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Am. J. Trop. Med. Hyg., 102(2), 2020, pp. 451–457
doi:10.4269/ajtmh.19-0209

Nontraumatic Myelopathy in Malawi: A Prospective Study in an Area with High HIV Prevalence

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Abstract. Nontraumatic myelopathy causes severe morbidity and is not uncommon in Africa. Clinically, patients often present with paraplegia, and extrinsic cord compression and transverse myelitis are most common causes. Data on exact pathogenesis are scanty because of limitations in diagnostic methods. In Queen Elizabeth Central Hospital, Blantyre, Malawi, we recorded consecutive patients presenting with nontraumatic paraplegia for maximally 6 months between January and July 2010 and from March to December 2011. The diagnostic workup included imaging and examining blood, stool, urine, sputum, and cerebrospinal fluid (CSF) samples for infection. After discharge, additional diagnostic tests, including screening for virus infections, borreliosis, syphilis, and schistosomiasis, were carried out in the Netherlands. The clinical diagnosis was, thus, revised in retrospect with a more accurate final differential diagnosis. Of 58 patients included, the mean age was 41 years (range, 12–83 years) and the median time between onset and presentation was 18 days (range, 0–121 days), and of 55 patients tested, 23 (42%) were HIV positive. Spinal tuberculosis ($n = 24$, 41%), tumors ($n = 16$, 28%), and transverse myelitis ($n = 6$, 10%) were most common; in six cases (10%), no diagnosis could be made. The additional tests yielded evidence for CSF infection with *Schistosoma*, *Treponema pallidum*, Epstein-Barr virus (EBV), HHV-6, HIV, as well as a novel cyclovirus. The diagnosis of the cause of paraplegia is complex and requires access to an magnetic resonance imaging (MRI) scan and other diagnostic (molecular) tools to demonstrate infection. The major challenge is to confirm the role of detected pathogens in the pathophysiology and to design an effective and affordable diagnostic approach.

INTRODUCTION

Nontraumatic myelopathy is not uncommon in tropical medicine. Recent onset paraplegia is often the presenting clinical syndrome and may be caused by compressive disorders such as tumors or infections (abscesses and granulomatous disease) as well as non-compressive disorders such as transverse myelitis caused by infections that may include HIV, the human T-cell lymphotropic virus (HTLV-1), and syphilis. Schistosomiasis may cause myelopathy through both mechanisms.

In Africa, tuberculous spondylitis is common, particularly among HIV-infected individuals. The clinical manifestations are caused by destruction of vertebrae or by a paraspinal abscess.[1–3] Schistosomiasis is endemic in many regions in Africa, and spinal cord schistosomiasis (SCS) has been well described in tourists and expatriates.[4] It is usually caused by ectopic deposition of *Schistosoma* eggs in the spinal cord, and occasionally, adult worms have been found in the leptomeningeal veins.[5,6] Compression of the spinal cord occurs because of granulomatous inflammation with prominent motor disturbance (most common presentation) or there may be necrosis of the myelum, resulting in a rapidly progressive transverse myelitis with a sharp sensory level (less common).[7] Other causes include HTLV-1–associated myelopathy, malignancies (primary tumors of the spine or due to metastasis), degenerative disease, and (infective) myelitis.[8,9]

Nontraumatic myelopathy is not uncommon among medical and surgical admissions at Queen Elizabeth Central Hospital (QECH), Blantyre, Malawi, which functions as a tertiary referral hospital in the southern region of Malawi. As diagnostic facilities are limited, the cause often remains unknown. In a study performed between 2000 and 2002 at QECH, 16 of 33 patients with nontraumatic myelopathy were presumed to have SCS.[10] In addition, HIV infection is common (24% among urban adult population in Malawi, 70% among medical admissions, and 20% among surgical admissions), and a sharp increase in tuberculosis has followed the introduction of HIV in the 1990s.[11] The HIV infection has been implicated in various neurological syndromes as well, including myelopathy, but it is currently unknown to what extent HIV infection or associated viral infections may play a role. Similarly, there is no information on the contribution of benign or malignant tumors. According to the current practice at QECH, all patients presenting with recent onset paraplegia are empirically treated for schistosomiasis with praziquantel.

We attempted to describe consecutive cases of recent onset nontraumatic paraplegia in the medical and surgical departments of QECH, to describe (groups of) diagnoses, and to provide recommendations for management.

METHODS

Between January and July 2010 and from March to December 2011, all consecutive patients in QECH, Blantyre, Malawi, with nontraumatic paraplegia of less than 6 months duration were studied. Clinical assessment was not different from routine practice; this included a detailed history and

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physical examination, in which the neurological findings were recorded using the standard neurological examination of spinal injury by the American Spinal Injury Association (ASIA) (http://asia-spinalinjury.org/wp-content/uploads/2016/02/International_Stds_Diagram_Worksheet.pdf).

On discharge from the hospital, the neurological examination was repeated, and the ASIA score was recorded. Subsequently, the patients were referred to a rehabilitation clinic.

In addition, radiological imaging (chest X-ray, spinal X-ray, ultrasound, and MRI) were performed as appropriate.

Laboratory procedures at QECH. If indicated, an HIV test was obtained. Full blood and CD4 counts were carried out. Urine was tested for protein, glucose, and cells by dipstick rapid diagnostic tests.

Lumbar puncture was performed if clinically indicated, and routine analysis of cerebrospinal fluid (CSF) included protein and glucose levels; total leukocyte count and differentiation; and staining with Gram stain, Ziehl–Neelsen stain, and India ink.

Schistosomiasis was diagnosed by demonstration of *Schistosoma* eggs by microscopic examination of concentrated samples of urine (filtration) and stool (Kato–Katz method). Where possible, three consecutive stool samples and three consecutive urine samples were collected and examined per patient. Microscopy findings were scored as positive or negative; the number of eggs found was not recorded.

Although other helminthic infections were occasionally detected, these were not included in this report.

Radiological imaging. This included a chest or spinal X-ray and an ultrasound. The radiological examinations were not standardized but were at the discretion of the attending clinician who was guided by the clinical presentation, that is, the symptoms and signs at presentation. MRI scan services were restricted, and an MRI scan was only performed when clinically indicated. The MRI scans were reported by a radiologist (SK).

Surgical intervention. If indicated, the spinal lesion was surgically explored for drainage or removal of a mass. In some cases, specimens could be examined by a pathologist for histological diagnosis.

Additional laboratory procedures. Additional examinations were retrospectively performed in stored samples of serum, urine, stool, and CSF by the Erasmus University Medical Center, Department of Virology and Department of Medical Microbiology and Infectious Diseases, and the Leiden University Medical Center, Department of Parasitology, in the Netherlands.

The presence of DNA of *Schistosoma* species in frozen-stored urine, stool, and CSF samples was performed by real-time polymerase chain reaction (PCR) as described for stool samples before.[12] Only one stool and one urine sample per patient were analyzed by this PCR. Antibodies against *Schistosoma* species were determined as described before with minor modifications.[13] The *Schistosoma* egg antigen ELISA test result was considered negative if < 100 and equivocal if between 100 and 200.

Intrathecal production of *Schistosoma*-specific antibodies was investigated as described before.[14] The albumin index (albumin in CSF/albumin in serum) was used as a measure for integrity for the blood–brain barrier (BBB). If the albumin index was < 0.0090, the BBB was assumed intact and intrathecal anti-*Schistosoma* IgG production could be examined by calculating the anti-egg versus anti-worm antibody index, which is defined as follows:

$$(E_c/W_c)/(E_s/W_s)$$

where Wc = anti-worm IgG in CSF, Ws = anti-worm IgG in serum, Ec = anti-egg IgG in CSF, and Es = anti-egg IgG in serum.

If > 4, the index indicates intrathecal schistosomiasis; if 2–4, the index is equivocal; and if < 2, the index is negative.[14]

Borreliosis was diagnosed by quantitative determination of specific IgG in serum and CSF against recombinant antigens of *Borrelia burgdorferi*, using a commercially available chemiluminescence immunoassay (DiaSorin, Saluggia, Italy) that was performed according to the manufacturer's instructions.

Syphilis was diagnosed by a commercially available *Treponema pallidum* particle agglutination assay (TPPA) (Serodia, Fujirebio Inc., Tokyo, Japan). Serum and CSF were examined for the presence of specific antibodies against *T. pallidum* by serial dilution according to the manufacturers' instructions.

Tuberculosis was diagnosed according to the guidelines of the Malawi Tuberculosis Control Programme and included examination of sputum, lymph node aspirate, or pleural fluid specimens with Ziehl–Neelsen stain and radiological imaging. In addition, the presence of *Mycobacterium tuberculosis* in CSF was examined by a commercially available PCR assay according to the manufacturer's protocol (Hain Lifescience, Nehren, Germany).

Molecular virology screening. All samples were screened for the presence of viral pathogens by real-time (reverse-transcriptase) PCRs with primers and probes used in a routine setting of Erasmus University Medical Center molecular viral diagnostics.[15]

For detection of HSV-1, HSV-2, CMV, EBV, VZV, HHV-6, HHV-8, *Enterovirus*, *Parechovirus*, and JC virus in CSF samples, a semiautomatic workflow was including a Xiril-α (pre-extraction sample handling), MagNa Pure96 (nucleic acid extraction), Xiril-γ (PCR-setup), LC480-II, and middleware software AuroraFlow (Roche Diagnostics, Almere, the Netherlands). Total nucleic acids were isolated using an input and output volume of 100 μL and 300 μL, respectively. For the detection of chikungunya virus, HIV-1, HIV-2, hepatitis B virus (HBV), and HTLV-1 in serum, nucleic acids were extracted using MagNa PureLC (Roche Diagnostics, Almere, the Netherlands), with the High Pure 200 extraction protocol and the total nucleic acid isolation kit, with an input and output volume of 100 μL and 200 μL, respectively. Because of the limited amount of sample volume, the samples had a final dilution of 6–60× compared with routinely analyzed samples in the diagnostic setting, depending on the available sample volume.

Input volumes for real time reverse transcription polymerase chain reaction (RT-PCR) assays for RNA viruses were 8 μL for entero- and parechoviruses and 20 μL for HIV-1, HIV-2, and chikungunya virus. Input volumes for real-time PCR assays for DNA viruses were 8 μL (for EBV, CMV, VZV, HHV-6, HHV-8, and JC), 10 μL (for HSV-1 and HSV-2), or 20 μL (for HBV). The extracted RNA or DNA was amplified as described previously.[15]

For HTLV-1 infection, 5 μL of RNA was used. The extracted RNA was converted to cDNA and amplified essentially as described, using primers P-tRNA (gamma F) (5'-CADKTGGGGGCTCGTCCGGGAT-3) and POL-3 (delta R) (5′-GGCCTGGAGGCGYTCHRGTTTAAMGG-3′).[16] The PCR

TABLE 1
Baseline data of 58 patients enrolled with presumed nontraumatic paraplegia of less than 6 months duration according to HIV status

	HIV positive*	HIV negative*	HIV unknown
Number	23	32	3
Age mean, years (SD)	38.3 (10.7)	41.3 (20.5)	58.3 (20.7)
Age range (years)	16–57	12–83	36–77
Male, number (%)	12 (52)	23 (72)	2 (67)
Time between onset and presentation (days), mean (SD)	31 (33)	26 (29)	20 (30)
On antiretroviral therapy (ARV), number (%)	17 (83)	NA	NA
Time on ARVs (months), number of patients (%)		NA	NA
0–4	2 (12%)		
5–8	3 (18%)		
9–12	1 (6%)		
13–24	1 (6%)		
> 24	10 (59%)		
Symptoms (n = 57)			
Fever	11 (19%)	11 (19%)	0
Cough	3 (5%)	3 (5%)	0
Abdominal pain	6 (11%)	8 (14%)	2 (4%)
Weight loss	9 (16%)	14 (25%)	1 (2%)
Back pain	18 (32%)	24 (42%)	2 (4%)
Paresthesia	23 (40%)	27 (47%)	3 (5%)
Weakness	23 (40%)	29 (51%)	3 (5%)
Dysuria	5 (9%)	4 (7%)	1 (2%)
Sphincter disturbance	12 (21%)	16 (28%)	2 (4%)
Signs (n = 56)			
American Spinal Injury Association score on admission, number (% of score A, B, C or D)			
A (complete, no motor or sensory function preserved in sacral segments S4–S5)	8 (35%)	13 (41%)	2 (67%)
B (incomplete, sensory function below the neurological level and includes preserved in S4–S5)	4 (17%)	4 (13%)	1 (33%)
C (incomplete, motor function preserved below the neurological level, and preserved below the level in ≥ 50% of muscles, with grade < 3)	6 (26%)	8 (25%)	0
D (incomplete, motor function power preserved below the neurological level, and preserved below the level in ≥ 50% of muscles with ≥ grade 3)	5 (21%)	7 (22%)	0
Laboratory tests (n = 56)			
Hemoglobin, mg/dL (SD)	12.2 (3.2)	11.7 (3.0)	13.2 (1.1)
Total leukocyte count in cells × 10^3/mm^3 (SD)	7.7 (7.2)	6.8 (3.56)	5.2 (1.2)
Platelets in cells/mm^3 (SD)	314 (119)	277 (155)	289 (120)
CD4 count (range) in cells/mm^3	222 (157) 39–535	NA	NA

NA = not applicable.
* No statistically significant differences between HIV positive and HIV negative were observed.

temperature profile was 7 minutes at 95°C, 40 cycles of 40 seconds at 95°C, 1 minutes at 65°C and 2 minutes at 72°C, and final extension 10 minutes at 72°C.

A subset of samples was analyzed previously using a metagenomics approach in a virus discovery study.[17]

Clinical and final diagnosis. Based on the clinical assessment during admission, a most likely clinical diagnosis was made, and medical or surgical treatment was commenced as appropriate. After reviewing of the additional laboratory results, a most likely final (differential) diagnosis was made in retrospect.

Neuroschistosomiasis was diagnosed using a positive PCR test result in the CSF or on evidence of intrathecal anti-schistosomal antibody production. Neurosyphilis was diagnosed by using TPPA in serum and in CSF, with an intact BBB. Neuroborreliosis was diagnosed if evidence was found for intrathecal production of anti-*Borrelia* IgG with an intact BBB. Myelopathy associated with HSV-1, HSV-2, CMV, EBV, VZV, HHV-6, HHV-8, *Enterovirus*, *Parechovirus*, JC virus, and HTLV-1 was diagnosed on the presence of a positive PCR result in the CSF. *M. tuberculosis* infection of the central nervous system was confirmed by CSF analysis including Ziehl–Neelsen staining and PCR. Spinal tuberculosis was considered in case of a positive Ziehl–Neelsen stain of the sputum, and/or X-rays of the chest and spine, in combination with an MRI suggestive of tuberculosis, or a total leukocyte

count and differential cell count, and protein and glucose levels in the CSF suggestive of tuberculosis. Tumors or metastases were either diagnosed by histological examination of a biopsy or material obtained during surgery.

Data collection and analysis. The data were entered on a patient record form and subsequently analyzed using SPSS 24. Standard tabulation and descriptive methods, such as means, were used for descriptive purposes. Means were compared using independent sample *t*-test and proportions by using chi-squared test. A significance level of $P < 0.05$ was used. Logistic regression was used to explore whether combinations of variables were associated with common final diagnoses.

Ethical approval and informed consent. The study received approval from the College of Medicine Research and Ethics Committee and College of Medicine, Blantyre, Malawi. Informed consent was obtained from all patients.

RESULTS

The total number of patients enrolled was 58, of which 37 (64%) were male. The mean age was 41.0 years (SD, 17.5; range, 12–83 years). The median time between the onset of symptoms and presentation was 18 days (range, 0–121 days). The presence of HIV antibodies was examined in 55 patients, of which 23 (42%) tested positive. Baseline characteristics of the included patients are summarized in Table 1.

According to the ASIA scale at admission and at discharge, 12 patients improved, whereas three deteriorated and 32 had stable disease; for 11 patients, the ASIA score at discharge was not recorded. Eight patients died during hospitalization.

The mean hemoglobin was 12.0 mg/dL (SD, 3.1; range, 4.0–20.5), the total leukocyte count was 7.1×10^3 cells/mm^3 (SD, 5.3; range, 1.9–29.2), and the mean platelet count was 293×10^3 cells/mm^3 (SD, 139; range, 19–640).

In 39 patients, a lumbar puncture was performed, and in eight of these, an increased leukocyte count ≥ 5 cells/mm^3 was found (range, 8–80). The CSF protein levels were raised in 28 patients, with mean 3.6 (SD 2.4) and in the range of 0.49–8.18 mg/dL (normal 0.15–0.40 mg/dL).

In Supplemental Table 1, clinical, laboratory, radiological, and pathological information of the 58 cases are shown with the clinical diagnosis made during admission and the most likely final (differential) diagnosis in retrospect, after analysis of additional laboratory procedures.

Detection of schistosomiasis. In 57 of the 58 included patients, an attempt to diagnose schistosomiasis could be made by either microscopy or PCR analysis of urine ($n = 57$, 98%) or stool ($n = 47$, 81%).

Three consecutive urine samples could be examined by microscopy in 46 patients (79%). For stool, this was in 24 patients (41%). *Schistosoma* eggs were seen in seven patients (12%). In six patients, eggs were demonstrated in stool: in five cases, *Schistosoma mansoni* was found, and in one case, *Schistosoma haematobium* was found. In three patients, *S. haematobium* eggs were demonstrated in urine. In two patients, eggs were found both in stool and urine samples; one had double infection with *S. mansoni* and *S. haematobium*, and one had *S. haematobium* eggs in both sample types. The PCR analysis demonstrated *Schistosoma* spp. DNA in another seven patients ($n = 2$ in stool and $n = 5$ in urine). The presence of *Schistosoma* eggs observed in three patients ($n = 2$ in stool and $n = 1$ in urine) could not be confirmed by PCR. In total, 14 of the 57 examined patients (25%) were microscopy and/or PCR positive, so these patients were considered to have active schistosomiasis.

No DNA of *Schistosoma* spp. could be detected in any of 39 (67%) tested CSF samples.

Of 52 serum samples examined, 13 patients (25%) were found positive for antibodies against *Schistosoma* worm or egg antigens; 34 patients (65%) were negative, and in five patients (10%), the result was equivocal. In the CSF of 17 patients examined, using the egg-worm index, two patients had a score of > 4, whereas in another two patients, the result was equivocal (score 2–4). Hence, neuroschistosomiasis was included in the final differential diagnosis in these four cases (Supplemental Table 1).

Detection of virus infections. Of 55 serum samples tested for HIV at presentation in QECH, using routine screening with two rapid antibody tests, 23 (40%) were positive, with a mean CD4 count of 221 cells/mm^3 (range, 39–535); in 67%, the CD4 count was < 200 cells/mm.^{3}

The additional laboratory investigations retrospectively performed in the Netherlands were carried out on 50 serum samples and 35 CSF samples. Using routine real-time RT-PCR assays, HIV-1 was detected in 11 of 50 (22%) of serum samples and in nine of 35 CSF samples (26%); all but one had a CD4 count < 200 mm^3. In eight patients, these findings correlated in serum and CSF; in one patient, there was lack of serum. In seven of nine who were positive for HIV in CSF, HIV-1 was the only virus detected; in one HIV-1–positive patient, EBV also was demonstrated in CSF as well as HBV in serum. Another HIV-1–positive patient was also positive for human *cyclovirus*.

Cyclovirus was detected using a metagenomics approach in 15% and 10% of serum samples, and CSF samples, respectively.[17]

Hepatitis B virus was detected in the serum of six patients, two of whom had hepatocellular carcinoma. In one HIV-1–negative patient, HHV-6 was detected in CSF.

No evidence was found for VZV, CMV, HSV-1, HSV-2, enterovirus (including polio), parechovirus, JCV, or HTLV-1 infections (only CSF samples examined) or HIV-2 and chikungunya virus (both CSF and serum samples examined) (Supplemental Table 1).

Detection of bacterial infections. No positive Ziehl–Neelsen stain was found in the CSF samples examined.

All 41 examined CSF samples tested for mycobacterial infection by PCR were negative.

Antibodies against *T. pallidum* were detected by using TPPA in eight of 53 (15%) examined serum samples. In four of those patients, the CSF was enriched for *T. pallidum*–specific IgG, suggesting neurosyphilis that was, therefore, considered to be in the differential diagnosis in these four cases (Supplemental Table 1).

None of the 53 examined CSF samples were enriched in *Borrelia*-specific IgG.

Table 2 shows the distribution of symptoms, ASIA score, and main laboratory findings at presentation according to the most likely final differential diagnosis.

Using multivariate logistic regression, HIV status was found predictive of the diagnosis of spinal tuberculosis ($P = 0.018$). The total white cell count (TWC) and ASIA score were not predictive of this diagnosis.

TABLE 2
Distribution of symptoms, ASIA* score, and relevant laboratory results at presentation according to the most common final diagnoses

Final diagnosis	Fever	Cough	Dysuria	Hematuria	Abdominal pain	Paresthesia	Weakness	Weight loss	Sphincter dysfunction	ASIA score (number per category)	Hb (mg/dL)	Leukocyte count $\times 10^3$/mL (SD)	Leukocyte count in CSF† (cells/mm‡)	Protein level in CSF: mean in mg/dL (SD)§	Glucose level in CSF: mean in mg/dL (SD)
Spinal tuberculosis (n = 24)	9 (38%)	3 (13%)	4 (17%)	3 (13%)	9 (38%)	23 (96%)	24 (100%)	9 (38%)	9 (38%)	A 10; B 6; C 5; D 3	12.7 (2.4)	12.5 (20.4)	< 5:9 ≥ 5:7	3.8 (2.6)	3.2 (0.8)
Tumor (benign or malignant) (n = 16)	6 (38%)	2 (13%)	3 (19%)	2(13%)	5 (32%)	14 (88%)	16 (100%)	7 (44%)	9 (56%)	A 7; C 5; D 4	11.3 (3.0)	6.9 (4.5)	< 5:16 ≥ 5:0	4.4 (2.5)	3.3 (0.6)
Transverse myelitis (n = 6)	1 (17%)	1 (17%)	1 (17%)	1 (17%)	1 (17%)	4 (67%)	4 (67%)	1 (17%)	4 (67%)	A 2; B 1; C 2; D 1	12.9 (3.7)	5.3 (1.6)	< 5:5 ≥ 5:1	1.2 (1.0)	3.1 (0.7)

* American Spinal Injury Association.
† Cerebrospinal fluid.
‡ Cut-off for abnormal result: ≥ 5 cells/mm^3.
§ Normal value: 0.15–0.40 mg/dL.

In Table 3, the most likely final diagnoses are summarized in categories according to HIV status. Of 58 patients studied, myelopathy was diagnosed in 46 (79%), whereas in others, radiculopathy by disk herniation (two patients, 3%) or polyneuropathy (4 patients, 7%) was considered likely. In four patients (12%), the diagnosis remained entirely unknown, whereas in two patients, the most likely primary differential diagnosis was not established.

DISCUSSION

This study shows the diversity of differential diagnoses and the challenges in making a firm final diagnosis of the cause of paraplegia in a resource-limited setting. In 10 patients (17%), the clinical diagnosis could be confirmed; in eight cases, confirmation was possible as surgery was indicated (laminectomy, drainage, or tumor excision with subsequent histological examination of the surgical specimen), and in two other cases with transverse myelitis, EBV and HSV-2 virus were found respectively, in the CSF by PCR, in the absence of another diagnosis.

In 23 patients (41%), spinal tuberculosis was considered the most likely final diagnosis. A positive HIV test appeared to be a predictor for spinal tuberculosis. However, the CSF of all patients tested for mycobacteria by PCR was negative. This may be caused by the limited sensitivity of this test of < 40% that may be negatively influenced by the small volume CSF used and the freezing of the sample before analysis in this study.[18] Of the 23 patients with presumed spinal tuberculosis, tuberculosis (TB) was considered likely in 16 patients because of clinical features (draining abscess, gibbus, abnormal chest X-ray showing pleural effusion, or miliary TB) or spinal X-ray (destruction of vertebrae and paraspinal mass). In the other seven patients, TB was the most likely diagnosis based on only a suggestive MRI result. The value of the MRI has been emphasized and may distinguish between spondylitis and non-spondylitis tuberculosis.[2]

Spinal tuberculosis was more common in HIV-positive patients (14 [61%] compared with HIV-negative patients (9 [28%]), and HIV infection was the only predictor found. This is in agreement with a study from South Africa where spinal tuberculosis was diagnosed in 50% and 11% of patients who were HIV positive and negative, respectively.[3]

The prevalence of schistosomiasis in the patients studied was high (25%), and in half of these patients, an active infection could only be demonstrated by a positive PCR result for stool or urine specimens. Sampling of urine and stool proved difficult in this setting, and the contribution of microscopically diagnosed cases may, therefore, have been underestimated. No conclusive evidence for neuroschistosomiasis could be found, as all CSF samples tested were negative in the PCR. Detection of *Schistosoma* DNA in CSF is a sensitive method for detection of neuroschistosomiasis if DNA can be extracted from a large volume of CSF.[19] Because of the limited amount of available material, DNA could only be isolated from 200 μL of CSF. On the other hand, in 25% of the patients, antibodies against *Schistosoma* spp. were found, of which two patients had evidence for intrathecal production of schistosome-specific antibodies (and two with equivocal results). In these cases, neuroschistosomiasis infection was thought to be in the differential diagnosis of nontraumatic myelopathy. This low number of possible neuroschistosomiasis cases was

TABLE 3
Final diagnosis categories

Diagnosis	Number (% of 58 patients examined)	Mean age, years (range)	HIV positive (n = 23)	HIV negative (n = 32)	HIV unknown (n = 3)
Spinal tuberculosis	24 (41%)	38 (12–65)	14 (61%)	9 (28%)	1 (33%)
Malignancy	14 (24%)	51 (25–83)	0	12 (38%)	2 (67%)
Prostate	2	–	–	–	1
Liver	2	–	–	–	–
Bladder	1	–	–	–	–
Burkitt's lymphoma	1	–	–	–	–
Plasmocytoma	1	–	–	–	1
Other/not known	7	–	–	–	–
Transverse myelitis	6 (10%)	41 (23–61)	2 (9%)	4 (13%)	0
Schistosomiasis	2	–	–	2	–
Schistosomiasis or syphilis	1	–	–	1	–
EBV	1	–	1	0	–
HSV -2	1	–	0	1	–
HIV	1	–	1	0	–
Benign tumors	2 (3%)	25 (23–28)	0	2 (6%)	0
Schwannoma	1	–	–	1	-
Hemangioma	1	–	–	1	–
Disk prolapse	2 (3%)	–	1 (4%)	1 (3%)	0
Polyneuropathy	4 (7%)	–	3 (13%)	1 (3%)	0
Unknown	6 (10%)	–	3 (13%)	3 (9%)	0

First listed diagnosis in differential diagnosis, according to HIV status.

unexpected, given earlier reports in which schistosomiasis was estimated to cause half the cases of nontraumatic myelopathy cases in Malawi.[10] The reason for this difference is unclear. Recent reports suggest that the incidence of schistosomiasis in Malawi has not declined, in view of poor control of schistosomiasis and the reported high morbidity due to schistosomiasis among the local population and continued risk of infection in travelers returning from Malawi.[20–22] The increased awareness of *Schistosoma* infection as a cause of paraplegia and empirical treatment with praziquantel in local health facilities may have caused improvement or cure rates, possibly resulting in early treatment and/or a referral bias. A highly sensitive and easy to use point-of-care test to demonstrate an active *Schistosoma* infection would facilitate any presumptive diagnosis of neuroschistosomiasis.[16] The performance of such a test and its contribution to the differential diagnosis of nontraumatic myelopathy should be evaluated in a prospective study.

Among viral infections, HIV infection was most common with a high prevalence in CSF samples examined (n = 9; 26%). Most of these patients were profoundly immunosuppressed. Viral infection with EBV or HIV was considered the cause of transverse myelitis in two patients (based on virus detection by PCR). In another patient, VZV infection was considered based on the recent clinical presentation with herpes zoster. In another study in Malawi in which 14 patients with viral meningitis were described, EBV has been found in 50% of cases. In that study, CMV and HSV-1 were also found and all patients were HIV positive.[23] The high prevalence of *cyclovirus* in CSF of patients included in this study was surprising. The clinical relevance is unclear, but this virus has been implicated in acute nervous system infections in Vietnam.[17,24] Further study is needed in other patient groups including healthy controls before conclusions can be drawn concerning the pathogenicity of this virus. No cases of HTLV-1–associated myelopathy could be demonstrated, although both HTLV-1 and HTLV-2 circulate in Malawi and have been detected among mothers and children.[25]

Evidence for neurosyphilis was found in four patients and, thus, contributed to the differential diagnosis.

Limitations of the study. This study followed the current clinical practice regarding diagnosis and management of patients presenting with non-traumatic myelopathy. Given the limited resources a practical approach was often followed, and a confirmed histological diagnosis was only made in a minority of patients, restricted to those in whom surgery was indicated. MRI imaging is not unrestricted in our setting but contributed considerably in those in whom the diagnosis was largely unclear. Invasive diagnostic procedures aimed at spinal lesions carry risk and this should be balanced against a thorough clinical assessment including imaging and subsequent therapeutic approach.

This study shows the predominance of tuberculosis as the cause of nontraumatic myelopathy, largely driven by HIV infection. In most cases, spinal tuberculosis can already be expected on evidence of tuberculosis found elsewhere (sputum examination, chest X-ray, and lymph node aspiration). The MRI imaging may provide strong support for tuberculosis. Recently, the use of the Xpert MTB/RIF assay in urine was reported as an aid to the diagnosis of tuberculous spondylitis.[26] Starting anti-tuberculous treatment based on these findings seems justified in the absence of other diagnostic possibilities. In patients with a mass that compresses the cord, surgical intervention is necessary. This shows that paraplegia patients should be assessed in a multidisciplinary team by internists or pediatricians, respectively, and orthopedic surgeons to determine the best approach to diagnosis and management.

Although only a few potential cases of SCS were identified, empirical treatment with praziquantel seems still justified in high prevalence areas, as treatment is safe and cheap.

Paraplegia is a devastating neglected (tropical) syndrome for which a minimum of diagnostic tools including MRI scanning should be available to limit prolonged and irreversible morbidity as the result of misdiagnosis, exposure to inappropriate drugs, and invasive procedures.

Received March 15, 2019. Accepted for publication November 5, 2019.

Published online December 12, 2019.

Note: Supplemental table appears at www.ajtmh.org.

Acknowledgment: We are grateful to Nico Nagelkerke for statistical advice.

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