

Asian Pacific Journal of Tropical Disease

journal homepage: <http://www.apjtc.com>Original article <https://doi.org/10.12980/apjtd.7.2017D7-95>

©2017 by the Asian Pacific Journal of Tropical Disease. All rights reserved.

Central nervous system infections at the Hospital Universitario de Santander: An autopsy study in the period of 2004–2015

Julio César Mantilla Hernández^{1,2}, Sergio Alejandro Gómez Ochoa^{2,3*}, Kihara Alejandra Jerez Torra^{2,3}¹Department of Pathology, Universidad Industrial de Santander, Bucaramanga, Colombia²Grupo de Inmunología y Epidemiología Molecular (GIEM), Universidad Industrial de Santander, Bucaramanga, Colombia³School of Medicine, Health Sciences Faculty, Universidad Industrial de Santander, Bucaramanga, Colombia

ARTICLE INFO

Article history:

Received 9 May 2017

Received in revised form 31 May 2017

Accepted 28 Jul 2017

Available online 25 Sep 2017

Keywords:

Central nervous system infections

Autopsy

Opportunistic infections

ABSTRACT

Objective: To describe the neuropathological findings in autopsy performed for individuals with CNS infections and compare the data obtained with the information referred in the literature.

Methods: We reviewed the protocols of autopsy performed at the Department of Pathology of the Universidad Industrial de Santander (UIS) during 2004–2015 and selected those with CNS infection as a final diagnosis, and then evaluated the pathological findings and demographic variables.

Results: Among 3 117 autopsy protocols reviewed, 200 reported CNS infection, with 130 in males (65%) and 70 in females (35%), and with an average age of 26.5 years. A total of 114 cases were caused by opportunistic agents mainly including *Cryptococcus neoformans* (19%), *Toxoplasma gondii* and *Mycobacterium tuberculosis* (16% each). In addition, 63.71% presented HIV co-infection.

Conclusions: The results of this study indicate that there may be significant variations in the causative agents of CNS infection both in the national (in the case of *Cryptococcus neoformans* infection) and international context (in the case of enterovirus and cytomegalovirus infection). For this reason, similar studies are needed for the characterization of these pathogens regionally, which may contribute to the clinical suspicion of specific infectious agents.

1. Introduction

Central nervous system (CNS) infection is nowadays a significant problem because of the sustained increase in the number of cases reported in recent years; CNS infection with the sudden onset of symptoms, the poor prognosis and the derivated sequelae requires urgent care and, in some cases, they could be of medical or surgical emergencies, such as in the cases of subdural empyema and epidural abscess[1].

In Colombia so far there have been some studies of autopsy reports related to CNS infections; however, these studies are limited to HIV patients. Regarding this, there are no researches

evaluating the general population of patients who died with a CNS infection. Therefore, the aim of this study was to describe the neuropathological findings in autopsy performed for individuals with CNS infections in the period of 2004–2015 in the Department of Pathology of the Universidad Industrial de Santander (UIS) and compare the data obtained with the information referred in the literature.

2. Materials and methods

This retrospective descriptive study exposed the demographic and etiological characteristics of autopsies performed on patients that died from CNS infections in the period from 2004 to 2015.

We performed a retrospective review of 3 117 protocols of scientific medical autopsies performed at the Department of Pathology of the UIS of patients that died at the Hospital Universitario de Santander (HUS) or were referred from other hospitals in Bucaramanga metropolitan area between January

*Corresponding author: Sergio Alejandro Gómez Ochoa, School of Medicine, Health Sciences Faculty, Universidad Industrial de Santander, Carrera 32 N. 29-31, Bucaramanga, Santander, Colombia.

Tels: +57 0376365294, +57 3114682361

E-mail: sagomez.182@gmail.com

The journal implements double-blind peer review practiced by specially invited international editorial board members.

2004 and December 2015. Out of the reported autopsies, 200 (6.41%) autopsy protocols reported CNS infections. Of these, data about the socio-demographic information (age and sex), diagnosis, etiologic agent and comorbidities were obtained.

For the execution and analysis of this study, a database was created by using Excel where all data from autopsies were registered for choosing relevant data.

All evaluated cases, who died in the HUS, underwent medical scientific autopsy upon request of the treating physician and with previous authorization of a family member according to the Decree 786 of 1990.

The study obtained the authorization of the Director of the Department of Pathology of the UIS for review of the autopsy protocols, included histological preparations and photographs, and took into account the existing rules on research involving human subjects referred to in the Declaration of Helsinki of the World Medical Association and in the Resolution 8430 of 1993 of the Ministry of Health of Colombia. According to the above documentation, this study is classified as an investigation without risk[2].

3. Results

In the reviewing of the autopsy protocols, there were 200 cases with CNS infectious disease, of which 130 (65%) were males, with an average age of 26.5 years. Moreover, 47% of the cases presented an evident cause of immunosuppression.

Of the evaluated autopsy protocols, 86 cases (43%) had CNS infections whose etiological agent was not related to immunosuppressive states (Table 1), highlighting pyogenic infections in a total of 59 cases (68.6%). Of these, 45 (76.27%) had no specific etiologic agent, while in the remaining 14 cases, 6 (10.34%) were caused by *Streptococcus pneumoniae*, 5 cases (8.62%) by *Staphylococcus aureus*, 2 cases (3.44%) by *Neisseria meningitidis* and one (1.72%) by *Salmonella* spp. Additionally, a predominance of male gender (67.79%) was found. With respect to age range, it was observed that the most representative groups were the age group of 0 to 20 years and the one over 60 years with a total of 24 (40.68%) and 13 cases (22.03%) respectively.

Moreover, the most frequent comorbidities were pneumonia in 17 cases (29.31%), bronchopneumonia in 11 cases (18.96%), liver involvement in 8 cases (13.79%), protein-calorie malnutrition in 3

cases (5.17%), HIV infection in 2 cases (3.44%) and Waterhouse Friderichsen syndrome in 5 cases (8.62%).

Secondly, a total of 25 cases (29.06%) were infected with virus, in which it was not possible to specify the causative agent in 13 cases (52%). However, 6 cases (24%) were infected with the rabies virus, 3 cases (12%) infected with dengue virus and 3 cases (12%) with the herpes virus. As for the gender distribution, 17 (68%) were females and the age group of 0–20 years had the highest number of cases. Regarding comorbidities, 5 cases had HIV infection (20%), 7 cases had liver involvement (28%), 6 cases had pneumonia (24%) and 5 cases had bronchopneumonia (20%).

Finally, 2 cases (2.32%) had parasitic infections, in which one case (1.16%) was related to *Plasmodium falciparum* and the other (1.16%) related to *Taenia solium*; the ages of the cases were identified to be 20 and 69 years respectively. Meanwhile, only one case (1.16%) of infection with fungi was found in this group, which was caused by *Paracoccidioides* spp. in a man aged 59 years old.

On the other hand, opportunistic infections occupied a major role in this study, with 114 cases (57%) of the evaluated autopsies. *C. neoformans* was the opportunistic agent most frequently found [38 cases (19% of total)]. Meanwhile, *M. tuberculosis* and *T. gondii* ranked second in frequency with 32 cases (16% of total) each (Table 2). As for infection with *T. gondii*, there were 4 cases (2% of total) of congenital toxoplasmosis in 2 newborns and 2 infants. Finally, it is remarkable that in the patients infected by *T. gondii* there were 18 cases of pneumonia as comorbidities, with 9 cases (28.12%) of pyogenic pneumonia, 3 cases (9.37%) caused by *Pneumocystis jirovecii*, 2 cases (6.25%) by *Histoplasma capsulatum*, 2 cases (6.25%) by *C. neoformans* and finally 2 cases (6.25%) by cytomegalovirus.

Less frequent opportunistic agents were also found causing CNS infection, such as *Trypanosoma cruzi* (*T. cruzi*) in 5 cases (2.5% of the total), in which 4 were related to HIV infection and one with cardiac transplantation. Other immunosuppression related pathogens described were fungi of the *Mucor* genus, HIV and cytomegalovirus, which were identified in 2 cases (1.01% of the total) each. There was eventually only one case of aspergillosis in a male individual of 67 years old with a history of cardiac transplantation.

Table 1

Infections of the CNS with etiological agent not related to immunosuppressive states.

Item		Pyogenic infections	Viral infections	Parasitic infections
Absolute frequency		59 cases	25 cases	2 cases
Relative frequency		68.6%	29.06%	2.32%
Age groups	Children (< 20)	24 cases	12 cases	1 cases
	Adults (20–60)	22 cases	10 cases	0 cases
	Elderly (> 60)	13 cases	3 cases	1 cases
Sex	Men	40 cases (67.79%)	8 cases (32%)	1 cases (1.16%)
	Women	19 cases (32.20%)	17 cases (68%)	1 cases (1.16%)
HIV coinfection		2 cases (3.44%)	5 cases (20%)	No cases

Table 2

Opportunistic agents most frequently identified in the autopsy cases.

Item		<i>C. neoformans</i>	<i>T. gondii</i>	<i>M. tuberculosis</i>
Absolute frequency		38 cases	32 cases	32 cases
Relative frequency (%)		19%	16%	16%
Age groups	Children (< 20)	3 cases	4 cases	3 cases
	Adults (20–60)	31 cases	28 cases	26 cases
	Elderly (> 60)	4 cases	0 cases	3 cases
Age range		19–71 years	1 day–57 years	4–74 years
Sex	Men	29 cases (76.31%)	24 cases (75%)	22 cases (68.75%)
	Women	9 cases (23.69%)	8 cases (25%)	10 cases (31.25%)
Associated infections or organs involved		Disseminated cryptococcosis: 13 (34.22%)	Meningoencephalitis: 32 (100%)	Pulmonary and CNS: 17 (53.12%)
		Isolated meningoencephalitis: 25 (65.78%)		Other organs involved: 15 (46.88%)
HIV coinfection		30 cases (78.94%)	24 cases (75%)	12 cases (37.5%)
Other non-HIV immunosuppression causes		Treatment with corticosteroids: 1 case (2.63%)	SLE: 1 case (3.125%)	Treatment with corticosteroids: 1 case (3.125%)
		Malnutrition: 1 case (2.63%)	Malnutrition: 1 case (3.125%)	

Note: A total of 114 cases were evaluated, and the Top 3 most frequently identified opportunistic agents are described in this table.

SLE: Systemic lupus erythematosus. *C. neoformans*: *Cryptococcus neoformans*; *T. gondii*: *Toxoplasma gondii*; *M. tuberculosis*: *Mycobacterium tuberculosis*.

4. Discussion

The sociodemographic variables presented here are similar to those reported in similar studies in the region, which only presented lower average age[3-5].

Bacterial meningitis is the most common suppurative CNS infection and, unlike the viral one, has a high fatality rate, which is consistent with the findings in this study. According to multiple studies, *Streptococcus pneumoniae* is the most common cause of meningitis in adults and an etiologic agent in all age groups[6]. In Colombia, only one study on acute meningitis has been reported, which estimated an incidence rate of 3.8 per 100000 individuals and identified *Streptococcus pneumoniae* in 25.4% of cases[7].

Regarding the age groups, a higher prevalence was found in the children and the elderly, which is similar to that found in the study of Thornórdardóttir *et al.*[8]. Enteroviruses account for 50% to 80% of all aseptic meningitis. This fact was not evident in our study, in which no infection was caused by this agent, which is related to the limitations in performing diagnostic tests in the cerebrospinal fluid (CSF) for these viruses.

Finally, according to the histopathological findings, it was possible to identify 6 cases of encephalitis caused by rabies virus, a problem that has been already controlled in developed countries, which reveals a significant public health issue and the need of action in order to strengthen the epidemiological surveillance and improve the prevention strategies for this disease. In addition, 3 cases were caused by dengue virus, which is related to the fact that the Santander Department is one of the endemic areas of dengue in Colombia.

Moreover, *C. neoformans* was the most prevalent pathogen identified (19% of the total and 33.62% of this group), which differs from that reported in regional and Latin American studies referring *T. gondii* as the main causal agent in HIV infection, a comorbidity found in 28 (73.68%) individuals affected by this

fungus[3-5,9].

Less often, *T. gondii* infection was observed in 16% of cases, differing from other studies published in Latin America[10] and in our country, which have reported significantly higher prevalence, such as 28.3% reported by Mantilla *et al.*, 56.5% by Lizarazo *et al.* and 57.1% by Castaño-Osorio *et al.*[3-5]. This difference can be attributed to the fact that in the above studies the assessed total cases suffered from comorbidity of HIV infection, which significantly raised the risk of an opportunistic infection. Moreover, another important reason for this difference in results is the institutional policy that has been implemented in the HUS since 2004, in which it is recommended that any patient with tomographic findings suggesting this agent and concomitant HIV infection has to receive empirical antibiotic treatment with trimethoprim-sulfamethoxazole which has significantly decreased mortality in our hospital.

Similarly, in 16% of total cases the causative agent of *M. tuberculosis* represented a significantly higher prevalence than that reported by other regional and local studies[3,4,11]. It is noteworthy that in this group only 37.5% of patients presented HIV coinfection. Therefore, the higher frequency of CNS involvement by this agent was found, and this prevalence was higher even when compared with other studies that included only HIV individuals. This difference could be explained by the inequality for the implementation of the Bacillus Calmette–Guérin (BCG) vaccine in Colombia, evidenced in a minor change in the inequality indicator compared with other vaccines in the national scheme varying from 0.19 in 2000 to just 0.16 in 2003 in the Gini index, which leads to the fact that the population was not vaccinated against the disease with meningeal involvement even without an immunosuppression, as seen in many patients in this study[12].

Differently, there are less prevalent opportunistic pathogens reported in this study, such as the case of *T. cruzi* found mainly in HIV infected individuals. Multiple case reports have presented this

kind of coinfection in our country; both Fica *et al.* and Hernández *et al.* reported this coinfection in young female adults[13,14]. On the other hand, we reported a case of Chagas disease reactivation in a patient with solid organ transplantation, a condition that is of importance in endemic areas because of the increase in reported cases, which makes it necessary for the clinicians of these regions to take into account reactivation or a primary infection by *T. cruzi* in transplanted patients.

Finally, other CNS opportunistic infections were encountered, such as mucormycosis in two cases (1% of total), which had a low percentage both in the total and in the fungal infection group when compared to other studies on fungal CNS infections[15]. Similarly, cytomegalovirus infection [2 cases (1%)] was another rare finding that differs from what has been reported in developed countries, where this agent plays a greater role in CNS infections. Meanwhile, in our country similar studies have not reported CNS infection with this organism both in HIV infected and immunocompetent patients[3,4].

The results of this study indicate that there may be variations in the causative agents of CNS infection both in the national (in the case of *C. neoformans* infection) and international context (in the case of enterovirus and cytomegalovirus infection). In addition, less prevalent agent showed its importance in this report, highlighting conditions such as transplantation and HIV-related immune suppression as determinants of possible CNS compromise. Because of this, similar studies are needed for the regional characterization of these pathogens, which may contribute to the clinical suspicion of specific infectious agents.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

We would like to thank the Department of Pathology of the Universidad Industrial de Santander for supporting the development of this study.

References

- [1] García-Gómez A, Amador-Carpio M, Pradere-Pensado JC, Nistal-Mena J, Gutiérrez-Gutiérrez L. [Patients with central nervous system infection]. *Rev Cub Med Mil* 2015; **44**(1): 11-23. Spanish.
- [2] Ministry of Health of Colombia. [Resolution 008430 of 1993. By which establishes the scientific, technical and administrative norms for the investigation in health]. Bogotá: Ministry of Health of Colombia; 1993. Spanish. [Online] Available from: <https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/DIJ/RESOLUCION-8430-DE-1993.PDF> [Accessed on 4th May, 2017]
- [3] Castaño-Osorio JS, Sanchez G, Franco D, González MM, Giraldo AM. [Determination of the clinical-epidemiological characteristics of neuroinfection in patients diagnosed with HIV/AIDS in the department of Quindío]. *Infectio* 2007; **11**: 173-82. Spanish.
- [4] Lizarazo J, Castro F, De Arco M, Chaves O, Peña Y. [Opportunistic infections of the central nervous system in patients with HIV treated at the University Hospital Erasmo Meoz, Cúcuta, 1995-2005]. *Infectio* 2006; **10**: 226-31. Spanish.
- [5] Mantilla JC, Cárdenas N. [Neuropathological findings of HIV-AIDS infection: an autopsy study at the Hospital Universitario de Santander, Bucaramanga, Colombia]. *Colombia Médica* 2009; **40**: 422-31. Spanish.
- [6] Bijlsma M, Brouwer M, Kasanmoentalib E, Kloek A, Lucas M, Tanck M, et al. Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: a prospective cohort study. *Lancet Infect Dis* 2016; **16**(3): 339-47.
- [7] Tique V, Alvis N, Parodi R, Bustos A, Mattar S. [Acute meningitis in Córdoba, Colombia, 2002-2004]. *Rev Salud Pública* 2006; **8**(Suppl 1): 33-44. Spanish.
- [8] Thornórdardóttir A, Erlendsdóttir H, Sigurðardóttir B, Harðardóttir H, Reynisson IK, Gottfredsson M, et al. Bacterial meningitis in adults in Iceland, 1995-2010. *Scand J Infect Dis* 2014; **46**(5): 354-60.
- [9] Velásquez-Pérez L, Ramírez-Crescencio MA. [Neurological disease surveillance and mandatory reporting: a trend and outcome of the national neurological institute of health in Mexico city from 2005 to 2011]. *Gac Med Mex* 2014; **150**(6): 540-51. Spanish.
- [10] Ramírez-Crescencio MA, Velásquez-Pérez L, Ramírez-Crescencio MA, Velásquez-Pérez L. Epidemiology and trend of neurological diseases associated to HIV/AIDS. Experience of Mexican patients 1995-2009. *Clin Neurol Neurosurg* 2013; **115**(8): 1322-5.
- [11] Agudelo-Gonzalez S, Murcia-Sanchez F, Salinas D, Osorio J. [Opportunistic infections in patients with HIV in the university hospital of Neiva, Colombia. 2007-2012]. *Infectio* 2015; **19**(2): 52-9. Spanish.
- [12] Acosta N, Rodríguez J. [Inequality in childhood vaccination coverage in Colombia, years 2000 and 2003]. *Rev Salud Pública* 2006; **8**(Suppl 1): 102-15. Spanish.
- [13] Fica A, Salinas M, Jercic MI, Dabanch J, Soto A, Quintanilla S, et al. [Chagas disease affecting the central nervous system in a patient with AIDS demonstrated by quantitative molecular methods]. *Rev Chilena Infectol* 2017; **34**(1): 69-76. Spanish.
- [14] Hernández C, Cucunubá Z, Parra E, Toro G, Zambrano P, Ramírez JD. Chagas disease (*Trypanosoma cruzi*) and HIV co-infection in Colombia. *Int J Infect Dis* 2014; **26**: 146-8.
- [15] Sethi PK, Khanna L, Batra A, Anand I, Sethi NK, Torgovnick J, et al. Central nervous system fungal infections: observations from a large tertiary hospital in northern India. *Clin Neurol Neurosurg* 2012; **114**(9): 1232-7.