

Challenges in the diagnosis and treatment of CNS demyelinating disorders in Zambia

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Abstract

Demyelinating disease occurs in a population of black adult Zambians whose genetic and environmental risk factors for multiple sclerosis are thought to be rare. The diagnosis of demyelinating disease was based predominantly on compatible clinical history and neurologic exam findings, and in some cases, more definitely established by cerebrospinal fluid exam and imaging findings. When available, laboratory studies excluded other known causes of CNS demyelination. Timely evaluation and treatment with disease-modifying therapies was related to the patient's employment status. Lack of financial means to go abroad was a major hurdle in a patient's ability to receive treatment. Significant barriers often prohibit timely diagnosis and prevent proper management of these patients.

Keywords: Demyelination, multiple sclerosis, neuromyelitis optica (NMO), disease-modifying therapies

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Introduction

Multiple sclerosis (MS) and neuromyelitis optica (NMO), also known as Devic's disease, are inflammatory, demyelinating disorders of the central nervous system (CNS) with variable presentation and clinical course. MS has long been thought to be rare among the black population of Africa, whereas NMO has been well-documented to occur more commonly in non-white racial groups.^{1,2}

Cases of CNS demyelinating disease have been reported in some African countries, including South Africa,¹ Kenya,^{3–5} Uganda,⁶ Cameroon,⁷ Ethiopia,⁸ Senegal,⁹ and Zimbabwe,¹⁰ but there have been no well-documented cases of MS or NMO in Zambia. In this short report, we describe four black adult Zambians with recurrent or relapsing inflammatory demyelinating disease of the CNS and the various barriers to a timely diagnosis and optimal management.

Methods

The four patients described here in Table 1 were seen at the University Teaching Hospital (UTH) in Lusaka, Zambia, between 2014 and 2016. UTH is the largest hospital in Zambia with 1655 beds. It is the main teaching hospital for the University Zambia School of Medicine, and as such, is used to train

local nurses, medical students, and residents. UTH offers both inpatient and outpatient care and is a center for specialist referrals from across the country. During the period of the study, there were only two adult neurologists in the entire country, serving a population of 14.5 million.

Illustrative case histories

Case 1

This 22-year-old female with no significant past medical history presented to UTH Neurology Clinic with two to three weeks of generalized weakness, right worse than left. The weakness was initially mild, but then progressed, particularly in the right leg, making it difficult for her to ambulate. She also reported right upper, greater than lower, extremity numbness. In addition, she endorsed one to two weeks of blurry vision in the right eye. Two years prior, she recalls a similar episode of right-sided weakness and numbness that resolved without intervention. On neurologic exam, extraocular movements were intact with nystagmus in all directions, there was a mild right pyramidal syndrome, and mild cerebellar syndrome, right worse than left, with ataxic gait (Expanded Disability Status Scale (EDSS)=6.5). Magnetic resonance imaging (MRI)

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Table 1. Clinical profiles of the four patients described in the text.

	Case 1	Case 2	Case 3	Case 4
Age	22	32	41	20
Sex	Female	Female	Female	Female
First attack	Hemiparesis and Hemi-sensory loss	Transverse myelitis	Hemiparesis	Transverse myelitis; optic neuritis
CSF exam	ND	D	ND	ND
MRI-WML	ND	Diffuse PV; thoracic lesion	Diffuse PV lesions	Diffuse total spinal lesion
Therapy	None	IVMP $\times$ 5 days; interferon beta-1a	None	IVDM $\times$ 5 days
Outcome	Stable	Stable	Stable	Fair
First relapse- free interval	2 years	2 years	11 months	6 months
Second attack	Hemiparesis and hemi-sensory loss	Optic neuritis	Optic neuritis; aphasia	Paraparesis
CSF	D	ND	ND	ND
MRI-WML	Diffuse PV, SC, JC; CC	ND	Cerebellum; medulla; diffuse PV; cervical	ND
Diagnosis	RRMS	RRMS	RRMS	NMO
Therapy	IVMP $\times$ 5 days; glatiramer acetate	IVMP $\times$ 4 days; fingolimod	IVMP $\times$ 5 days; interferon beta-1a	IVDM $\times$ 5 days
Outcome	Stable	Fair	Stable	Fair

ND: not done; D: done; WML: white matter lesions; PV: periventricular; SC: subcortical; JC: juxtacortical; CC: corpus callosum; IVMP: intravenous methylprednisolone; IVDM: intravenous dexamethasone; RRMS: relapsing–remitting multiple sclerosis; NMO: neuromyelitis optica; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging.

of the brain confirmed the diagnosis of MS (Figure 1(a)). She was treated with intravenous methylprednisolone 1 gram daily for five days with significant improvement in her symptoms. Seven months later, she was treated with another round of intravenous steroids for a presumed flare. She was able to obtain a one-year supply of glatiramer acetate, free of charge, from South Africa nine months after her diagnosis through the Zambian Ministry of Health. She is currently stable with mild residual deficits.

Case 2

This 32-year-old female developed gradual difficulty walking and paresthesias in her lower extremities. Initial neurological exam was unremarkable (EDSS = 0). Over the next month, she developed a squeezing sensation in her chest, right-hand weakness, and difficulty with bilateral vision (EDSS = 3.0). MRI of the brain showed multiple periventricular and subcortical T2 hyperintensities and MRI of the total spine showed T2-hyperintense lesions in the cervical and thoracic spine. With the aid of her employer, she flew to South Africa where

extensive neurological evaluation including blood work, cerebrospinal fluid (CSF) exam, and repeat imaging confirmed the diagnosis of relapsing–remitting multiple sclerosis (RRMS). She was given five days of intravenous methylprednisolone and then commenced on interferon beta-1a. She remained stable over two years with annual visits to her neurologists in South Africa. She then developed blurry vision in the right eye for which she received four days of intravenous dexamethasone in Zambia for presumed optic neuritis. The following month, she flew back to South Africa where she was switched to fingolimod. While on fingolimod, she continued to have progression of disease based on increase in size of her spinal lesions on repeat MRI. This prompted her neurologists in South Africa to switch her to mycophenolate mofetil out of concern for seronegative NMO (serum aquaporin-4 antibodies had been negative twice), rather than RRMS. She is currently stable on this therapy with no further clinical or radiologic progression. The patient's visits to South Africa and medications continue to be covered through her workplace.

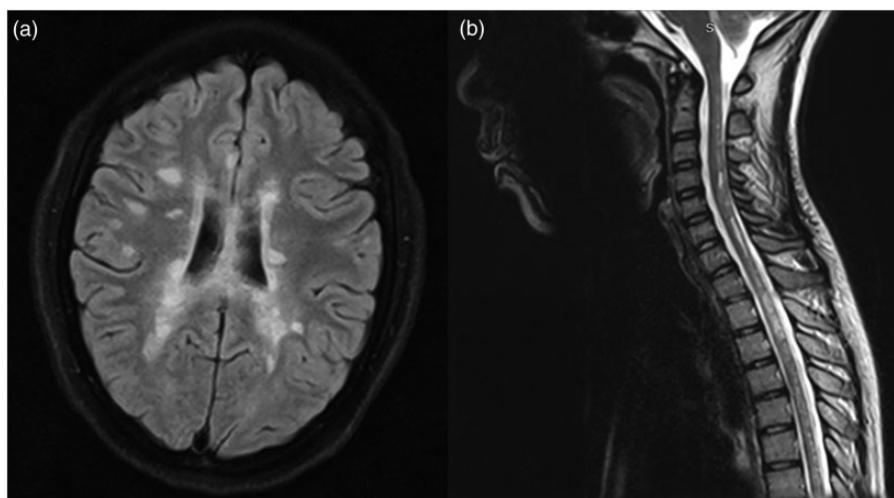


Figure 1. (a) Axial fluid-attenuated inversion recovery magnetic resonance (MR) image of the brain (*Case 1*) showing multiple T2-hyperintense lesions in the juxtacortical, subcortical, and periventricular white matter, some of which demonstrate enhancement on T1 post-gadolinium images. (b) Sagittal T2-post-gadolinium MR image of the whole spine (*Case 4*) showing longitudinally extensive spinal cord lesion with patchy “cloud-like” enhancement of these lesions.

Case 3

This 41-year-old female developed progressive weakness of her right lower extremity. Upon initial evaluation, she was felt to have a stroke and was prescribed aspirin and an antihypertensive. Several months later, she had difficulty walking and could no longer write (EDSS = 5.5). Brain MRI showed periventricular white matter lesions that were felt to represent small-vessel disease. Eleven months later, she developed difficulty with language and right-eye blurry vision. With the help of her employer, she was flown to India for a neurological evaluation. MRI of the brain and whole spine in India showed T2-hyperintense lesions in the periventricular region, right cerebellum, bilateral medulla, and throughout the cervical spine. She was diagnosed with RRMS and treated with five days of intravenous methylprednisolone with improvement of her symptoms. The patient was given a six month supply of interferon beta-1a in India. She has applied through the Zambian Ministry of Health for an additional one year supply of medication. This will be procured overseas free of charge but the patient will need to re-apply for interferon beta-1a in subsequent years.

Case 4

This 20-year-old female was admitted to UTH for bilateral lower extremity weakness and right-eye vision loss. Her symptoms started three months prior to admission with descending weakness of the right leg over one day that progressed to involve the

left leg over two weeks. Two months later, she lost vision in the right eye. On neurologic exam, she had an afferent pupillary defect of the right eye, spastic paraparesis, and loss of vibration and proprioception in the toes bilaterally (EDSS = 7.0). Computed tomography (CT) of the head was normal. MRI of the total spine was consistent with NMO (Figure 1(b)). She was treated with intravenous dexamethasone 180 mg for five days and physical therapy with mild improvement in lower extremity strength and ambulation. However, she continued to suffer from demyelinating attacks, which were again treated with five days of intravenous dexamethasone 180 mg. She was referred to hematology for azathioprine because of lack of steroid responsiveness. Since azathioprine is unavailable locally, attempts are now being made to procure it from abroad with the assistance of the Zambian Ministry of Health. This will be at no charge to the patient.

Results and discussion

The profiles of the patients described here are as follows: black Zambian African adults, all female, average age 28.5 (range 20–41), two or more different acute neurologic attacks of a disseminated disorder separate in time and space, response to intravenous corticosteroids, and MRI evidence of white matter lesions consistent with a McDonald criteria diagnosis of MS or consensus criteria for NMO.

In Zambia, as in other southern African countries, the disease has been accepted to be rare or nonexistent. Our case studies suggest that demyelinating disease is present and may even be rising in black Zambians. This is likely an underestimate, as many patients in Zambia have no access to a neurologist. The increasing prevalence of these disorders in Africa may reflect better education and use of modern diagnostic techniques; however, an absolute increase in numbers cannot be excluded.¹¹ The higher incident rates in communities where MS was previously under-recognized may also present new research opportunities for the study of etiological factors of this disease, especially genetic and environmental factors. Larger epidemiological cross-sectional and longitudinal studies are needed to determine the true prevalence, incidence, and pattern of CNS demyelinating disorders in the black Zambian population.

Recognizing the possibility of MS as a diagnosis based purely on clinical grounds is difficult given the dearth of clinical neurological training in Zambia. In an epidemiological study of MS in South Africa, the diagnosis of MS was made by a neurologist in 91% of respondents.¹² Even if patients are managed in a referral neurology clinic at UTH, confirmatory diagnostic testing such as neuroimaging may be difficult to obtain because of cost and maintenance of the CT or MRI scanner in a resource-limited setting. There is also significant cultural taboo around obtaining a lumbar puncture, which prohibits prompt and accurate diagnosis.¹² There are unique circumstances surrounding if and how patients receive care that is largely dictated by economics. In addition, the average yearly income in Zambia is equivalent to United States \$1680,¹³ and each exam corresponds to approximately 13%–20% of a patient's yearly salary. If the hurdles to obtaining neuroimaging are surpassed and a diagnosis of MS is confirmed, treatment options are often limited or unavailable in Zambia. Limited funding also contributes to shaping the treatment of MS, in a country where 64% of the population lives on less than one dollar per day. All of the patients in this report obtained their disease-modifying therapies (DMTs) outside Zambia, namely South Africa or India. One patient's DMT was fully covered through her employer, another's DMT was partially covered, and the remaining two relied on the government.

While the increased availability of modern diagnostic tools and the presence of neurologists certainly contributed to these first described cases of MS in Zambia, unique genetic and environmental factors

should also be considered. Further, while these MS presentations have a similar age of onset, gender distribution, clinical presentation and steroid responsiveness than cases reported elsewhere in North America and Europe, there may be unique phenotypes of CNS demyelinating diseases in this population that may be missed. Modi et al. (2001) reported nine cases of a potentially distinct inflammatory demyelinating disease of the CNS, or a varied form of MS, presenting as acute demyelinating encephalomyelitis (ADEM) or NMO in South Africa.¹⁴

Although increased economic resources are critically needed, a shortage of neurologists to care for these patients is as great a problem.¹⁵ The better we understand the barriers to making a diagnosis of relapsing–remitting demyelinating disease in this patient population, the greater the opportunities for improvement in management and outcomes. It may also help guide further resource utilization and encourage outside assistance for this resource-limited setting.

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Author contributions are as follows: Dr Misikin was involved in conceptualization of the study, acquisition and interpretation of the data, and drafting of the manuscript. Dr Saadi was involved in acquisition and interpretation of the data, and drafting of the manuscript. Dr Chikoya was involved in critical revision of the manuscript. Dr Sloane was involved in critical revision of the manuscript. Dr Koralnik was involved in critical revision and finalization of the manuscript. Dr Siddiqi was involved in conceptualization of the study, acquisition and interpretation of the data, and critical revision and finalization of the manuscript.

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Conflicts of interest

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