CLINICAL SCIENCE

Neuroinfection survey at a neurological ward in a Brazilian tertiary teaching hospital

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OBJECTIVES: This study was undertaken to characterize the neuroinfection profile in a tertiary neurological ward.

INTRODUCTION: Neuroinfection is a worldwide concern and bacterial meningitis, tetanus and cerebral malaria have been reported as the commonest causes in developing countries.

METHODS: From 1999 to 2007, all patients admitted to the Neurology Ward of Hospital das Clínicas, São Paulo University School of Medicine because of neuroinfection had their medical records reviewed. Age, gender, immunological status, neurological syndrome at presentation, infectious agent and clinical outcome were recorded.

RESULTS: Three hundred and seventy four cases of neuroinfectious diseases accounted for 4.2% of ward admissions and the identification of infectious agent was successful in 81% of cases. Mean age was 40.5 ± 13.4 years, 63.8% were male, 19.7% were immunocompromised patients and meningoencephalitis was the most common clinical presentation despite infectious agent. Viruses and bacteria were equally responsible for 29.4% of neuroinfectious diseases; parasitic, fungal and prion infections accounted for 28%, 9.6% and 3.5% respectively. Human immunodeficiency virus (HIV), herpes simplex virus 1 (HSV1), *Mycobacterium tuberculosis, Treponema pallidum, Taenia solium, Schistosoma mansoni, Cryptococcus neoformans* and *Histoplasma capsulatum* were the more common infectious pathogens in the patients. Infection mortality rate was 14.2%, of which 62.3% occurred in immunocompetent patients.

CONCLUSION: Our institution appeared to share some results with developed and developing countries. Comparison with literature may be considered as quality control to health assistance.

KEYWORDS: Infectious Diseases; Nervous System; Tropical Medicine; Epidemiology; Neurology.

INTRODUCTION

Neuroinfection is a worldwide concern and an important cause of morbidity and mortality. Bacterial meningitis, tetanus and cerebral malaria have been reported as the commonest causes of neuroinfection in developing countries.[1,2] Mainly resulting from African countries, these data may not only reflect the poorest communities of developing countries, but also the inadequacy of hospital infrastructure and laboratory resources associated with civil war in many of these countries.[3] However, differences in economical, political and climatic characteristics, and quality of health assistance, could contribute to distinct epidemiological data. The current study was undertaken to determine the frequency and characterize clinical aspects of neuroinfection admitted to our tropical neurological ward.

MATERIALS AND METHODS

This retrospective study was approved by the Ethics Committee of Hospital das Clínicas, São Paulo University School of Medicine, Brazil. Our tertiary teaching hospital has 970 beds, of which 26 belong to the Neurology Division which also has an infectious diseases ward that receives the majority of infectious cases. From 12 December 1999 to 12 December 2007, all patients admitted because of neuroinfection had their medical records reviewed. The main inclusion criterion was positive infectious pathogen identification, including our previously reported cases.[4,5] Although we had patients with undetermined infectious agents, we also included patients who had neurological manifestations and cerebrospinal fluid (CSF) abnormalities that suggested infectious disease. Clinical improvement occurring after antibiotic treatment and other non-infectious etiologies were excluded. Age, gender, immunological status, neurological

syndrome, infectious agent and clinical outcome were recorded when the inclusion criteria had been fulfilled. Neurological syndromes were classified as: meningitis; meningoencephalitis; stroke; and, myelitis.[6] Confirmed by electroneuromyographic studies, peripheral nervous system (PNS) encompassed spinal roots, plexuses or peripheral nerve affection.[7] Clinical involvement of cerebellar and/or brain stem structures was recorded as posterior fossa and brain space occupying lesion was applied when abscess or granuloma were seen during imaging studies despite neurological signs. Simultaneous or serial inflammation of the meninges, brain, medulla and spinal roots were classified as overlap involvement. Computerized tomography (CT), magnetic resonance imaging (MRI) and extensive blood and CSF analyses were carried out in all patients. The infectious agent was identified from CSF (Gram staining, culture, antibody detection or protein chain reaction) or nervous tissue samples (histology and/or culture). The outcome was classified as death, and unaltered or improved based on neurological examination at hospital discharge.

RESULTS

Between 1999 and 2007, 8760 patients were admitted. Cerebrovascular diseases and pulse therapy for multiple sclerosis and non-infectious inflammatory neuropathies were the main reasons for admission. Initial diagnosis of neuroinfection occurred in 416 patients, but 42 were excluded after laboratorial investigation: systemic lupus erythematosus (3), chronic idiopathic meningitis with low glucose level (1), Vogt-Koyanagi-Harada disease (2), Behçet disease (17), sarcoidosis (5), meningeal carcinomatosis (2), undetermined eosynophilic meningitis (2) and Rasmussen's encephalitis (10). The inclusion criteria were fulfilled by 374 patients (4.2%, 374/8760), mean age was 40.5 ± 13.4 years (range: 13–88 years), and 63.8% were male. Sixty-nine (18.4%, 69/374) patients were immunocompromised as a result of solid organ transplantation (7), acquired immuno-deficiency syndrome (AIDS; 42), diabetes mellitus (7), chronic hepatopathy (3), systemic lupus erythematosus (4), aplastic anemia (2), neoplasia (2) and T-cell dysfunction (2). The most common clinical presentation was meningoence-phalitis (211/374) in immunocompromised and non-mmu-nocompromised patients (Table 1). The infectious pathogen was identified in 81% (303/374) of cases, and presumed viral and bacterial neuroinfections were assumed in 8% (30/374) and 10.9% (41/374) of patients, respectively.

Virus accounted for 29.4% (110/374) of admissions (Table 2). Human immunodeficiency virus (HIV) was the most commonly identified virus with self-limited aseptic meningoencephalitis during the seroconversion period, followed closely by herpes simplex virus 1 (HSV1). Three non-immunocompromised-patients with HSV1 infection died as a result of hemorrhagic form despite serial treatment with acyclovir, intravenous methylprednisolone, pulse therapy and plasmapheresis. JC virus (JCV) infection occurred in association with immunodeficiency (one patient had ovarian cancer and two had AIDS).

Also, 29.4% (110/374) of admissions were as a result of bacterial infection (Table 3). *Mycobacterium tuberculosis* was the main pathogen identified by positive polymerase chain reaction (PCR) in 82.6% (19/23) of patients and histological study in the remainder. Another important agent was *Treponema pallidum*. Although intravenous penicillin G (24 million/day) had been administered for 21 days, no response was observed in two patients with progressive general paresis and only slight improvement occurred in patients with meningovascular syphilis. PNS involvement was commonly observed in bacterial infection. Polyradiculitis was diagnosed in two patients with tuberculosis and peripheral neuropathy appeared with *Mycobacterium leprae* (three), and *Bartonella henselae* (one) infection.

Parasites comprised 28% (105/374) of neurology ward (NW) admissions, of which *Taenia solium* and *Schistosoma mansoni* were the most common. Accounting for 64.8% of parasitic infection, all cases of *T. solium* presented with meningoencephalitis in 66 non-immunocompromised and two immunocompromised patients. Status epilepticus owing to the degenerating intraparechymatous larval form of *T. solium* was the main clinical presentation (n = 55). Moreover, intraventricular vesicles caused ventriculitis in three non-immunocompromised patients, two of whom underwent endoscopic resection and one died. In addition, two other non-immunocompromised patients developed hydrocephalus owing to racemous cysts in the spinal cord with clinical improvement after ventricular drainage. *S. mansoni* was identified in 21 (20%) non-immunocompro-mised patients representing the most important cause of myelitis (n = 20) in our series; however, one presented with stroke. Antiparasitic drugs were only used in neurocysti-cercosis and schistosomiasis when parasitic eggs had been found in stools or a rectal biopsy. *Schistosoma japonicum* caused brain space occupying lesion in one non-immuno-compromised patient who had just returned from Japan.

Table 1 - Neuroinfectious syndromes in 374 Brazilian patients (1999–2007).

Neurological syndrome	Infectious agent				
	Virus non-I/I n = 110 (29.4%)	Bacteria non-I/I n = 110 (29.4%)	Parasites non-I/I n = 105 (28%)	Fungus non-I/I n = 36 (9.6%)	Prion non-I/I n = 13 (3.5%)
Meningitis	32/-	16/-	-/-	-/-	-/-
Meningo-encephalitis	26/29	28/1	66/17	14/16	13/-
Brain space occupying lesion	-/-	28/4	1/-	5/1	-/-
Stroke	-/-	5/-	1/-	-/-	-/-
Posterior fossa	1/-	-/4	-/-	-/-	-/-
Overlap involvement	12/-	2/-	-/-	-/-	-/-
Myelitis	8/2	16/-	20/-	-/-	-/-
Peripheral nervous system	-/-	6/-	-/-	-/-	-/-

non-I: non-immunocompromised, I: immunocompromised, -: no observation.

Table 2 - Viral neuroinfection in a Brazilian neurological ward (1999–2007).

Infectious agent	Neurological syndromes				
	Meningitis non-I/I n	Meningoencephalitis non-I/I n	Posterior fossa non-I/I n	Overlap involvement non-I/I n	Myelitis non-I/I n
HSV1 (n = 23, 20.9%)	-/-	23/-	-/-	-/-	-/-
HSV2 (n = 4, 3.7%)	-/-	1/-	-/-	3/-	-/-
HZV (n = 4, 3.7%)	-/-	-/-	-/-	4/-	-/-
CMV (n = 5, 4.5%)	-/-	-/-	-/-	5/-	-/-
Mumps (n = 3, 2.7%)	2/-	-/-	1/-	-/-	-/-
HTLV1 (n = 6, 5.4%)	-/-	-/-	-/-	-/-	6/-
HIV (n = 25, 22.7%)	-/-	-/25	-/-	-/-	-/-
JCV (n = 3, 2.7%)	-/-	-/3	-/-	-/-	-/-
BKV (n = 1, 0.9%)	-/-	-/1	-/-	-/-	-/-
Measles (n = 2, 1.8%)	-/-	2/-	-/-	-/-	-/-
Enterovirus non-polio (n = 4, 3.7%)	-/-	-/-	-/-	-/-	2/2
Undetermined (n = 30, 27.3%)	30/-	-/-	-/-	-/-	-/-

non-I: non-immunocompromised, I: immunocompromised, HSV: herpes simplex, types 1 and 2, HZV: herpes zoster virus, CMV: cytomegalovirus, HTLV1: human T-lymphotropic virus type 1, HIV: human immune-deficiency virus, JCV: JC polyomavirus, BKV: BK polyomavirus, -: no observation.

Triggering meningoencephalitis in immunocompromised-patients, *Toxoplasma gondii*, *Trypanosoma cruzi and Strongyloides stercoralis* were isolated in 11, 2, and 2 patients, respectively.

Accounting for 9.6% (36/374) of cases, fungi caused more severe disease, longer hospital stay (data not shown) and higher mortality rate than other infectious agents. brain space occupying lesion owing to *Penicillium marffenei*, *Cryptococcus neoformans* and *Paracoccidioides braziliensis* occurred in one immunocompromised, two non-immuno-compromised and three non-immunocompromised patients, respectively. Presenting with meningoencephalitis, the identified agents were *C. neoformans* (four non-immu-nocompromised, five immunocompromised patients), *Histoplasmosis capsulatum* (five non-immunocompromised patient, one immunocompromised patient), *Zygomicetes*

Table 3 - Bacterial neuroinfection in a Brazilian neurological ward (1999–2007).

Infectious agent	Syndromes							
	Meningitis non-I/I n	Meningoence-phalitis non-I/I n	Brain space occupying lesion non-I/I n	Stroke non-I/I n	Posterior fossa non-I/I n	Overlap involvement non-I/I n	Myelitis non-I/I n	Peripheral nervous system non-I/I n
Listeriamonocytogenes (n = 8, 7.3%)	-/-	2/-	2/-	-/-	-/4	-/-	-/-	-/-
Mycobacterium tuberculosis (n = 23, 20.9%)	-/-	15/-	2/-	-/-	-/-	-/-	4/-	2/-
Mycobacterium bovis (n = 1, 0.9%)	-/-	-/1	-/-	-/-	-/-	-/-	-/-	-/-
Mycobacterium avium (n = 2, 1.8%)	-/-	-/-	-/2	-/-	-/-	-/-	-/-	-/-
Mycobacterium leprae (n = 3, 2.7%)	-/-	-/-	-/-	-/-	-/-	-/-	-/-	3/-
Nocardia sp. (n = 1, 0.9%)	-/-	-/-	1/-	-/-	-/-	-/-	-/-	-/-
Brucella sp. (n = 2, 1.8%)	-/-	-/-	-/-	-/-	-/-	2/-	-/-	-/-
Tropheryma whippelii (n = 1, 0.9%)	-/-	1/-	-/-	-/-	-/-	-/-	-/-	-/-
Actinomyces. bovis (n = 2, 1.8%)	-/-	-/-	-/2	-/-	-/-	-/-	-/-	-/-
Bartonella henselae (n = 1, 0.9%)	-/-	-/-	-/-	-/-	-/-	-/-	-/-	1/-
Treponema pallidum (n = 17, 15.5%)	3/-	2/-	1/-	-/-	-/-	-/-	11/-	-/-
Borrelia burgerdoferi (n = 8, 7.3%)	-/-	7/-	-/-	-/-	-/-	-/-	1/-	-/-
Undetermined (n = 41, 37.3%)	13/-	1/-	22/-	5/-	-/-	-/-	-/-	-/-

non-I: non-immunocompromised, I: immunocompromised, -: no observation.

(five immunocompromised-patients), *Pseudallescheria boydii* (two non-immunocompromised patients, one immunocompromised patient), and *Aspergillus fumigatus* (two immunocompromised patients). In addition, *Cladophialophora batiana*, *Phialophora fonsecae* and *Chromomycetes* accounted with one non-immunocompromised patient each and *Candida sp.* and *Rhodotorula sp.* with one immunocompromised-patient each. Particularly, zygomicosis occurred in five diabetic patients with disseminated cerebral presentation.

Progressive dementia, myoclonus and periodic sharp wave complexes on electroencephalogram (EEG) were present in all patients with prion disease (n = 13). Moreover, clinical and electrophysiological features of inferior motor neuron disorder were seen in three patients, and 14.3.3 protein was present in four patients in whom PCR analysis was carried out.

Considering the clinical outcome, 14.2% (53/374) of patients died, of whom 62.3% (33/53) were non-immunocompromised patients (Table 4). Despite having neurological disability at hospital discharge, 82% (307/374) of patients had improved neurological status (Table 5). All patients with presumed viral infection (n = 30) and 34% (14/41) of patients with undetermined bacterial meningitis were asymptomatic at hospital discharge.

Table 4 - Neuroinfection mortality in a Brazilian neurological ward (1999–2007).

Infectious agent	Patients	
	non-immunocompromised n	Immuno-compromised n
Virus (n = 7, 13.2%)		
HSV1	3	-
CMV	1	-
JCV	-	3
Bacteria (n = 2, 3.8%)		
Mycobacterium tuberculosis	1	-
Tropheryma whippelii	1	-
Parasite (n = 6, 11.3%)		
Taenia solium	-	1
Strongyloides stercoralis	-	2
Toxoplas,a gondii	-	1
Trypanosoma cruzi	-	2
Fungus (n = 25, 47.2%)		
Cryptococcus neoformans	5	3
Histoplasmosis capsulatum	5	1
Zygomycetes sp.	-	5
Penicillium marneffei	1	-
Cladophialophora bantiana	1	-
Pseudallescheria boydii	-	1
Phialophora fonsecae	1	-
Candida sp.	-	1
Chromomycetes	1	-
Prion (n = 13, 24.5%)	13	-

HSV1: herpes simplex virus 1, CMV: cytomegalovirus, JCV: JC polyomavirus
-: no observation.

DISCUSSION

In our study, neuroinfection predominated in young adults and males. Considering similar results published by Chapp-Jumbo (mean age 34.1 years, 62.9% males) in Africa and Tan et al. (mean age 42.5 years, 56% males) in North-America,[8,9] these data did not seem to be influenced by geographical area or quality of health assistance and could reflect high environmental exposition (recreational and working activities) of young persons, particularly males.

In comparison to developed countries' data, our admission and agent identification rates were closer to the data series published by Tan et al (3.8% and 68.9%, respectively) than African teaching infectious disease ward, where admission rates ranged from 11% to 23% and the identification rate was 45%.[8,9,10] In addition, the frequency of undetermined neuroinfection was less than 31% in Tan et al.[9] As reported by these authors, undetermined neuroinfection was frequently diagnosed in non-immunocompromised patients in our series. Indeed, our neuroinfection mortality was closer to rates in North America that ranged from 1.7% to 12% than the 47% reported by Chapp-Jumbo.[8,9,11] Analogously to North-American NW results,[9] prion and fungi were the more important lethal agents in our patients. However, a high mortality of fungal infection was a common finding, not only in North-American, but also in African studies.[8,10,12]

In our study, pathogen identification occurred in 81% of patients, being higher than results reported in developed countries.[9,11] It could possibly be an overestimation as a result of our inclusion criterion requiring positive agent identification, which could also explain 100% identification in parasitic and fungal infections. Another contributing factor was virus recognition in more than 72% of meningoencephalitis cases. According to the literature, virus identification ranged from 15.3% to 81.5% with the highest values being observed in industrialized countries.[13] Particularly in suspected viral neuroinfection, we follow the international consensus that recommends repetition of virological tests in serum and CFS.[14] Ordinary agents causing meningococcal, pneumococcal, streptococcal, staphylococcal and hemophilus meningitis were not observed in our series possibly as a result of referral bias. For example, common causes of meningitis could be treated by the Internal Medicine or Infectious Diseases services of our hospital whose patients were not included in our study or could be referred to Hospital Emílio Ribas, which is an infectious diseases center located in same geographical area as our institution.

Table 5 - Outcome of neuroinfectious diseases in a Brazilian neurological ward (1999–2007).

Outcome	Infectious agent				
	Virus n = 110 (%)	Bacteria n = 110 (%)	Parasite n = 105 (%)	Fungus n = 36 (%)	Prion n = 13 (%)
Death	7 (6.4)	2 (1.8)	6 (5.7)	25 (69.4)	13 (100)
Unaltered	9 (8.2)	1 (0.9)	1 (1)	1 (2.8)	-
Improved	94 (85.4)	107 (97.3)	98 (97.3)	10 (27.8)	-

(%): percent; -: no observation.

Some infectious diseases are commonly associated with under-development. Considering that more than 90% of tuberculosis cases in the world are found in developing countries,[15] it is not surprising that neurotuberculosis was the most frequent bacterial infection in our series. Moreover, neglected tropical diseases have high morbidity with neuro-paludism and schistosomiasis being the first and second identified causes in Africa, respectively.[10,16] Similar to these reports, our series showed a great number of parasitic diseases in which cysticercosis and schistosomiasis were the main causes with low mortality and high morbidity. Cysticercosis has been considered as a biological marker of social and economic development, an identified cause of epilepsy in 26.3% to 53.8% of patients, and is endemic in most of developing countries.[17,18] In addition, more than 200 million people have schistosomiasis in tropical countries and 600 million people live in its transmission zones, where the snail habitat has increased as a result of the implementation of agriculture and fresh water exposition combined with lack of sanitary systems.[19] Brazil is considered the country most affected by schistosomiasis in the Americas and takes part in one of the American developing vaccine programs.[20,21] Schistosomiasis has been associated with liver fibrosis, portal hypertension and hepatosplenomegaly as the more severe clinical impairments, but our study showed myelitis as another infection-associated disability. According to Wadhwa et al,[22] *C. neoformans* was the most common cause of fungal meningitis in our series. However, some reports showed other agents, such as *Candida albicans* in an African study or aspergillosis and zygomicosis in an Indian patholo-gical report, in which cryptococcosis accounted for 2% of histological samples.[12,23] *Histoplasma capsulatum* was the second more frequent fungus in our cases, possibly because of its high prevalence in Brazil.[24] Also, regional variability in the fungal aetiological spectrum would possibly be expected in countries that have continental dimensions with distinct ecological settings.

CONCLUSION

This retrospective study had methodological limitations related to scarce epidemiological reports from tropical countries. Taking into account the characteristics of our institution, our results did not represent a tropical neuroin-fection profile but could be considered as a panel commonly found in other tropical tertiary NW and certainly different from infectious disease ward admissions at same institution. Although comparison with literature data could be a matter of debate owing to differences in health facilities, period and design of studies, and type of population or ward, it could be used as a tool to control the quality of health assistance.

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