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RESEARCH ARTICLE

NEUROSYPHILIS IN A NON-HIV PATIENT: CASE SERIES IN A HOSPITAL TERTIARY OF PORTUGAL

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ABSTRACT

Background: The clinical spectrum of neurosyphilis (NS) has changed over time. The majority of cases are reported in HIV-infected patients, but the epidemiology of modern NS is not well defined because of the paucity of population-based data.
Objective: To describe the clinical spectrum and characteristics of NS in HIV-negative patients.
Materials and Methods: Diagnosticated cases of NS by diagnosis-related group presenting at Centro Hospitalar Gaia-Espinho a period of 6 years were identified. Diagnosis of NS was based on clinical presentation, routine CSF biochemistry (protein and leukocytes) and serological evidence serum and CSF Venereal disease research laboratory (VDRL) and Treponema pallidum haemagglutination assay (TPHA) tests.
Results: We identified 47 clinical records and excluded 7 HIV positive cases, 1 case diagnosed in 2001 and 6 cases of unlikely diagnosis. In the other, the median age was 61 years with a male predominance (79.79%). We not identify asymptomatic patients and later forms were the most representative (57.58%) with a predominance of general paralysis (54.55%). All patients had serum and cerebrospinal fluid TPHA positive titers. VDRL performed in CSF was positive in 12 (36.36%). In 13 patients (39.39%) showed CSF pleocytosis and 27 (81.82%) elevated CSF protein were found. In the study by neuroimaging in 25 patients (75.76%) showed abnormalities.
Conclusions: Neurosyphilis has various clinical manifestations, laboratory, and neuroimaging findings, but all studies lack specificity. Every patient with neurological or psychiatric symptoms that are without unambiguous causes should have blood tests for syphilis. When serology proves positive, patients should undergo CSF examination.

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INTRODUCTION

With the advent of penicillin, the incidence of tertiary syphilis has greatly declined. The disease is now considered unusual in developed countries, except in the context of (Goh, 2005) of people with untreated syphilis will later develop the disease in the CNS (central nervous system) (Sparling, 2010), and this can happen at any time after the initial infection. In a review of 2003 of syphilis, the authors stated that "NS is extremely rare in the era of antibiotics (Golden *et al.,* 2003). Nevertheless, in recent years, the number of reported cases is increasing, both in immunocompetent individuals and in immunocompromised patients (Marra *et al.,* 2010). The clinical manifestations of NS are extremely varied, and for practical purposes, they can be divided into early and late NS depending on the duration of illness (Zetola *et al.,* 2007). Early symptomatic NS involves diffuse inflammation of the meninges resulting in signs and symptoms of meningitis: a headache, photophobia, nausea, vomiting, cranial nerve palsies, and occasionally seizures or, as in most cases, be asymptomatic. It occurs within the first year after the initial infection and resolves regardless of treatment. The late form of NS can be considered a tertiary manifestation of the disease, but it is important to note that the appearance of neuropsychiatric signs and symptoms in NS may present at any time after the infection (Sparling, 2010). Late NS can further be subdivided into dementia progressive (known as general paralysis of the insane or dementia paralytica) and locomotor ataxia (Tabes Dorsalis) forms. This late form has the longest period of latency between the primary infection and onset of symptoms of all forms of NS, with the interval of an average of about 20 years, but sometimes just three years (Christina and Marra, 2016). Once that originate in the inflammatory process of the disease, there is often an overlap of two or more forms. The traditional terminology used for NS lacks precise definition, and pathologically many cases may have meningeal, vascular, and parenchymal involvement. Thus, the patient's classification into groups depending on their mode of presentation reflects their predominant clinical syndromes

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(Timmermans and Carr, 2004). There are sporadic reports of cases of NS with the atypical clinical presentation in world literature. However, documentation to series of cases of NS from Portugal is unknown. The objective of this study is to describe the clinical spectrum of patients with NS in adults HIV negative, encoded in All Patient Diagnosis Related Groups (AP-DRG) over 6-years (January 2009 to December 2014), in a tertiary Hospital Gaia-Espinho (CHVNG-E). The effectiveness of the laboratory diagnosis of these cases was evaluated and associated with the patient clinic.

MATERIALS AND METHODS

The CHVNG-E is a 612-bed tertiary hospital with care full-service facility. The AP-DRG is a tool (Cláudia Borges, 2015) which uses patient discharge information to classify patients into clinically meaningful groups. To this end, we analyzed the hospitalizations of CHVNG-E between years 2009 to 2014, with AP-DRG corresponding to the NS. The authors request for authorization to the Board of Directors and the Hospital's Ethics Committee for clinical processes of consultation to patients admitted on CHVNG-E with the diagnosis of NS. Note that it ensured the necessary confidentiality of patients, so this work did not include names or other data that can identify, in particular, each patient. The review of the clinical process has developed a data extracted on age, sex, clinical presentation of symptoms, a status of HIV, blood and cerebrospinal (CSF) fluid serology, biochemistry and cell count CSF, imaging studies, diagnosis, and therapy. Image studies included computed tomography (CT) and magnetic resonance imaging (MRI). For diagnostic categories (Timmermans and Carr, 2004) the authors used clinical and laboratory features and entered them into templates:

Category I - Neuropsychiatric disorders (psychosis, delirium, and dementia);
Category II - Cerebrovascular accident (CVA);
Category III - Ocular (presentation with uveitis, visual loss, or optic nerve dysfunction);
Category IV - Myelopathy (dysfunction of the spinal cord, including tabes dorsalis);
Category V – Seizure;
Category VI - Brainstem/cranial nerves (signs restricted to the brain stem and cranial nerves).

The categories, CVA, ocular, brainstem/cranial nerves, and seizure were considered as early forms and the neuropsychiatric disorders and myelopathy as late. In the confirmation of diagnosis, we used clinically and laboratory criteria assuming as definitive when the Venereal Disease Research Laboratory(VDRL) test was reactive in the CSF and probable when showed Nº cells /mm3 of ≥ 5 or protein concentrations of > 45 mg/dl (Khalil, 2010) or T. pallidum hemagglutination (TPHA) ≥1:320 in the CSF (Luger *et al.,* 2010), in the context of exposure syphilis.

RESULTS

We identified 47 clinical records with a diagnosis of NS during the study period. We excluded seven patients HIV-positive and one with a diagnosed illness in 2001. Also, based on the criteria of diagnosis were identified 12 cases of definite NS (30.77%), 21 cases of probable NS (53.85%) and 6 cases of unlikely of NS (15.38%), these also excluded (Fig 1). Of the remaining 33 selected, the mean age was 61.3, with a median of 61 years, whose minimal age was 39 and a maximum of 87 years, both men. There were 7 (21.21%) women, with an average age of 53.5 and a median of 53 years. The results showed only symptomatic patients (Table 1). The category I, the most representative with 18 (52.94%), and the category II with 7 (20.59%) it accounted for 73.53%. The other, the category III was found in 5 patients (14.71%). The clinical presentation of dementia was identified in 11 patients (30.56%) and psychosis in 7 (19.44%), which corresponded to the entire category I. The motor neurological deficit found in 7 patients (19.44%), in the whole of category II and one patient (2.94%) with tetraparesis associated with category IV. The optic nerve dysfunction ocular were found in 4 patients (11.12%) that corresponded to 4/5 of the category V. The seizures, category V, were identified in 2 patients (5.56%) being that one of them joined the paresis of the VI cranial nerve, one patient (2.94%) in category VI. Regarding the results, they showed 55.88% of late and 44.22% in early forms. In the analysis of laboratory results (Table 2), all patients had positive TPHA titer in the patient's serum and CSF. In the distribution of serum in 4 (12.12%) the TPHA was <1:640 and in 29 (87.88%) ≥ 1:640. In 33 samples of CSF for TPHA <1:320 we identified 17 (51.52%) and TPHA ≥ 1:320 were 16 (48.48%). The serum of two patients was not reactive for the RPR (Rapid Plasma Reagin), being that for dilutions of RPR <1:32 met in 19 (57.58%) and to RPR of ≥ 1:32 in 14 (42.42%). The VDRL (Venereal Disease Research Laboratory) performed on CSF was positive in 12 (36.36%) and negative in 21 (63.64%). In 13 patients (39.39%) CSF showed pleocytosis and 27 (81.82%) had elevated protein concentration in CSF.
All patients underwent imaging studies of the brain by CT or MRI. In 25 patients (75.76%) showed the following changes, gaps in the brain (14 /41.43%), cerebral atrophy (8/24, 24%), leukoencephalopathy (2/6.06%) and medium contrast enhancement in the spinal cord at C3 (1/3.06%). The remaining 8 (24.24%) were not identified changes. In therapy for 32 patients was used the Penicillin G 4 million units IV every 4 hours for 14 days and in the other patient the ceftriaxone (2 g/day for 14 days).

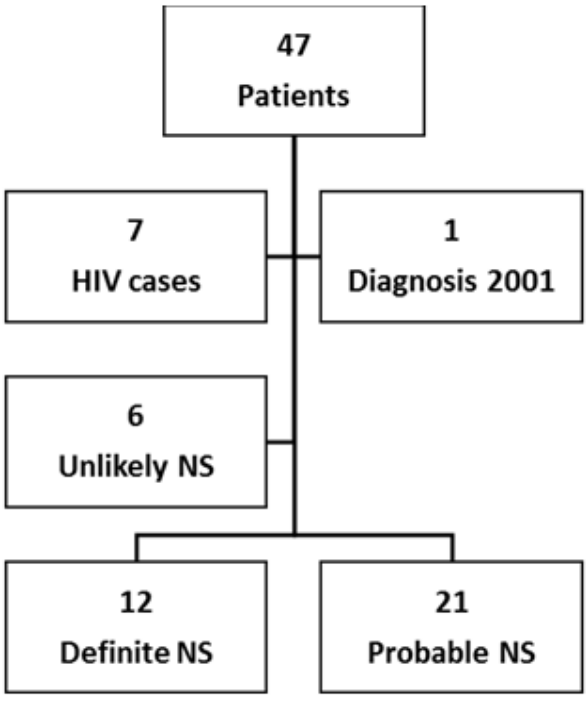

Fig. 1. Diagnostic Flow Chart for NS between years 2009 to 2014

Table 1. Category distribution with clinical manifestations

Category		Nº	%	Clinical manifestations	Nº	%
I	Neuropsychiatric disorders	18	52.94	Dementia	11	30.56
				Psychosis	7	19.44
II	Cerebrovascular accident	7	20.59	Aphasia	1	2.78
				Dysarthria	1	2.78
				Focal neurological deficit	7	19.44
III	Ocular	5	14.71	Visual loss	2	5.56
				Blurry vision	2	5.56
				Red eyes (Bilateral uveitis)	1	2.78
IV	Myelopathy	1	2.94	Tetraparesis	1	2.78
V	Seizure	2	5.88	Seizures	2	5.56
VI	Brainstem/cranial nerves	1	2.94	VI pair paresis	1	2.78
	Total	34	100	Total	36	100

Table 2. Results of serology, cytochemical and neuroimaging studies

Treponema pallidum haemagglutination assay [TPHA]					
Serum			CFS		
Cut-off	Nº	%	Cut-off	Nº	%
< 1/640	4	12.12	< 1/320	17	51.52
≥ 1/640	29	87.88	≥1/320	16	48.48
TOTAL	33	100	TOTAL	33	100
Rapid plasma reagin test [RPR] - Serum			Venereal disease research laboratory [VDRL] - CFS		
Cut-off	Nº	%	Cut-off	Nº	%
< 1/32	19	57.58	Negative	21	63.64
≥ 1/32	14	42.42	Positive	12	36.36
TOTAL	33	100	TOTAL	33	100
Cytochemical CSF study					
Nº cells/uL	Nº	%	Proteins	Nº	%
< 5 / mm3	20	60.61	≤ 45 mg/dl	5	15.62
≥ 5 / mm3	13	39.39	> 45mg/dl	27	84.38
TOTAL	33	100	TOTAL	32	100
Neuroimaging study					
Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)				Nº	%
Myelopathy C3				1	3.03
Atrophy				8	24.24
Ischemic gaps				14	42.43
Leukoencephalopathy				2	6.06
Normal				8	24.24
TOTAL				33	100

DISCUSSION

The incidence NS is more difficult to estimate, due to the lack of specific registration systems, and its epidemiological and clinical pattern has changed dramatically in the last decades. Thus, most NS cases are asymptomatic or forms early, and there has been a decline very important in the incidence of late form the tabes dorsalis (Christina, 2016). Since the beginning of the antibiotic era, the Treponema pallidum has remained extremely sensitive to penicillin making the cure of the disease as possible and stop the progression of syphilis in their different stages. The NS represents the continuum of the disease syphilis that understands your beginning invasive - the period of spirochetemia very significant - usually during the first weeks or months of asymptomatic infection and its spread (Rebecca *et al.,* 2006). Meanwhile, the clinical presentation of NS has been changing. Whereas 69% of cases were typical from 1965 to 1984, 86% of cases were atypical from 1995 to 2005 (Bhai, 2015). NS has a wide spectrum of neurocognitive symptoms that, apart from being non-specific, are also common to many neurologic and psychiatric disorders. Early involvement of the central nervous system is thought to occur in many patients infected with syphilis. The incubation period can vary from less than 2 years up to 20 years (Costiniuk *et al.,* 2013). The spectrum of neurological manifestations includes meningitis, cerebral vascular accidents, myelopathy, an involvement of cranial nerve, and symptoms of demyelination and seizures, which may be confused with other diagnostics neurology. The high index of suspicion and sagacity of the clinician is, therefore, imperative in the diagnosis of NS. NS is divided into the early, and late disease and its forms include asymptomatic, meningeal, meningovascular, and parenchymal, which includes general paresis and tabes dorsalis (Christina, 2016). Early neurosyphilis may be asymptomatic or may present as meningitis or meningovasculitis. Parenchymal NS is the most common presentation among symptomatic cases, presenting with a clinical psychiatric picture, including dementia, depression, rage, psychosis, and cognitive impairment (Kambe *et al.,* 2013). Late NS tends to affect the brain and spinal cord, typically presenting as tabes dorsalis, general paresis, sensory ataxia, or bowel/bladder dysfunction. The frequency of psychiatric signs and symptoms associated with NS reported in the literature ranges from 33% to 86% (Yao *et al.,* 2012). The most common presenting neuropsychological symptoms comprise personality change and hallucinations (in 48% of patients) (Yao *et al.,* 2012). In studies carried out, after the introduction of penicillin, show a decrease in late forms, mainly of tabes dorsalis. In fact, in our series the prevalence of this entity was only a patient [2.94%], but the neuropsychiatric disorders were found in 18 patients [52.94%] that resembles the studies conducted before the pandemic of HIV patients. Contemporary series, included patients with HIV, reported a low prevalence of general paralysis. However, in a study of 77 patients performed in

Denmark (Anne Grethe Danielsen *et al.,* 2004) between 1980 and 1997, were identified 50% of general paralysis, another study in a tertiary care hospital in north India (Sunil Sethi *et al.,* 2005) found dementia in 20% and a retrospective review of 149 patient records of NS in China [18], among symptomatic NS patients, 23 (15.4%) had syphilitic meningitis, 36 (24.2%) meningovascular NS, 64 (42.9%) parenchymal (including general paresis [58, 38.9%] and tabes dorsalis [6, 4.0%]). A study from South Africa (Timmermans and Carr, 2004) by Timmermans and Carr reported that the classical presentation of NS had not changed in 161 NS patients from 1990 to 1999, although tabes dorsalis had become rare. Their patients had clinical syndromes that were identical to those described in the pre-antibiotic era, i.e. neuropsychiatric presentations, strokes, cranial nerve and brainstem dysfunctions, seizures with or without encephalopathy and spinal cord disease, both acute and indolent. There is no gold standard test to diagnose or rule out NS. The CSF is a sensitive indicator of the active neurosyphilitic infection. The centers for disease control and prevention has established the two diagnostic categories: definitive and probable neurosyphilis. The former is defined as any stage of syphilis and a reactive CSF-VDRL. Probable is defined as any stage of syphilis, a nonreactive CSF-VDRL, CSF-pleocytosis or elevated protein, and clinical signs or symptoms consistent with syphilis without an alternate diagnosis to account for these (Khalil, 2010). A reactive CSF-VDRL is considered diagnostic for NS, but this test may be negative (specific, but only about 50% sensitivity) in as many as 70% of individuals with NS, and the diagnosis in such cases may be based solely on the CSF WBC count (Hooshman *et al.,* 1972).

The CSF WBC count in syphilis is lymphocyte-predominant. A cutoff of greater than or equal to 5 cells/uL has been the standard in HIV-negative subjects (Timmermans and Carr, 2004). Several studies have evaluated the performance measures of detecting the intrathecal production of T. pallidum specific IgG in the diagnosis of NS, but data have been inconsistent, so this method is not used in the routine diagnostics (Prange *et al.,* 1983; Moskophidis and Peters, 1996). In our study, the VDRL in CSF was reactive in 12 patients [36.36%], which is within the range reported 30-70% (Golden *et al.,* 2003) in immunocompetent patients. All patients had positive TPHA in serum and cerebrospinal fluid. It is noted that the TPHA in the CSF at 16-patients [48.48%] they were ≥1/320, and from these nine patients [75%] were classified as NS definitive. A study for the usefulness for the diagnosis of TPHA in CSF suggested that the title ≥1/320 (Luger *et al.,* 2000) was a predictor for the diagnosis. Random positive TPHA findings in CSF do not always indicate NS, and they may simply mean that passage of antibodies from the blood is occurring. Thus, TPHA is considered to be a technique with high sensitivity and low specificity. Therefore, authors such as Luger *et al.* 2000 have suggested that the mere presence of high TPHA titers in CSF could be considered to have diagnostic value regarding NS.

The diagnosis of NS is usually based on medical history, physical examination and findings in the LCR. Regarding the latter is well known that NS produces pleocytosis and raised proteins, which are inflammatory markers non-specific, but high sensitivity. They are indicative of active infection before and during the antibiotic treatment. Anyway, it considers that a pleocytosis than 20/mm3 is very suggestive of NS (Lukehart, 1988). In our study of 33 patients with NS, the assessment the cytochemistry of CSF showed proteinorraquia isolated in 18 (54.55%), isolated pleocytosis in 4 (12.12%) and association 9 (27.27%). That is 32 patients (96.97%) had a CFS with inflammatory characteristics. Only one patient (3.03%) of 53 years admitted by dementia, was assumed as probable NS because to present a TPHA> 1:320 in CSF, with proteinorraquia of 40 mg/dl. In a study of 149 patients, carried out during 8 years in the Republic of China [18], the cytochemistry of CSF examination showed pleocytosis in 59.1% and proteinorraquia in 56.4% of patients and 40.3% in both. Thus, as in our study, the diagnosis of NS cannot be excluded. The neuroimaging studies do not identify pathognomonic findings (Khalil, 2010) for the diagnosis of NS. Normal neuroimaging findings are also common. The most prominent diagnostic phenomenon associated with NS are, atrophy, white matter lesions, cerebral infarction, medium contrast enhancement and (Jeong *et al.,* 2009).

In our study, the most frequent findings were the gaps (ischaemic 14 patients/ 42.43%) and cerebral atrophy (8 patients/24.24%), and in 8 patients (24.24%) the study of the image was normal. These results do not coincide with the study conducted in India (Sunil Sethi *et al.,* 2005) of 25 patients in a period of 13 years, who identified abnormalities in the imaging study in 7 patients (28%). Otherwise, the study realized at Zhongshan Hospital (Hui-Lin Zhang *et al.,* 2013) from the 149 hospitalized patients enrolled a total of 111 patients were underwent MRI, and 67 (60.4%) patients had abnormal findings, that included cerebral infarction ischemic stroke (38 patients, 34.2%), and cerebral atrophy (15 patients, 13.5%). This hospital-based study opens up the possibility for the lack of some cases. However, as these patients are usually allowed to intravenous therapy, and as our hospital was the only reference center for this area during the study period, the data can reasonably be extrapolated to the general population. Since its introduction in the 1940s, penicillin remains the mainstay of therapy to treat NS. The ideal dose of penicillin is not known as no randomized comparative trials were done. What became clear early on was that higher doses of penicillin for a longer duration yielded the greatest impact on serological tests and CSF abnormalities (Khalil, 2010). Today, the recommended treatment regimen for NS is 18–24 MU of intravenous aqueous penicillin G daily, either as a continuous infusion or divided every 4 h, for 10–14 days. Limited data on the use of ceftriaxone suggest that 1–2 g intravenously or intramuscularly for 10–14 days yields acceptable results. In our study 32 patients were treated with penicillin G and one patient with ceftriaxone.

Conclusion

The NS presents itself with several clinical manifestations, laboratory and neuroimaging studies may be normal, and all are nonspecific. The importance of a rapid diagnosis of NS should be emphasized because early treatment and effective not only prevents the progression of the disease as it can allow a full recovery. Therefore, it is recommended that each patient with neuropsychiatric symptoms without question unequivocally should conduct a study of serum for syphilis. The study of the CSF continues to be the most important tool for diagnostic and evaluation of any patients with seropositivity for syphilis associated with neurological signs and symptoms are not specific. We reported 33 cases of NS over a period of 6 years, and 16-patients [48.48%] they had a CFS-TPHA titer ≥1/320. However, this may be an

underestimation because the asymptomatic cases are susceptible of being lost by the lack of adequate recommendation for screening for the study of CSF.

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