caribbean and Cuba reveal that the incidence of NMOSD varies between 0, 05-4 per 100 000 and the prevalence ranges from 0,5-4 per 100 000.[7] Mean age at onset was found to be between 33 to 46 years but NMOSD has been described in paediatric cases and older adults.[7] 66-88% of NMOSD are estimated to be female, which is in keeping with female dominance in auto-immune diseases.[7] In relapsing NMOSD, female prevalence is approximately 80% compared to an almost equal gender distribution in monophasic disease.[7]

NMOSD may have a higher prevalence in the black population; however this may be over-estimated due to the lower incidence of MS in this race group.[8,9] Ethnicity has also been shown to affect clinical phenotype and outcome.[7] Due to the uncommon occurrence of NMOSD and most of the epidemiological data being documented prior to the revised 2015 diagnostic criteria, the true demographics of this disorder is not well known.

1.2.1.4 LETM in NMOSD

As stated earlier, LETM is the most specific finding of NMOSD, and is less common in other demyelinating diseases.[1,3] The LETM lesion in NMOSD is characterised by a hypointensity on T1-weighted images (T1WI), a hyperintensity on T2-weighted images (T2WI), may enhance after gadolinium administration, typically involves the central grey matter and may cause cord swelling.[3,10] The cervical and upper thoracic

cord is more commonly affected in NMOSD.[10] Another distinct characteristic of cervical LETM in NMOSD is the extension of the lesion into the medulla.[3,10]

The LETM lesion in this spectrum of disorders tends to fragment into smaller lesions after treatment with steroids and during remission.[10] Additionally, recurrent attacks of myelitis may lead to spinal cord atrohy.[10] This emphasises the importance of obtaining spinal cord imaging early during the presentation of a myelopathy as it may be missed if the MRI is done later in the course of the disease.

1.2.1.5 NMOSD Antibodies

The discovery of AQ4-AB revolutionised the diagnosis of NMOSD as it allowed this condition to be considered as a distinct demyelinating disorder. This antibody was first included in the 2006 diagnostic criteria due to its high specificity in diagnosing NMO and distinguishing it from MS.[1] As already mentioned, AQ4-AB detection allowed for the broadening of the phenotype of NMOSD and lead to the current 2015 diagnostic criteria.[3]

Although patients with LETM may meet NMOSD criteria irrespective of AQ4-AB status, there are some observed differences based on the AQ4-AB status. There is a greater chance of relapse in patients with LETM who are positive for AQ4-AB and this is estimated to be about 60% within 1 year of initial LETM.[3,11] LETM and AQ4-AB negative patients are more commonly associated with a monophasic disorder.[3,11] In a study of 76 LETM patients, Kitley *et al* (2013) found a higher proportion of females,

especially women older than 45 years of age, in those that were AQ4-AB positive, versus younger males (less than 35 years) with more common involvement of the conus in those that were AQ4-AB negative.[12] Furthermore, positive AQ4-AB status is strongly associated with systemic auto-immune disorders.[3,12]

The sensitivity and specificity of the AQ4-AB differs depending on which assay is used. Based on a recent meta-analysis, the approximate sensitivity for the cell based assay (CBA) is the highest at 76% whereas the tissue-based assay (TBA) and the enzyme-linked immunosorbent assay (ELISA) test were 59% and 65% respectively.[13] The mean specificity of all 3 tests were between 97-99%.[13] This is extremely beneficial as there in minimal doubt to the diagnosis when the test is positive. However, it may be challenging when the test is negative as the lower sensitivity may yield false negative results. A further challenge is that the CBA is not easily available and thus negative results from less sensitive tests do not exclude the diagnosis.

Retesting of a suspected false negative result should be during an acute attack or relapse and, if possible, before immunotherapies are instituted or during a treatment-free period or with a more sensitive test.[3,14] This is due to the observation that antibody levels are highest during relapses and are reduced with immunosuppressive therapy.[3,14]

Between 10-30% of NMOSD patients remain AQ4-AB negative despite the most sensitive cell based assays.[15] Some of these patients have been shown to have antibodies targeting myelin oligodendrocyte glycoprotein (MOG).[3,15] Some features of MOG-AB positive NMOSD included a less female dominance, younger age and was more associated with optic neuritis (versus myelitis), caudal myelitis, monophasic attacks and better recovery.[3,15] Some of these features are strikingly similar to the phenotype observed in AQ4-AB negative cases and thus MOG antibodies may be responsible for this group of patients. This suggests that there may be an alternative pathogenesis in these patients, yet this remains to be determined.[3]

1.2.1.6 NMOSD and systemic autoimmune disease overlap

There is a strong association between LETM and non-organ specific systemic autoimmune conditions, especially Sjogren's syndrome (SS) and systemic lupus erythematosus (SLE).[16,17] In a large study of NMOSD, 47% of patients were found to have positive antinuclear antibody (ANA) or extractable nuclear antigen (ENA) antibodies, with 3% fulfilling clinical diagnostic criteria for SLE or SS.[16] Interestingly, AQ4-AB were not found in any patients with SLE or SS who did not have clinical features of NMOSD and this finding was reproduced in other similar studies.[16-18] Thus, the presence of AQP4-AB with LETM in the clinical context of SLE or SS likely represent the coexistence of two autoimmune conditions rather than LETM being the complication of SLE/SS.[16,17]

NMOSD has also been associated with other autoimmune diseases such as thyroid disease, myasthenia gravis and celiac disease.[3,18] These autoimmune diseases are not known to cause destructive CNS pathology and thus further emphasizes the point that NMOSD may coexist with systemic autoimmune disease.[18]

From a practical point of view, any patient presenting with LETM should be tested for AQ4-AB and investigated to meet NMOSD diagnostic criteria, regardless of possible or known rheumatological disease.[3,18] If other autoimmune antibodies are found in the presence of LETM, a co-existing rheumatological or autoimmune disease should be pursued based on the clinical presentation.[3,18] The presence of LETM and a rheumatological diagnosis actually favours the concurrent diagnosis of NMOSD, and LETM should not be considered due to the rheumatological disease itself.[3,18]

1.2.1.7 Human immunodeficiency virus (HIV) and NMOSD

The co-occurrence of human immunodeficiency virus (HIV) and NMOSD is uncommon and the literature regarding this association consists predominantly of case reports.[19-22] At the time of clinical presentation of these reported cases, some were receiving highly active antiretroviral therapy (HAART) and the cluster of differentiation 4 (CD4) counts and HIV viral loads were variable.[19-22] Almost all received intravenous (IV) steroids and a few received long term immunosuppression with inconsistent responses.[19-22] Prior to 2017, only 3 patients were documented to be both HIV and AQ4-AB positive.[20-22]

A recently published review of NMOSD patients in the Kwa-Zulu Natal province of South Africa revealed the largest documented number of HIV positive patients with NMOSD.[23] A retrospective review was performed over 9 years and 12 HIV positive patients with a NMOSD presentation were identified.[23] Of the 10 HIV positive patients that were tested for AQ4-AB, 4 were dual HIV and AQ4-AB positive.[23] As this was a retrospective review, it is uncertain if the HIV seroconversion in these patients occurred prior or subsequent to their NMOSD presentation.[23]

Considering the HIV epidemic in South Africa, co-existence with NMOSD seems to be unusual. However, in the correct clinical context, both diagnoses may occur. Due to the scarcity of literature, there is no evidence to guide treatment in these rare instances. Balancing immunosuppression in an already immunocompromised patient may pose a therapeutic dilemma.

1.2.1.8 Treatment of NMOSD

Treatment of NMOSD is aimed at reducing AQ-4 AB induced central nervous system inflammation. [24] Disability is dependent on the severity and number of attacks.[24,25] Goals of therapy are therefore directed at reducing attack severity and preventing future attacks.[24,25] The specific therapeutic options include immunosuppression, B-cell depleting agents and plasma exchange (PLEX).[24,25]

There are no prospective randomised controlled trials to guide therapy and thus treatment guidelines are based on case studies and expert opinion.[24,25] Intravenous

methylprednisolone (IVMP) at a dose of 1000mg per day for at least 3 to 5 days is the recommended guideline for initial treatment of an acute attack of NMOSD.[24,25] If there is no significant improvement after IVMP, 5 cycles of PLEX should be considered in an attempt to aid recovery.[24,25] Intravenous cyclophosphamide or intravenous immunoglobulin (IVIG) may be of benefit in acute refractory cases.[24,25]

Low dose oral prednisolone and PLEX may be used long-term as preventative therapy.[24] Prednisolone also serves as a bridge between acute and preventative treatment and can be used as an adjunct if dual preventative therapy is required.[25] Due to the high side effect profile of long term prednisolone use, steroid-sparing agents are typically instituted.[24,25] Azathioprine (AZA), mycophenolate mofetil and rituximab are generally recommended as 1st line preventative agents whereas mitoxantrone and methotrexate are reserved for refractory cases.[24,25] The selection of long term immunosuppression should be based on patient side effect profile, comorbidities, availability, cost and physician's familiarity with the use of the agent.[24,25] To re-emphasize, there is no class I evidence available to direct therapy in NMOSD and thus optimal dosages and duration of treatment is unknown.[24,25] However, based on case series and expert opinion, these agents seem to be moderately to highly effective.[24,25]

Immunomodulatory drugs used in the treatment of MS may adversely affect outcome in NMOSD and thus need to be avoided.[24,25] Interferon beta, natalizumab and fingolimod have been shown to worsen disease activity in NMOSD.[24] Thus,

differentiating between NMOSD and MS is essential in order to select appropriate treatment.

1.2.2 LETM in MS

Unlike LETM in NMOSD, spinal cord lesions in MS tend to be shorter (two or less spinal segments) and predominantly involve lateral and dorsal white matter asymmetrically within the cord.[2,3,26] Chronic or progressive MS may produce coalescent cord lesions that appear as indistinct hyper-intensities on MRI and may mimic a LETM.[3,26] However, there have been reports of LETM occurring in adult MS patients at an estimated frequency of about 3%.[2,27] In contrast to NMOSD, LETM in MS may be shorter (4,5 versus 7,1 vertebral lengths) and is less likely to be associated with cord expansion, hypointensity on T1WI or gadolinium enhancement.[2] Up to 15% of relapsing remitting MS in children may have a LETM.[2,3]

Within the previously termed “optico-spinal variant of MS”, the frequency of LETM was found to be much higher, up to 59%.[2,27] However, according to the new NMOSD diagnostic criteria, these patients most likely represent NMOSD and thus should no longer be considered a variant of MS.[3]

Brain imaging in a patient with LETM may aid in differentiating typical MS or NMOSD features.[3,26] Typical areas of involvement in MS include peri-ventricular, juxtacortical, infratentorial and spinal cord.[26] The revised 2010 McDonald criteria should be used in a patient suspected of having MS and these criteria need to be excluded if a

diagnosis of NMOSD is made.[3,26] As eluded to earlier, this differentiation is vital to guide therapy.

1.2.3 LETM in ADEM

ADEM is characterised by encephalopathy, large multifocal areas of cerebral demyelination and may involve small segments of the spinal cord.[26] In a minority of adult patients, ADEM has also been reported to cause spinal cord lesions which are longer than two vertebral segments.[2] In paediatric ADEM, LETM has been reported in up to 90% of cases.[2,26] Thus, paediatric LETM is less specific for NMOSD and occurs with a higher frequency in ADEM and MS.[3]

A preceding infection occurs in the majority of patients with ADEM.[2] Therefore, an infection may infrequently cause LETM via the induction of ADEM.[2] However, infections are more likely to result in LETM directly.[2]

1.3 Infective causes of LETM

About 10% of TM constitute infectious or para-infectious causes which, almost always, present with clinical and cerebrospinal fluid (CSF) features of meningitis.[26] Infectious agents that have been reported to directly cause LETM include syphilis, Human T-lymphotropic virus 1 (HTLV1), CNS tuberculosis (TB) and parasitic infections such as Schistosomiasis, Toxocara canis and Ascaris Suum.[2,26,27] Hence, features of meningitis in the presence of LETM should prompt urgent investigation to diagnose a suspected infection and expedite specific therapy.

Infections may also indirectly cause LETM by activating ADEM or NMOSD.[2] The infectious agents documented to induce NMOSD consist of varicella zoster virus, cytomegalovirus, Epstein Barr virus, HIV, dengue, hepatitis A, mycoplasma pneumonia and TB.[2] Thus, the presence of a specific infection does not always implicate the infection as the cause of a LETM and a diagnosis of NMOSD or ADEM should be considered in the correct clinical context.[2]

1.3.1 TB and LETM

About 1% of all TB cases constitute CNS TB, of which approximately half involves the spine.[28] It is estimated that 7% of patients with spinal TB have intramedullary lesions in the form of radiculomyelitis, TM, intraspinal granulomas and thrombosis of the anterior spinal artery.[28] LETM is very rarely a complication of TB myelitis but several cases have been described.[26,28] One needs to also consider that a syrinx or intraspinal tuberculoma, which may complicate TB meningitis/myelitis, may produce an intraspinal hyperintensity on T2WI but these have different characteristics to a typical LETM.[26,28]

Interestingly, pulmonary TB has been associated with NMOSD by a number of case reports.[2,28] The proposed mechanism is an immune-mediated inflammatory demyelination initiated by pulmonary TB. [28] Therefore, pulmonary TB may lead to a LETM via activation of NMOSD or CNS TB may lead to a LETM. Both of these

mechanisms need to be considered in any patient with a LETM and suspected TB, especially due to the increased incidence of TB in a high HIV setting.

1.3.2 HIV and LETM

To recapitulate, HIV has been suggested to possibly trigger NMOSD, or HIV could predispose to opportunistic infections which could cause LETM or may also trigger NMOSD.[2,27,28] The potential mechanisms of HIV causing LETM indirectly have been discussed yet there is a lack of evidence within the literature that HIV may cause LETM directly.

HIV-associated vacuolar myelopathy is a well described syndrome and has been found in up to a third of some post mortem series.[27] Radiological studies describing spinal cord MRI findings in patients with HIV have revealed predominantly cord atrophy, with or without signal changes.[27,29] These atrophic lesions may be longitudinally extensive but none were shown to cause cord expansion or enhance with contrast.[27,29] Vacuolar myelopathy may cause an atrophic cord with signal change that possibly meets the LETM definition. However, a diagnosis of LETM due to HIV-associated vacuolar myelopathy needs to be made with caution and by exclusion, as there are more likely causes, especially if the clinical presentation is not chronic.

1.4 Miscellaneous causes of LETM

1.4.1 Neuro-inflammatory

1.4.1.1 Neurosarcoidosis

Neurosarcoidosis is an inflammatory granulomatous disease and accounts for 5-10% of systemic sarcoidosis.[26,27] The spinal cord is affected in only 0, 3% of sarcoidosis.[26] Intramedullary spinal cord lesions are generally iso-intense on T1WI, variable on T2WI, enhance with gadolinium and may cause cord expansion.[26] Myeloradicular enhancement with a LETM, in the context of respiratory disease, could favour a diagnosis of neurosarcoidosis.[26] A definitive diagnosis is made by biopsy of the CNS or systemic lesion.[26,27]

1.4.1.2 Neuro-Behcet's disease

Behcet's disease is a vasculitic disorder characterised by systemic features such as apthous and genital ulcers, uveitis, iritis and pathergy.[27,30] The occurrence of neuro-Behcet's varies between 5-50% of patients and is well described.[27] Spinal cord involvement is reported in up to 14% of Behcet's disease and when myelitis does occur, it tends to be longitudinally extensive and involve both gray and white matter.[27] Diagnosis of Behcet's disease is based on clinical criteria.[27]

1.4.2 Vascular

1.4.2.1 Spinal cord infarction

Spinal cord infarction develops within minutes, accounts for about 1% of all strokes and is most commonly due to occlusion of the anterior spinal artery.[26,27] Spinal or aortic vascular surgery, dissection of an aortic aneurysm or vertebral artery, hypotension, vasculitis or atherosclerosis may predispose to ischaemia of the spinal cord.[26,27] In the acute to subacute stage, ischaemia produces a longitudinally extensive hyperintensity on T2WI, may enhance post contrast, could result in cord enlargement and restricted diffusion is seen on diffusion-weighted imaging (DWI).[26] In the chronic stage, the classical MRI finding of "snake eyes" (T2-weighted hyperintesities in the ventral grey matter with sparing of the dorsal horns on axial images) is usually seen.[26] Ischaemic lesions may be distinguished by its tendency to affect specific areas of the cord, such as C1 to C3, C4 to C7, T3 to T7 and T8 to conus.[2]

1.4.2.2 Spinal dural arteriovenous fistula

Spinal dural arteriovenous fistulae (SDAF) are the most common type of spinal vascular malformations and lead to spinal venous congestion.[26] SDAF typically causes a chronic thoracic myelopathy, usually in elderly males and may be exacerbated by movement or the valsalva manoeuvre.[2] Venous hypertension results in cord oedema which is detected on MRI as a longitudinally extensive T2 hyperintensity.[2,26] The specificity of SDAF is increased if flow voids are present which indicate dilated intradural veins.[2,26] The gold standard for SDAF diagnosis is

spinal angiography and therapy such as embolization may be instituted at the same setting.[26,27]

1.4.3 Neoplastic - related

1.4.3.1 Intramedullary Spinal Cord Tumours

Most spinal tumours are extramedullary with metastatic disease being the most common.[26] Intramedullary spinal cord tumours are rare and consist largely of ependymomas and astrocytomas.[2,26] These tumours tend to present insidiously and radiologically appear hypo-isointense on T1WI, hyperintense on T2WI, extend across multiple segments and cause focal enlargement of the spinal cord.[2,26] Ependymomas avidly enhance post contrast whereas astrocytomas partially enhance.[26]

1.4.3.2 Paraneoplastic phenomenon

Paraneoplastic myelopathy is a well-described yet rare entity.[2] In some studies of paraneoplastic myelopathies, between 42-47% had LETM.[2,30] The most common antibodies found in paraneoplastic LETM include anti-collapsin response-mediator protein-5 (CRMP-5) and anti-amphiphysin.[2,30] These antibodies are both associated with small cell carcinoma of the lung and anti-amphiphysin is also associated with breast cancer.[2] Paraneoplastic LETM, in the absence of antibodies, has also been found in lymphoma, oesophageal and thyroid cancer.[2]

There have been suggestions that NMOSD may occur as a paraneoplastic phenomenon.[2,23] However, the current NMOSD diagnostic guidelines consider an underlying malignancy as an atypical feature or red flag for NMOSD.[3] Therefore, a LETM should be considered as paraneoplastic if found in the context of a malignancy and a neoplastic screen should be performed in any unexplained LETM.

1.4.3.3 Radiation myelopathy

Delayed post-radiation demyelination of the spinal cord might occur after treatment for throat, neck, mediastinal and thoracic tumours.[2,26] The LETM lesions usually develop 1-2 years post-radiation and may be associated with cord expansion and enhancement.[26,27] Chronic lesions show spinal cord atrophy.[26,27] A radiological clue to this diagnosis is the hyperintense signal change in the adjacent vertebral bodies on T1WI.[26] A specific history of previous radiation exposure is thus necessary in any LETM patient.

1.4.4 Metabolic

LETM may be caused by subacute combined degeneration of the spinal cord (SCD) due to vitamin B12 deficiency.[2,26] Copper deficiency is another cause of LETM and may occur in isolation or with SCD.[2,26] Both of these deficiency states produce similar clinical and radiological findings of a subacute to chronic dorsolateral spinal cord syndrome.[2,26] The LETM typically involves the posterior and lateral columns.[2,26] It is vital to check for vitamin B12 and copper levels in the setting of LETM as these deficiencies are potentially reversible.

1.5 Idiopathic LETM

In a study of 108 patients with isolated LETM, 42 were classified as having idiopathic sero-negative LETM.[31] AQ4-AB negative status was confirmed by using 3 different assays and MOG-AB was also tested.[31] Infectious, vascular, neoplastic, post radiation and metabolic causes of the LETM were excluded.[31] Unlike NMOSD, these patients had different clinical features such as male predominance, older age at onset and milder syndromes.[31] This suggests that this group of patients may represent a separate disease entity with a possible distinctive underlying pathophysiology.

1.6 Motivation for research study

Patients with LETM are not an uncommon presentation to our Neurology division. With the availability of MRI facilities and resources to detect AQP4-AB, patients can be efficiently assessed for NMOSD. Other diagnoses can also be explored with appropriate investigations. In our HIV epidemic setting, there is an opportunity to evaluate patients presenting with LETM and explore the possible interplay between HIV and LETM. To my knowledge, this will be the first research study specifically investigating LETM in South Africa.

Aim

The aim of this study is to describe the clinical profile of patients with longitudinally extensive transverse myelitis (LETM)

Study Objectives

1. Primary Objectives

    a) To describe the study population

    b) To describe the spectrum of disease causing LETM that is AQ4-Ab negative

    c) To develop a clinical diagnostic approach to patients with LETM in a South African setting

2. Secondary Objectives

    a) To compare AQ4-Ab positive and negative patients with LETM

    b) To compare HIV positive and negative patients with LETM

    c) To describe a relationship between AQP4-Ab and HIV in LETM patients

Methods

1. Study Design

   Prospective study

2. Study Setting

   The Neurology Division of the Department of Neurosciences, University of the Witwatersrand. Patients presenting to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Chris Hani Baragwanath Academic Hospital (CHBAH) and Helen Joseph Hospital (HJH) will be used.

3. Study population

   a) Inclusion Criteria

      i. All adult patients presenting with LETM

   b) Exclusion Criteria

      i. Children with LETM

      ii. Patients meeting the definition of LETM due to trauma

      iii. Patients meeting the definition of LETM secondary to spinal column pathology

4. Sampling Method

   A convenience sampling method will be used

5. Sampling Size

   A minimum of 10 patients with LETM meeting inclusion and exclusion criteria will be used

6. Sample Selection

   Patients presenting with LETM from the 1st of March 2015 to 31st of December 2016 will be used

7. Measurement Instruments/Tools

   Collection of data will be done by using a data collection sheet (see Appendix C)

8. Investigations – all investigations performed are routine in any patient presenting with a myelopathy, and no additional investigations will be requested for the study.

   a) The following investigations will be performed on all patients:

      - Full blood count (FBC)
      - Urea & electrolytes (UE)
      - Calcium, magnesium, phosphate (CMP)
      - Liver function tests (LFT)
      - HIV
      - C-reactive protein (CRP)
      - Erythrocyte sedimentation rate (ESR)
      - Serum angiotensin converting enzyme (S- ACE)
      - Syphilis
      - Full Autoimmune screen
      - Vitamin B12 level
      - Serum Copper and caeruloplasmin level
      - Thyroid stimulating hormone (TSH)
      - Cerebrospinal fluid analysis
      - MRI brain and spinal cord
      - AQP4-Ab (in patients with LETM on MRI)

   b) Other specific investigations will be performed if clinically indicated on an individual patient basis

9. Data Analysis
    a) Data will be captured using an excel spreadsheet
    b) This will be achieved using a descriptive clinical analysis
10. Ethics
    a) The protocol will be submitted for ethics approval to the Human Research Ethical Committee of the University of the Witwatersrand
    b) Consent will be obtained from each patient used in the study
    c) Data confidentiality: Each data sheet (see Appendix C) will be assigned a study number only. Neither patient names nor hospital numbers will be recorded. Any association between the study numbers, patient initials and identity of patients will be kept separate.
11. Study Strengths
    a) The first study to describe LETM patients in South Africa
    b) The first study to evaluate a potential relationship between HIV and LETM
    c) The first study to evaluate a potential relationship between HIV and AQP4-Ab
    d) The data will be collected from a single researcher only. This will ensure that the data is collected in a standardised manner and is reliable. The use of data collection sheets, will standardise the data collection process
12. Study Limitations
    a) Selection Sampling Bias:

       The study population only includes patients presenting to the Neurology division of the University of the Witwatersrand, and thus the sample is not a true representative of the entire population

b) Sample size:

The small sample size will limit the validity of results

13. Funding

The funding of this audit, if required, will be provided by the doctor conducting the audit. No extra cost will be imposed on the hospital or the patient. In essence the study will be self-funded

14. Timing

The study will commence once approval is received. The audits expected duration is approximately 30 months. Depending upon clinical commitments of the primary investigator, the audit time frame may be shorter or longer

The following Gantt chart shows the estimated timeline of the study:

	July - Dec 2014	Jan - Feb 2015	Mar - Jun 2015	Jul - Sep 2015	Oct - Dec 2015	Jan-Jun 2016	Jul - Dec 2016
Literature review							
Protocol preparation							
Protocol Assessment							
Ethics application							
Data Collection							
Data Analysis							
Writing up paper							

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Chapter 2: Proposed Manuscript

Background

Introduction

Transverse myelitis (TM) is a term used to describe inflammation of the spinal cord. A small segment of the spinal cord is usually involved. However, when TM is severe enough to cause T2 weighted hyperintensities extending across 3 or more vertebral segments on sagittal spinal magnetic resonance imaging (MRI), it is given the term: longitudinally extensive transverse myelitis (LETM).[1]

LETM is an infrequently encountered condition and the incidence of this radiological syndrome is not well described. Studies show that the frequency of LETM ranges from 2-10% of patients with TM.[2] The causes of LETM can be broadly divided into demyelinating, infectious, miscellaneous and idiopathic. The miscellaneous category includes neuro-inflammatory, vascular, neoplastic-related and metabolic causes.

Neuromyelitis Optica Spectrum Disorders (NMOSD)

The demyelinating causes of LETM include neuromyelitis optica spectrum disorders (NMOSD), multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM). LETM is the most specific radiological finding of NMOSD and is much less common in MS and ADEM.[1-3] The LETM lesion in NMOSD is characterised by a hypointensity on T1-weighted images (T1WI), a hyperintensity on T2-weighted images (T2WI), may enhance after gadolinium administration, typically involves the central grey matter and may cause cord swelling.[3,4] The cervical and upper thoracic cord is more commonly affected in NMOSD.[4] Another distinct characteristic of cervical LETM in NMOSD is the extension of the lesion into the medulla.[3,4]

LETM is 1 of 6 core characteristics of NMOSD, and thus only requires a positive aquaporin 4 -antibody (AQ4-AB) to confirm the diagnosis of NMOSD.[3] If the AQ4-AB is negative (or is not available) then 2 core clinical features need to be present in order to meet NMOSD diagnosis.[3] Making the diagnosis in this AQ4-IgG negative/unknown group is more challenging as more features need to be detected, however, it allows a positive diagnosis of NMOSD to be made in the absence of AQ4-IgG. This is of great benefit in situations where AQ4-Ab is not available or initially negative.

A review of population based studies in Europe, South Asia, the Caribbean and Cuba reveal that the incidence of NMOSD varies between 0, 05-4 per 100 000 and the prevalence ranges from 0,5-4 per 100 000.[5] NMOSD may have a higher prevalence in the black population; however this may be over-estimated due to the lower incidence of MS in this race group.[6,7] Due to the uncommon occurrence of NMOSD and most of the epidemiological data being documented prior to the revised 2015 diagnostic criteria, the true demographics of this disorder is not well known.

Human Immunodeficiency Virus (HIV) and NMOSD

The co-occurrence of human immunodeficiency virus (HIV) and NMOSD is uncommon and the literature regarding this association consists predominantly of case reports.[8-11] Prior to 2017, only 3 patients were documented to be both HIV and AQ4-AB positive.[9-11] However, a recent retrospective review of NMOSD patients in the Kwa-Zulu Natal province of South Africa revealed 12 HIV positive patients with NMOSD, 4 of which were dual HIV and AQ4-AB positive.[12] As this was a

retrospective review, it is uncertain if the HIV seroconversion in these patients occurred prior or subsequent to their NMOSD presentation.[12]

Considering the HIV epidemic in South Africa, co-existence with NMOSD seems to be unusual. Due to the scarcity of literature, there is no evidence to guide treatment in these rare instances. Balancing immunosuppression in an already immunocompromised patient may pose a therapeutic dilemma.

Infections and LETM

Infectious agents have been reported to directly cause LETM such as syphilis, Human T-lymphotropic virus 1 (HTLV1), CNS tuberculosis (TB) and parasitic infections.[2,13,14] Hence, features of meningitis in the presence of LETM should prompt urgent investigation to diagnose a suspected infection and expedite specific therapy.

Infections may also indirectly cause LETM by activating ADEM or NMOSD.[2] The infectious agents documented to induce NMOSD consist of varicella zoster virus, cytomegalovirus, Epstein Barr virus, HIV, dengue, hepatitis A, mycoplasma pneumonia and TB.[2] Thus, the presence of a specific infection does not always implicate the infection as the cause of a LETM and a diagnosis of NMOSD or ADEM should be considered in clinical context.[2]

LETM is very rarely a complication of TB myelitis but several cases have been described.[13,15] Interestingly, pulmonary TB has been associated with NMOSD by a number of case reports.[2,15] The proposed mechanism is an immune-mediated inflammatory demyelination initiated by pulmonary TB.[15] Therefore, pulmonary TB may lead to a LETM via activation of NMOSD or CNS TB may lead to a LETM. Both

of these mechanisms need to be considered in any patient with a LETM and suspected TB, especially due to the increased incidence of TB in a high HIV setting.

HIV has been suggested to possibly trigger NMOSD, or HIV could predispose to opportunistic infections which could cause LETM or may also trigger NMOSD.[2,14,15] However, there is a lack of evidence within the literature that HIV may cause LETM directly. HIV-associated vacuolar myelopathy is a well described syndrome which may cause an atrophic cord with signal change that possibly meets the LETM definition.[14,16] However, a diagnosis of LETM due to HIV-associated vacuolar myelopathy needs to be made with caution and by exclusion, as there are other possible causes, especially if the clinical presentation is not chronic.

Motivation for research study

In order to guide appropriate and prompt investigations, it is imperative to recognise LETM early. A working diagnosis needs to be formulated quickly as this has major implications on the management and future outcome of the condition. Patients with LETM are not an uncommon presentation to our Neurology division. With the availability of MRI facilities and resources to detect AQP4-AB, patients can be efficiently assessed for NMOSD. Other diagnoses can also be explored with appropriate investigations. In our HIV epidemic setting, there is an opportunity to evaluate patients presenting with LETM and explore the possible interplay between HIV and LETM. To my knowledge, this will be the first research study specifically investigating LETM in South Africa.

Aims:

i.) To describe the clinical characteristics and aetiology of patients with LETM in a South African setting

ii.) To describe LETM in HIV positive patients

Methods

22 Adult patients presenting with LETM to the division of Neurology of the University of the Witwatersrand in Johannesburg, South Africa, were included in this prospective study. Patients were recruited from Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Chris Hani Baragwanath Academic Hospital (CHBAH) and Helen Joseph Hospital (HJH). The study population were recruited and monitored over approximately 2 years (July 2015 to March 2017). Clinical, laboratory, radiological and other ancillary investigations were used to determine the cause of the LETM in each patient. Treatment modalities and response were recorded. Extended Disability Status Scale (EDSS) scores were determined at LETM onset, best EDSS post-treatment and outcome EDSS at final follow-up. Information was initially recorded on a standardised data collection sheet and then captured on an excel spreadsheet. The study was approved by the University of Witwatersrand Human Research Ethics Committee.

Statistical analysis

Stata (version 13) was used for all statistical analyses. Patient ages are reported as medians with interquartile ranges (IQR). A proportions test was used to determine the difference between the proportions of patients LETM diagnosis and of the level of clinical myelopathy. A 2-tailed Fisher's exact test was used to determine the significance of association between LETM diagnosis and I.) Clinical symmetry of myelopathy, II.) HIV status, III.) Cluster of differentiation 4 (CD4) count and IV.) Viral load.

Results

LETM Diagnosis and Demographics

The aetiology of LETM in this population was as follows: NMOSD was the most common diagnosis as 15 patients (68%) were diagnosed using the 2015 NMOSD criteria and 7 (32%) had non-NMOSD causes (p=0,0159). Among the 15 NMOSD patients, median age was 38 years (IQR 27-47), 14 were female, 13 were of African race and 2 were Caucasian. Within the 7 non-NMOSD group: 4 patients (18%) had an infective cause, 1 (5%) had an ischaemic myelopathy and 2 (9%) had an unknown or idiopathic LETM. Based on clinical, CSF and ancillary investigations, TB meningomyelitis was diagnosed in 3 of the 4 patients with an infective cause and 1 patient had no identifiable infectious agent. The median age of the infective group was 21 years (IQR 16,5-32,5), gender was equal (2 males and 2 females) and all 4 patients were of African race. The patient with an ischaemic myelopathy was a 62 year old Indian male who developed an acute myelopathy after vascular surgery. The ischaemic LETM was confirmed by restricted diffusion on MRI. The idiopathic group consisted of a 49 year old female and a 19 year old male, both were of African race. Demyelinating, infective, neuro-inflammatory, vascular, neoplastic, paraneoplastic, radiation-induced and metabolic causes for LETM were excluded in these 2 patients diagnosed as idiopathic LETM.

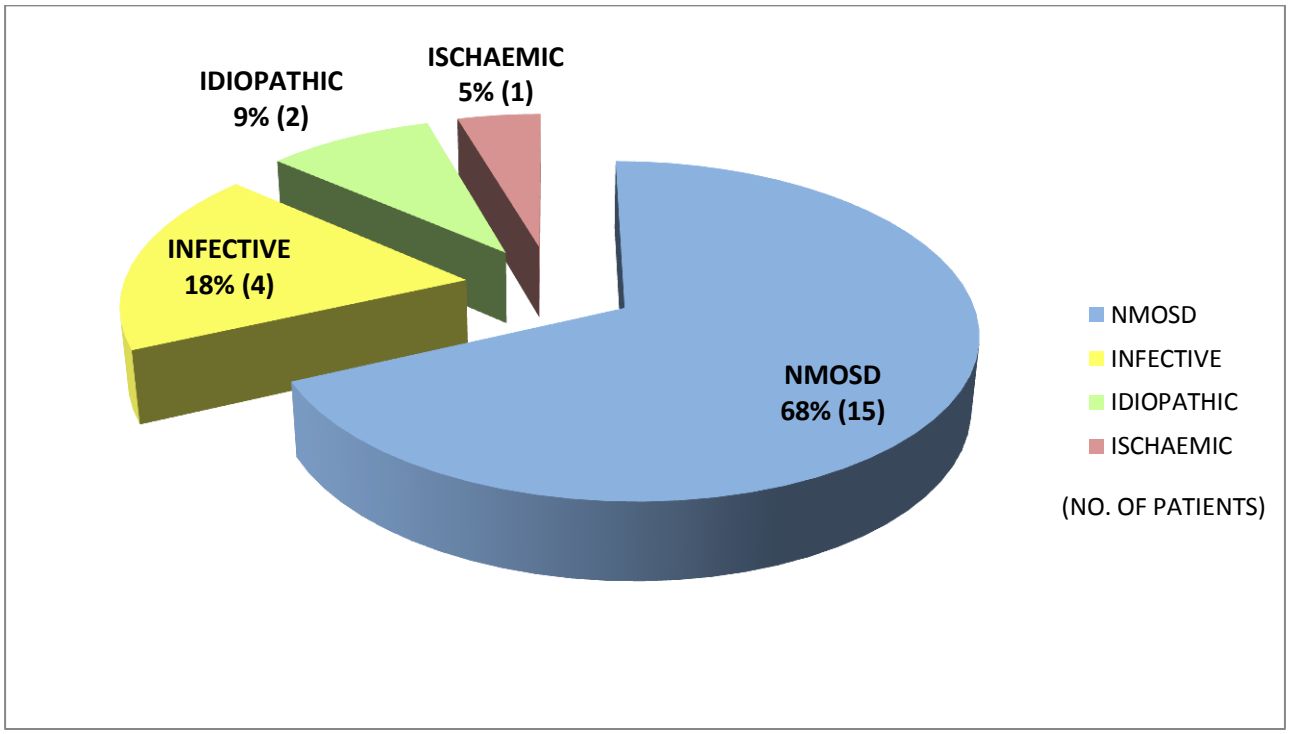


Figure 1: LETM Diagnosis

Clinical presentation

Of the 14 patients that had a cervical myelopathy, NMOSD was the most common cause with 13 patients (93%), and 1 patient (7%) had an infective cause (p=0,0002). 8 patients had a thoracic myelopathy, only 2 patients (25%) were diagnosed with NMOSD and 6 (75%) had non-NMOSD aetiology (p=0,0455). Except the 1 patient with an infective cervical myelopathy, the rest of the non-NMOSD group had a thoracic myelopathy. The 3 patients with TB meningomyelitis presented with meningism in addition to their thoracic myelopathy. As expected in the NMOSD group, optic neuritis and brainstem syndromes were also present in various combinations with the LETM. The most common presentation in the NMOSD group was combined optic neuritis and a cervical myelopathy (7 patients). Table 1 shows clinically symmetrical versus asymmetrical myelopathies between the different diagnostic groups of LETM. A clinically asymmetrical myelopathy was much more common in the NMOSD patients (14/15 patients) compared to a mainly clinically symmetrical presentation in the infective group (3/4 patients) (p=0,016). The ischemic myelopathy was clinically symmetrical and both the idiopathic LETM patients had clinically asymmetrical myelopathies.

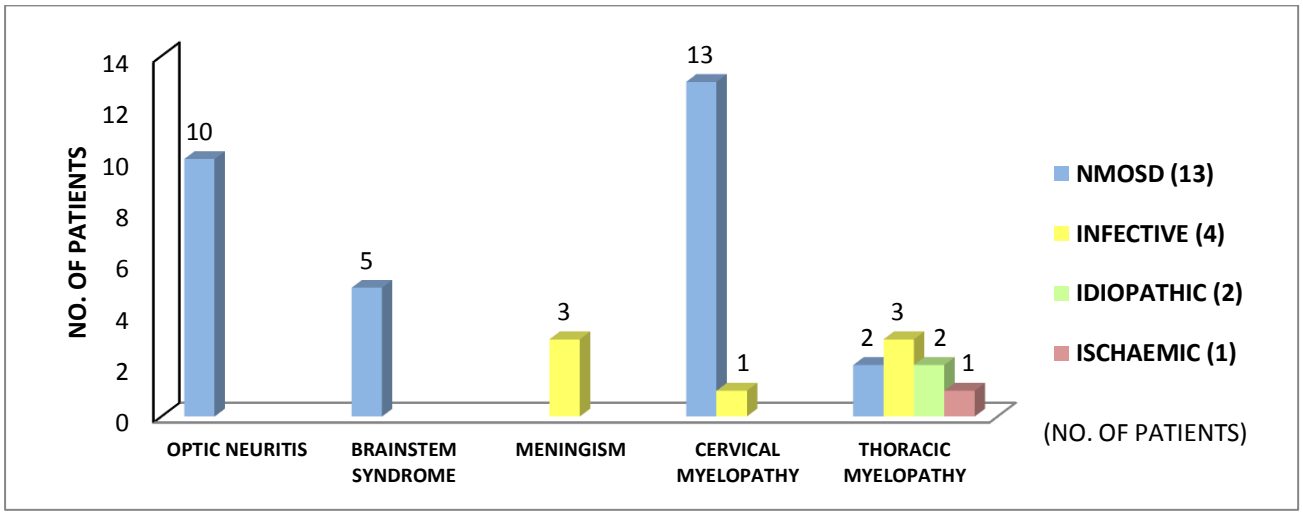


Figure 2: Clinical Presentation and LETM diagnosis

Table 1: Clinical symmetry of myelopathy

Diagnosis	Symmetrical (no.of patients)	Asymmetrical (no. of patients)	Total (no. of patients)
NMOSD	1	14	15
INFECTIVE	3	1	4
ISCHAEMIC	1	0	1
IDIOPATHIC	0	2	2

Radiological characteristics of LETM

The average length of the radiological LETM lesions in the total cohort was 7 vertebral bodies. Figure 3 shows the radiological extent of the LETM into different regions of the spinal cord (brainstem, cervical spine, thoracic spine and conus). 2 NMOSD patients had LETM lesions restricted to the cervical spine and 4 non-NMOSD patients (2 infective and 2 idiopathic) had LETM lesions restricted to the thoracic spine. However, most patients (16 of 22) had their LETM lesions extending into more than 1 region of the spinal cord. However, there were no patients in this study that had a LETM lesion extending the entire spinal cord (brainstem to conus or cervical spine to conus). Table 2 displays detailed radiological characteristics of the LETM lesions compared to diagnosis. Most LETM lesions (18/22 patients) caused expansion of the cord. Only 4 NMOSD LETM lesions showed patchy enhancement and all 3 TB patients displayed meningeal enhancement. Extension into the brainstem was seen in 11 NMOSD and 2 infective patients. Only 1 patient had a radiologically asymmetrical cord lesion, which corresponded with the asymmetrical clinical presentation.

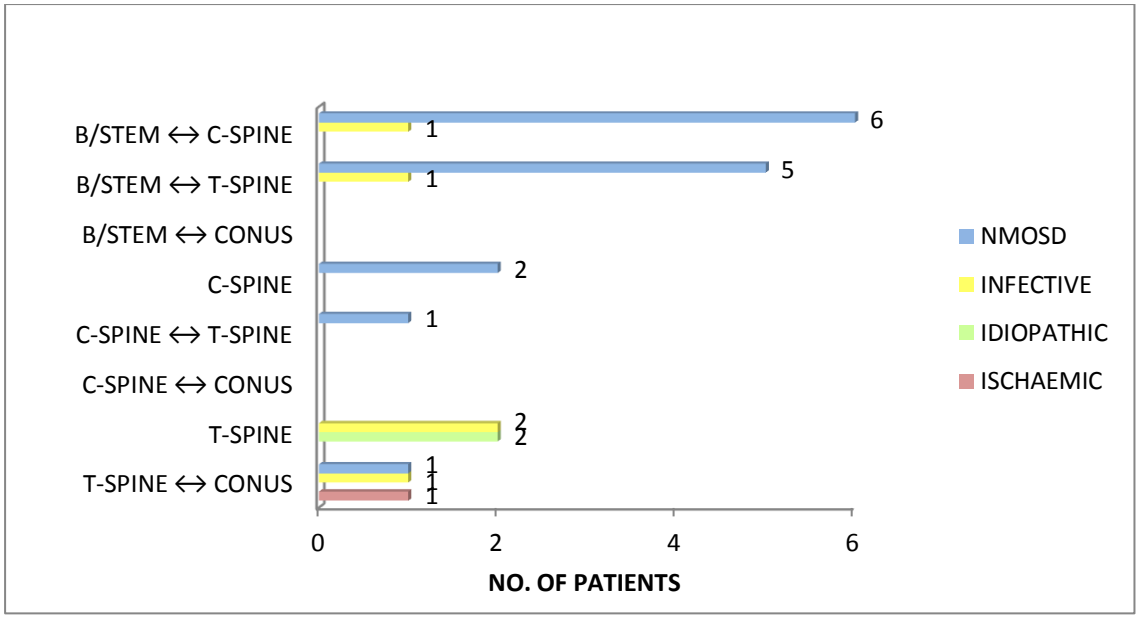


Figure 3: Radiological level of LETM

Table 2: LETM Radiological characteristics

MRI feature	NMOSD (15 patients)	INFECTION (4 patients)	ISCHAEMIC (1 patient)	IDIOPATHIC (2 patients)
T1 image	1 = ↑ 3 = iso 11 = ↓	2 =iso 2 = ↓	1 = iso	2 = iso
T2 image	15 = ↑	4 = ↑	1 = ↑	2 = ↑
Cord expansion	11 = yes 3 = no 1 = atrophy	4 = yes	1 = yes	2 = yes
Gadolinium enhancement	4 = patchy 10 = no 1 = not done	3 = meningeal 1 = no	1= not done	2 = patchy
T2 Axial image	12 = central 1 = complete 1 = asymmetrical 1 = indeterminate	2 = central 2 = indeterminate	1 = complete	1 = central 1 = complete
Extension to brainstem	11= yes 3 = no (1 = N/A)	2 = yes (2 = N/A)	(1 = N/A)	(2 = N/A)

(Abbreviations: ↓ = hypointense, iso = isointense, ↑ = hyperintense, N/A = not applicable as cervical cord not involved)

HIV

In terms of HIV status, 15 subjects were HIV negative and 7 were HIV positive. Of those that were HIV positive, 3 patients had TB myelitis causing LETM and 4 met NMOSD diagnostic criteria. HIV was more common in the infective group compared to the NMOSD group (75% versus 27%, p=0,117). In the HIV subgroup, CD4 counts were categorised into ≤200 cells/uL and >200 cells/uL, and viral loads were divided into ≤1000 and >1000 copies/ml. CD4 counts and viral loads were compared to LETM diagnosis. Lower CD4 counts were more common in the infective group and higher CD4 counts were seen in the NMOSD group (p=0,321). High viral load was associated with infective causes and low viral loads were detected in the NMOSD group (p=0,029). Table 2 shows the actual values of CD4 counts and viral load in the HIV subgroup, as well as whether highly active antiretroviral therapy (HAART) was being received or not at LETM onset. HAART was already initiated in 3 of the 4 NMOSD patients compared to no HAART in the infective HIV group.

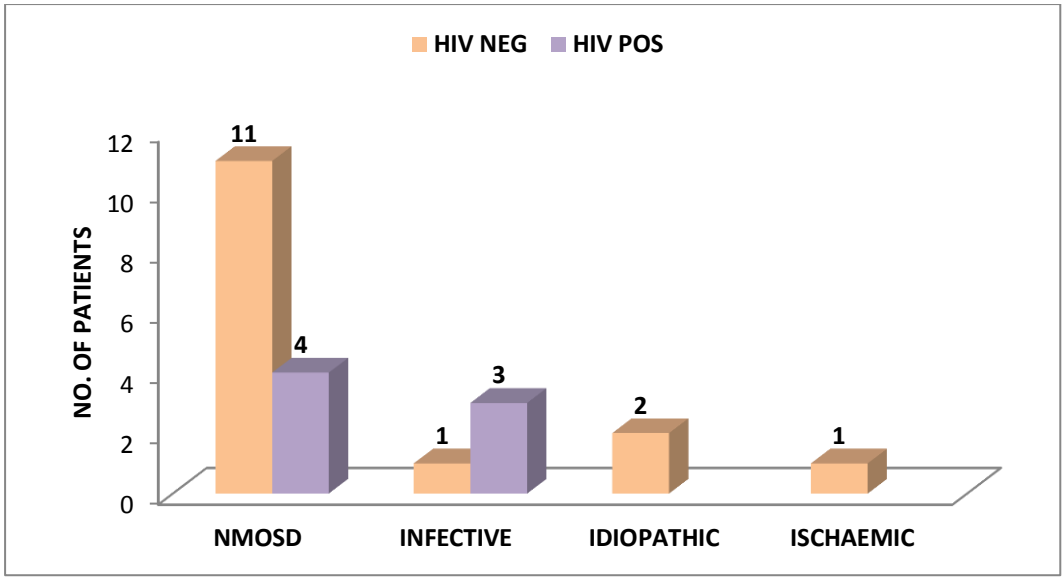


Figure 4: HIV status and LETM diagnosis

Table 3: CD4 count and Viral load in HIV positive patients

Diagnosis	CD4 (cells/uL)	Viral Load (copies/mL)	HAART at LETM onset
NMOSD (AQ4-AB positive)	784	LDL	Yes (5 years)
NMOSD (AQ4-AB negative)	492	171	Yes (1 month)
NMOSD (AQ4-AB negative)	503	69	No
NMOSD (AQ4-AB positive)	202	66	Yes (3 months)
INFECTIVE (TB)	106	287 526	No
INFECTIVE (TB)	146	1 950 000	No
INFECTIVE (TB)	101	690 471	No

HIV and NMOSD

The NMOSD group consisted of 8 patients that were AQ4-AB positive and 7 were AQ4-AB negative. 4 Patients had HIV and NMOSD dual diagnoses and in all 4 patients the HIV was confirmed before NMOSD diagnosis. These were divided into 2 patients that were HIV positive and AQ4-AB negative, and 2 that were both HIV and AQ4-AB positive. Thus, no trend was seen between HIV and AQ4-AB status (p=1,00).

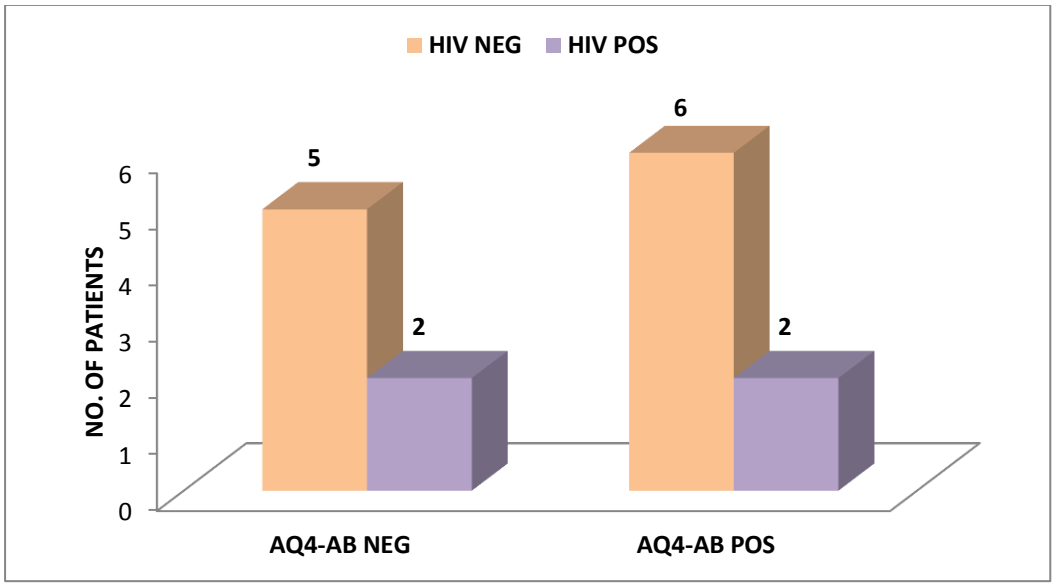


Figure 5: HIV status and AQ4-AB in NMOSD group

Treatment and outcome

NMOSD group

At initial presentation, 6 patients responded to intravenous methylprednisolone (IVMP) (1gram daily for 5 days), 5 patients responded to plasma exchange (PLEX) (alternate days for 5 cycles), 3 patients had no response to both IVMP and PLEX and 1 patient did not respond to IVMP (PLEX not given). Regarding relapses; 6 patients had no relapses, 6 patients had 1 relapse and 3 patients had 2 relapses. Of those with 1 relapse, treatment response at relapse was as follows: 3 responded to IVMP, 2 did not respond to both modalities and 1 died before relapse treatment could be initiated. Of the 3 patients with 2 relapses; 1 responded to PLEX at both relapses, 1 responded to PLEX (1^{st} relapse) and IVMP (2^{nd} relapse) and 1 had no response to treatment at both relapses. Long term treatment consisted of 10 patients on combined steroids and azathioprine, and 5 patients on long term steroids alone. At presentation of LETM, all patients had an EDSS ≥8, except 1 patient (EDSS of 5). Improvement in EDSS was variable with the most improvement in a patient from 9 to 2,5. In terms of outcome, EDSS divided into ≤5; 5 ≤ 8; 8 ≤ 9,5 and 10(death), consisted of 3, 4, 6 and 2 patients respectively.

Table 4: Treatment and outcome in NMOSD group

NMOSD Patient & AQ/HIV status	Initial treatment response	Relapse/s & treatment response	Long term treatment	EDSS at onset	Best EDSS post-treatment	Outcome EDSS
1. AQ4--/HIV-	IVMP	0	AZA+Steroids	8,5	7	7
2. AQ4+/HIV-	IVMP	0	AZA+Steroids	8	7	7
3. AQ4+/HIV-	PLEX	0	AZA+Steroids	9	2,5	2,5
4. AQ4+/HIV-	NIL to both IVMP & PLEX	0	AZA+Steroids	8,5	8,5	8,5
5. AQ4+/HIV+	NIL to both IVMP & PLEX	0	Steroids	8,5	8,5	8,5
6. AQ4-/HIV+	NIL to IVMP, PLEX not given	0	Steroids	8,5	8,5	8,5
7. AQ4-/HIV-	PLEX	1 – NIL to both IVMP & PLEX	AZA+ Steroids	9	7	9
8. AQ4-/HIV-	IVMP	1-IVMP	Steroids	5	3	3
9. AQ4+/HIV-	PLEX	1 – Died before treatment	AZA+Steroids	6	4	Died
10. AQ4-/HIV-	PLEX	1-NIL to both IVMP & PLEX	Steroids	8,5	5	Died
11. AQ4-/HIV-	IVMP	1-IVMPl	AZA+Steroids	8,5	7	7
12. AQ4-/HIV+	IVMP	1-IVMP	AZA+Steroids	9	7	7
13. AQ4+/HIV-	IVMP	1-PLEX 2-PLEX	AZA+Steroids	8	5	5
14. AQ4+/HIV+	PLEX	1-PLEX 2-IVMP	AZA+Steroids	9	4	8,5
15. AQ4+/HIV-	NIL to both IVMP & PLEX	1,2 - NIL to both IVMP & PLEX	Steroids	9,5	9,5	9,5

(Abbreviations: AQ4- = Aquaporin 4 antibody negative, AQ4+ = Aquaporin 4 antibody positive, HIV- = HIV negative, HIV+ = HIV positive, EDSS = Expanded Disability Status Scale, IVMP = intravenous methylprednisolone PLEX = plasma exchange, AZA = azathioprine)

Non-NMOSD group

Of the 4 infective LETM patients, 3 were given anti-TB treatment with dexamethasone and only 1 of these patients myelopathy improved slightly (EDSS of 8 to 7) and the other 2 TB patients remained with a EDSS of 8. The other 1 patient with an infective LETM received ceftriaxone and a solumedrol pulse and improved significantly (EDSS of 8,5 to 4). The patient with the ischaemic LETM did not respond to a solumedrol pulse and died 2 months after onset due to systemic complications. In the idiopathic LETM group, 1 patient responded to a solumedrol pulse (EDSS of 7 to 4) and was put on a steroid taper. The other patient with idiopathic LETM did not respond to a solumedrol pulse, however, a response to PLEX was seen (EDSS of 8 to 5).

Discussion

In keeping with the literature, NMOSD was the most common cause of LETM in this study. The age of patients and dominant female gender is also similar to the reported NMOSD demographics.[5] The majority of patients in the NMOSD group were of African race and this is may be due to the background population, however, there has been suggestions that NMOSD may be more prevalent in the black population.[6,7] The infective group consisted of only 4 patients and this may have been under-represented in this study as some infective LETM patients may be treated by infectious disease specialists or general physicians and are possibly not always referred to neurology. The median age was much younger in the infective group compared to the NMOSD group (21 versus 38 years) and thus age may direct diagnosis. The clinical context of the LETM also guides diagnosis as the ischaemic

myelopathy was suspected due to an acute onset after vascular surgery and the TB LETM patients had meningism and suggestive cerebrospinal fluid (CSF) results.

The level of myelopathy in determining the underlying aetiology was of clinical and statistical significance. The NMOSD group had a strong predilection for the cervical cord and almost all the non-NMOSD patients affected the thoracic cord. NMOSD is known to affect predominantly the upper cord and extend into the dorsal medulla.[3,4] This was represented in this cohort and correlated radiologically as 14 NMOSD patients had cervical involvement on MRI and 11 of these extended into the medulla. The fact that no lesion involved the entire cord further emphasizes a specific anatomical preference of the LETM lesion. Most NMOSD patients (14/15) presented with a clinically asymmetrical myelopathy, in contrast to typical descriptions of NMOSD causing a complete myelopathy.[3] This is a challenge to explain as only 1 of these patients had an asymmetrical radiological lesion on axial images, the rest were symmetrical (complete or central). This clinico-radiological discrepancy is not well described yet was a noteworthy result in this cohort.

The idiopathic group showed features of NMOSD in this study as they were both clinically asymmetrical but involved the thoracic cord which is not in keeping with typical NMOSD. These 2 patients may represent the myelin oligodendrocyte glycoprotein-antibody (MOG-AB) NMOSD subtype which has been reported to affect more males, involve the lower cord and have a milder phenotype.[3,17] Unfortunately, MOG-AB testing was not available and may also have been of benefit in testing the AQ4-AB negative NMOSD patients. A tissue-based assay was used to test for AQ4-AB which has a sensitivity and specificity of about 60% and 98% respectively.[18] Thus the idiopathic and AQ4-AB negative NMOSD patients may have had false negative AQ4-AB tests and using a more sensitive assay may have revealed more accurate

results. The idiopathic LETM patients could represent a separate disease entity which has been described within the literature.[19]

Despite a high HIV prevalence in our population, most of the LETM cohort was HIV negative. The HIV positive patients made up most of the infective group and were a minority in the NMOSD group. This is not surprising as HIV predisposes to opportunistic infections and it is uncommonly associated with NMOSD.[9-12] The CD4 count and viral load may direct an underlying cause as the infective group had low CD4 counts with high viral load and the NMOSD group had high CD4 counts with low viral load. Viral load as a predictor of diagnosis was found to be statistically significant. Interestingly, 1 patient was diagnosed with HIV and pulmonary TB 4 months before being diagnosed with NMOSD (AQ4-AB positive). This may represent activation of NMOSD by pulmonary TB which has been described in the literature.[2,15]

Treatment responses were variable in the NMOSD group. Responses were also inconsistent as some patients responded to different therapies during relapse/s or did not respond at all to a therapy that was initially beneficial. Thus, a reasonable approach in acute therapy is to use IVMP as 1st line treatment, irrespective of previous response, and use PLEX as 2nd line therapy. Some patients relapsed despite being on long-term immunosuppression but this may have been due to suboptimal dosing and compliance issues. LETM was associated with a high morbidity and mortality as only 4 patients had an EDSS <5 and 3 patients died.

The major limitation of this study was small sample size. The study was conducted over approximately 2 years and patient follow up was variable and relatively short compared to the chronicity of this syndrome.

Conclusion

NMOSD is a common cause of LETM and is suggested by cervical involvement compared to a thoracic LETM which suggests non-NMOSD causes. In HIV positive patients with LETM, NMOSD is less likely and alternative diagnoses should be excluded, especially infective causes. Nevertheless, NMOSD occurs in HIV positive patients and may be associated with a low viral load.

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Chapter 3: Appendix

I. Data collection sheet

1. DEMOGRAPHICS

Study No.
Age
Sex
Race

2. FIRST PRESENTATION

History
- Previous myelitis/optic neuritis
- Comorbidities
- Family History
Examination

3. INVESTIGATIONS

ANTI AQUAPORIN 4 Ab:

HIV:

SERUM

INFLAMMATORY	AUTOIMMUNE	METABOLIC	ENDOCRINE
CRP ESR Serum ACE Syphilis	ANA Anti SM ab Anti RNP Anti Ro Anti La RF	Vitamin B12 Copper Caeruloplasmin	TSH

CSF

Prot
Glucose
Poly
Lymph
RBC
Culture
Syphilis

MRI

BRAIN
SPINE
- Level of cord
- Length
- T1
- T2
- Gadolinium
- Axial

Other Investigations

4. DIAGNOSIS:
5. TREATMENT & FOLLOW-UP

II. Ethics Clearance Certificate

R14/49 Dr Ismail Moola

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150114

NAME: (Principal Investigator)	Dr Ismail Moola
DEPARTMENT:	Neurosciences Charlotte Maxeke Johannesburg Academic Hospital Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Longitudinally Extensive Transverse Myelitis: a Description Clinical Study
DATE CONSIDERED:	30/01/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof G Modi
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	15/07/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature

Date 16/7/15

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

R14/49 Dr Ismail Moola

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150114

NAME: (Principal Investigator)	Dr Ismail Moola
DEPARTMENT:	Neurosciences Charlotte Maxeke Johannesburg Academic Hospital Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Longitudinally Extensive Transverse Myelitis: a Descriptive Clinical Study
DATE CONSIDERED:	30/01/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof G Modi
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	22/03/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floo Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand th the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake t ensure compliance with these conditions. Should any departure be contemplated,from the research protocol a approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date fc annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. I this case, the study was initially review in January and will therefore be due in the month of January each yea Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 22/3/17

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

III. Plagiarism Report

DIVISION OF NEUROLOGY
Department of Neurosciences

University of the Witwatersrand

Department of Neuroscience, Division of Neurology, 7 York Road, Parktown, 2193, Tel No: 011 717 2774, Fax No: 011717 2775

28 March 2017

To whom it may concern/Postgraduate Research Committee

Re: "Turn it in" report - Dr Ismail Moola

MMED title: Longitudinally Extensive Transverse Myelitis: a Descriptive Clinical Study

This serves to confirm that the "Turn it In" report of Dr Ismail Moola's MMED was reviewed. The report identifies a similarity index of 9%. This relates mostly to the use of standardised definitions. The other information has been appropriately referenced.

Yours sincerely

PROF G MODI **MBBCh(Wits), MSc(Lond), PhD(Lond), FCP(SA), FRCP(Lond)**
Chief Specialist, Chair of Neurology