REVIEW ARTICLE

Prevalence of syphilis reactivity in patients with stroke, cognitive impairment and extrapyramidal syndromes: A retrospective study.

Authors
Giulia Ciccarese MD, PhD[1], Francesco Drago MD[1,2], Bianco Drago MD[3], Aurora Parodi MD[1,2]

Affiliations
[1]Dermatology Clinic, Ospedale Policlinico San Martino, Largo Rosanna Benzi, 10 16132, Genoa, Italy;
[2]DI.S.Sal., Section of Dermatology, University of Genoa, Via Pastore, 1, 16132, Genoa, Italy;
[3]Geriatric Unit, Department of Medical Sciences and Community Health, University of Milan, Milan, Italy.

Corresponding author:
Giulia Ciccarese, Dermatology Clinic, Ospedale Policlinico San Martino, Largo Rosanna Benzi 10, 16132 Genova, Italy. Tel. +390105555753, Fax +390105556509. Email: giuliaciccarese@libero.it

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Abstract

In the last two decades, there has been a resurgence of syphilis worldwide. However, epidemiological data on neurosyphilis are inconsistent for the lack of reporting data and diagnostic gold standard tests. The aim of the present study was to estimate the prevalence of syphilis reactivity in a cohort of patients with neurological diseases of our hospital. We retrospectively analyzed the medical records of the patients hospitalized at the Stroke Unit of the Neurology Clinic and those suffering from cognitive impairment hospitalized at the acute ward of the Geriatrics Clinic between January 2017 and December 2019. Also the patients who attended the Movement disorder outpatient clinic during the same study period were examined. To detect syphilis reactivity a qualitative specific treponemal test on patient's serum was performed: the Treponema pallidum haemagglutination assay (TPHA). A total of 652 patients were admitted and 315 of them (52%) were submitted to a routine screening for syphilis: 307 (97%) were negative while 8 (3%) had a positive syphilis serology. The TPHA-positive patients (4 males, 4 females) were 2 patients with stroke, 5 with cognitive impairment and 1 with Parkinsonism with a mean age of 83 years, suffering from multiple comorbidities. Although the patients we have retrospectively studied have not undergone lumbar puncture to confirm the diagnosis of neurosyphilis, the not negligible syphilis reactivity rate found in our series suggests that serological screening for syphilis should be reviewed as a routine screening test in neurology and geriatrics departments, especially if the clinical presentation of the neurological diseases is atypical.

Keywords: neurosyphilis, syphilis reactivity, stroke, cognitive impairment, Parkinsonism

Introduction

In the last two decades, there has been a resurgence of syphilis worldwide with the highest number of cases reported to the Center for disease control and prevention (CDC) in 2014–2015[1]. A previous study has estimated that a third of untreated syphilis patients will develop neurosyphilis, the tertiary stage of the disease[2]. In contrast to uncomplicated syphilis, epidemiological data on neurosyphilis are inconsistent due to the lack of reporting data and absence of diagnostic gold standard tests[3,4]. Neurosyphilis can have a variety of presentations: syphilitic meningitis classically occurs within the first 2 years after initial infection, meningovascular neurosyphilis usually appears from 5 to 10 years after primary infection, and parenchimatous syphilis (general PARESIS or tabes dorsalis) is considered as an evolution of one or more decades of disease[5,6]; moreover, it can be completely asymptomatic[7-9]. A recent literature review on the clinical presentation of neurosyphilis found that it was increasing, often with manifestations that are atypical for timing and type of lesions[10]. The aim of the present study was to estimate the prevalence of syphilis reactivity in a cohort of patients with neurological diseases admitted at the Neurology and Geriatrics clinics of our hospital.

Methods

We retrospectively analyzed all the patients hospitalized at the Stroke Unit of the Neurology Clinic and those suffering from cognitive impairment that were hospitalized at the acute ward of the Geriatrics Clinic (San Martino Hospital, Genoa, Italy) between January 2017 and December 2019. The patients who attended the Movement disorder outpatient clinic of our hospital during the same study period were also examined; this outpatient clinic was dedicated to the management and treatment of patients affected by extrapiramidal syndromes as Parkinson's disease and Parkinsonisms.

Data were obtained from a systematic review of the medical records of the all patients admitted in the above-mentioned department during the study period of 36 months. The collected data included: age, gender, comorbidities, a serologic test to assess syphilis rectivity and final diagnosis at the time of hospital discharge. The screening test for detecting syphilis reactivity was a qualitative specific treponemal test on patient's serum, performed in the diagnostic laboratory of our hospital: the Treponema pallidum haemagglutination assay (TPHA), whose result was reported in the patient's medical record. Indeed, according to the International Union against sexually transmitted infections (IUSTI) European Guidelines the screening for syphilis should be conducted with a Treponemal test first and, if positive, with a confirmatory test using an non Treponemal test to search for active disease[11-13].

Results

Overall, a total of 652 patients were admitted and 315 of them (52%) were submitted to a routine screening for syphilis: 99 patients in the Stroke Unit; 166 patients in the acute ward of the Geriatrics clinic and 50 patients in the Movement disorder outpatient clinic. The demographic, clinical and laboratory features of the screened patients are shown in Table 1.

Globally, of the 315 patients (mean age 80 years) that have been serologically screened for syphilis, 8 (3%) had a positive syphilis serology and 307 (97%) were negative. More specifically, the TPHA-positive patients (4 males and 4 females, mean age of 83 years) were 2 patients

with stroke, 5 with cognitive impairment and 1 with Parkinsonism, suffering from multiple comorbidities (Table 1). In the cases of TPHA positivity, a non treponemal test, the venereal disease research laboratory (VDRL), on patient's serum was found only in the medical record of one patient (the TPHA-positive man from the group of the movement disorder patients) and resulted negative. However, the non treponemal tests, as VDRL, may give false-negative results, especially in the very early and late stages of syphilis and might become non-reactive even without therapy[13,14].

None of the screened patients had a previous history of primary/secondary syphilis. Lumbar puncture for cerebrospinal fluid (CSF) examination and neurosyphilis confirmation was proposed to the TPHA-positive patients of our series but they all refused.

Discussion

Our study demonstrated that in a cohort of neurologic and geriatric patients of our Hospital, the overall prevalence of syphilis reactivity was 3%, without substantial differences between the departments. In the literature, there are very few cohort studies on this topic whereas single case reports of patients with neurosyphilis manifesting as stroke, dementia and movement disorders are increasing in the last years[10].

Ischemic stroke, defined as an acute focal neurological impairment in the territory of a brain or spinal cord vessel, results from the inflammatory response to the *Treponema pallidum* invasion of the vessels' wall (infectious inflammatory arteriopathy). More specifically, the pathogenesis of meningovascular neurosyphilis consists of a lymphoplasmocytic infiltration around the blood vessels of the thickened meninges together with a focal endarteritis ('Heubner arteritis') of the medium and large arteries. This inflammatory process, characterized by fibroblastic proliferation of the intima and thinning of the media, induces a progressive narrowing of the arterial lumen. Since also the small arteries may be damaged by endothelial and adventitial proliferation, all these lesions lead to progressive stenosis resulting in multiple areas of infarction[15]. Clinically, neurosyphilis-induced-stroke may present with symptoms and signs indistinguishable from ischemic stroke due to atheromatous disease[16-18]. The latter usually affects elderly patients with cardiovascular and cerebrovascular risk factors unlike the neurosyphilis-induced-stroke that has been mainly reported in younger patients[19,20]. The few cohorts studies investigating syphilis serology in stroke patients found a prevalence of syphilis reactivity similar to ours: 3,72% in a Portuguese[16], 4% in an Australian[17] and 8,4% in a Thai[18] study. Moreover, among these patients with positive serology, having an average age lower than our patients (67-72 years[16,17]), a significant rate (8-29%)[16-19] received a diagnosis of "definite or probable" neurosyphilis based on the CSF analysis and the subsequent specific treatment. Unfortunately, the patients of our series refused the lumbar puncture, therefore it was not possible to identify the cases of definite neurosyphilis.

Noteworthy, although neurosyphilis is an unusual cause of stroke (probably because of the scarsity of epidemiological surveys), it is a treatable cause of repeated ischemic events therefore it should always be suspected in such cases.

Cognitive impairment is one of the manifestations of general PARESIS, acronym that summerizes the main aspects of the late

neurosyphilis: Personality, Affect, Reflexes, Eye, Sensorium, Intellect and Speech[21]. Data on the association between cognitive impairment (that in the mild form occurs along a continuum from normal cognition to dementia[22]) and syphilis reactivity are scarce. A recent study in 1271 patients (mean age 73 years) of a memory clinic in Singapore found that 4,5% of them were syphilis reactive, with a rate higher in demented (5,9%) compared to non-demented (2,5%) patients[23]. An older survey in a demented Caucasian population (mean age 74 years) reported a 10,9% prevalence of syphilis reactivity[24]. The prevalence in our series (3%) resembles the prevalence of the Asian[23] more than that of the Caucasian population previously studied[24]; however, our screened patients with cognitive impairment were older (average age of 93 years) than patients of the previous studies, probably reflecting the fact that resident population in Liguria region is among the oldest in Europe[25]. The association between syphilis and dementia may be due to the spirochete-induced chronic neuroinflammation. Indeed, it has been described that several microorganisms, including spirochetes containing amyloidogenic proteins, can induce deposition of amyloid beta and tau phosphorylation in the brain[26]. *Treponema pallidum*, that can invade the central nervous system even in the primary stage of syphilis by hematogenous propagation or through axonal transport from the peripheral nerves, is able to evade the host defence mechanism and activate inflammatory processes that damage infected and neighbouring neuronal cells[27]. Studies in Alzheimer's disease patients demonstrated that infections by *Treponema pallidum* and/or other microorganisms induce neuropathological processes that can accelerate neurodegeneration: increased oxidative stress, formation of inflammatory mediators and increased production of beta-amyloid proteins[26,27]. Moreover, neuropathological studies have shown spirochetes infiltration into the brain tissue causing degeneration, fibrosis and progressive narrowing of cerebral blood vessels. The chronic hypoperfusion in the brain tissue leads to cerebral atrofy, lacunae and infarcts[28,29].

Regarding extrapyramidal syndromes, to our knowledge, there are not cohort studies but only sporadic case reports on neurosyphilis presenting as parkinsonism[23-25]. The authors investigated for syphilis when a Parkinsonian syndrome, which is characterized by bradykinesia, rigidity, rest tremor and postural instability, started at an early age and was accompanied by other neurological manifestations, as psychotic symptoms; in all the described cases, antibiotic treatment drammatically improved all the symptoms. In our series of 50 patients with movement disorders, we found syphilis reactivity in a 78-years old man who had not other neurological manifestation, differently from the other cases described in the literature[30-32]. Possible reasons for the development of movement disorders in syphilis are the spirochete-induced impairment of the basal ganglia and generalised cortical atrophy, as disclosed by the brain magnetic resonances performed by the few patients described in the literature[30-32].

Conclusion

Regrettably, the international guidelines do not make any specific mention of syphilis screening in patients with stroke, movement disorders and dementia[1], leaving physicians to their own clinical judgment. Nevertheless, syphilis is one of the treatable cause of these neurological diseases and its correct treatment can prevent further events[33-35].

Although the patients we have retrospectively studied have not undergone lumbar puncture to confirm the diagnosis of neurosyphilis, the not negligible syphilis reactivity rate found in our series (3%) suggests that serological screening for syphilis should be reviewed as a routine screening test in neurological diseases, especially if the presentation is in any way atypical.

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Due to the re-emergence of syphilis in recent years[36-38] neurosyphilis is a dignosis to consider and always suspect in patients with stroke, dementia and Parkinsonism, not only if of young onset. In patients with positive serology in whom there is no contraindication, lumbar puncture should be performed for CSF analysis. Finally, empiric treatment for neurosyphilis should be considered in patients unable to undergo lumbar puncture

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