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Original article

Stroke and syphilis: A retrospective study of 53 patients

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ABSTRACT

Objective. – The aim of this study was to describe the clinical, biological and radiological characteristics of patients with syphilitic vasculitis, and to assess the outcome after treatment.

Methodology. – A retrospective review was carried out based on the records of patients with ischemic stroke, and reactive CSF TPHA and VDRL results. None of these patients showed symptoms of any other diseases or had received high doses of penicillin.

Results. – A total of 53 patients with stroke met the diagnostic criteria for syphilitic arteritis. Their average age was 41 ± 12 years. Nine patients had a history of genital ulcer (17%), and the median duration of illness after presenting a chancre was 8 [range: 1–14] years. A prodromal syndrome was seen in 27 patients (50.9%) and included changes in mental status in 14 patients (26.4%), seizures in 10 cases (18.9%), headache in eight (15.1%) and memory loss in seven (13.2%). Neurological events included focal motor deficits in 29 cases (54.7%), ataxia in 11 (20.8%) and movement disorders in 15 (28.3%). HIV serology was performed in 31 patients and proved negative in every case. Disease evolution was generally favorable: 12 patients (22.6%) were autonomous at the time of hospital discharge; 29 (54.7%) had partially recovered; and only seven (13.2%) still had signs of severe sequelae.

Conclusion. – A diagnosis of syphilitic stroke should be suspected in young patients as a manifestation of syphilis, and tests for neurosyphilis should be routine in neurology departments to make a prompt diagnosis, thereby preventing psychological sequelae.

1. Introduction

Neurosyphilis is characterized by clinical polymorphism. While it is still is a common disease in the developing countries, in developed nations its incidence has decreased with the advent of penicillin therapy. However, it has resurfaced since the emergence of the human immunodeficiency virus (HIV) [1]. Also, the clinical features of neurosyphilis have changed over the past 13 years with an increase of

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atypical forms, including meningovascular syphilis (MVS), resulting from impairment of cerebral nervous system (CNS) meninges and blood vessels [2].

Indeed, MVS comprises up to 10–15% of all neurosyphilis cases [3,4]. It seems to be more frequent in the context of HIV, and numerous studies suggest that the coinfection leads to rapid progression of more virulent forms of neurosyphilis [5–8]. However, there have also been many reported cases of syphilitic vasculitis (SV) in immunocompetent young patients suffering a stroke [9,10].

A common presentation of MVS is a stroke-like syndrome preceded by a subacute encephalitic prodrome, including headaches, seizures and psychological abnormalities. Making a diagnosis can be complicated, especially as neuroimaging often shows cerebral or spinal cord infarcts and/or CNS vasculitis that are non-specific of the diagnosis which, in the end, is essentially supported by tests for non-treponemal antibodies as well as serological treponemal antibodies.

Intravenous penicillin G is the recommended treatment for neurosyphilis. However, the dose and duration of treatment have been controversial and, so far, not extensively evaluated [11]. Thus, the purpose of the present report is to describe and assess the clinical presentations of MVS and its radiological findings, and its management and follow-up after therapy.

2. Methodology

2.1. Cohort selection

In this cross-sectional study, data from 2001 to 2015 were collected retrospectively from patients attending the Neurology and Neurogenetics Department of the Medical & Pharmacy School, Mohammed Vth Souissi University, in Rabat, Morocco. Inclusion criteria were: a reactive *Treponema pallidum* hemagglutination assay (TPHA) as well as non-treponemal Venereal Disease Research Laboratory (VDRL) tests of blood and cerebrospinal fluid (CSF) from patients who had a stroke; absence of the usual vascular risk factors (diabetes, arterial hypertension; 22 patients were smokers, but all had meningitis); and negative findings for all investigations of infections or other disease processes, including normal electrocardiography (ECG; performed twice, at admission and on the following day), transesophageal echocardiography, cervical Doppler ultrasonography, serum electrolytes and lipid profiles.

2.2. Clinical investigations

CSF was examined to determine white blood cell counts, protein concentrations and detection of oligoclonal bands. HIV serology was tested in 31 patients. Imaging studies included contrast-enhanced computed tomography (CT) of the brain for all patients, plain and gadolinium-enhanced magnetic resonance imaging (MRI) of 27 patients, and angiography of 15 patients. Other collected patients' variables were: age at symptom onset; gender; medical history (especially sexual behaviors, history of genital ulcers, treatment for syphilis), duration of disease after chancre; onset modality; prodromal symptoms; clinical manifestations; biological and CSF features; radiological conclusions; and clinical outcome.

2.3. Treatment and follow-up

All patients received high-dose penicillin (10–30 MU/day) associated with corticosteroids (intravenous hydrocortisone hemisuccinate 100 mg/day for 3 days). Outcome was assessed by a complete physical examination, which was recorded at the time of discharge from hospital for all selected patients as well as after a 6-month follow-up.

2.4. Statistical analysis

Statistical analyses were performed using SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA). Demographic and disease characteristics of the patients are represented by descriptive statistics. Percentages and frequencies have been used for categorical variables, while means ± standard deviation (SD) were calculated for continuous variables, and medians and quartiles for discontinuous variables. Pearson's correlation, chi-square, Fischer's exact and Student's t tests have been used where appropriate.

3. Results

Out of 330 patients with neurosyphilis, 53 enrolled at the Neurology Department in Rabat had suffered a stroke. This cohort was recruited between 2001 and 2015, and their mean age was 41 ± 12 years, with 50% of them aged < 40 years. Seven were females (13.2%) and 46 were males (86.8%) with no statistical difference in age, as the mean age for women and men was 41 and 42 years, respectively.

High-risk sexual behaviors (no condom use, multiple partners) were noted in four patients (7.5%), and nine patients had a history of genital ulcers (17%), four of whom had been treated with benzathine penicillin G (2.4 MU in a single intramuscular injection). Median duration of illness after presenting with chancre was 8 [range: 1–14] years.

The onset of stroke was acute in 31 cases (58.5%) and subacute in 22 (41.5%), with the most common prodromal syndrome being changes in mental status, including altered personality and emotional lability, followed by seizures, headaches, memory loss and decreased visual acuity (Table 1).

These prodromal features began a few weeks to 1 year before the acute clinical neurological events appeared (Table 1). In addition, dysarthria was detected in nine patients (16.9%), characterized by poorly articulated, irregular and

Table 1 – Patients' prodromal and clinical features.

	Patients [*n* (%)]
Prodromal features	
Personality changes	14 (26.6)
Seizures	10 (18.9)
Headaches	8 (15.1)
Memory loss	7 (13.2)
Decrease of visual acuity	6 (11.3)
Insomnia	2 (3.8)
Clinical features	
Focal motor deficit	29 (54.7)
Ataxia	11 (20.8)
Movement disorders	15 (28.3)

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ultimately incomprehensible speech. This was associated in two cases with trembling lips, and in one case with chewing.

Cranial nerve impairment was also seen in 13 cases, affecting the cochleovestibular nerve in 11.3%, optic and oculomotor nerves in 5.7%, and facial nerve in 1.9%. The Argyll Robertson pupil sign was seen in five patients (9.4%).

CSF analysis revealed elevated cell counts and hyperprotein contents in all patients. The median cell count was 8 [range: 6–14] cells/μL, and the median protein concentration was 0.7 [range: 0.6–1] g/L. Electrophoresis was performed on CSF from 26 patients and showed oligoclonal bands in 16 of them (72.5%). The median VDRL titer was 1:16 [range: 16–32] and median TPHA titer was 1:1280 [range: 640–2560]. Tests for HIV coinfection were performed in 31 patients (58.5%) and proved negative in all cases, as the infection has been systematically controlled since 2010.

Brain CT scans demonstrated cerebral infarction in 50 patients (94.3%), cortical atrophy in eight (15%) and non-specific white-matter lesions in three (5.7%), with extra-axial enhancement indicating meningitis noted in two patients (3.7%). Brain MRI scans confirmed infarction in the territory of the middle cerebral artery (MCA) in 14 cases (26.41%; Fig. 1), acute infarction in the vertebrobasilar territory in 25 patients (26.4%; Fig. 2) and confirmed infarction in the deep MCA territory in three cases (5.6%; Fig. 3). In contrast, gadolinium administration showed no enhancement. Arteritis was demonstrated in six (11.3%) of the 15 patients who underwent conventional angiography.

Concerning treatment, all 53 patients were treated with four courses of high-dose penicillin (30 MU/day for 10 days) every 3 months. The use of intravenous corticosteroids (hydrocortisone hemisuccinate 100 mg) was systematic because of meningitis detected during CSF investigations. All patients also received 160 mg/day of an antiplatelet drug.

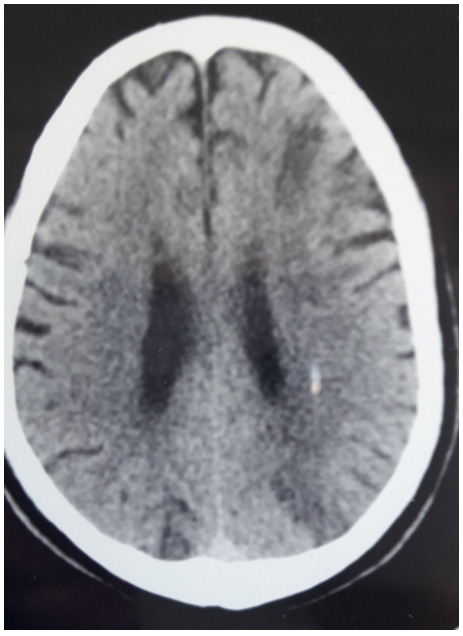

Fig. 1 – Non-contrast computed tomography (CT) shows diffuse hypodensity and sulcal effacement involving the left middle cerebral artery territories, consistent with acute infarction.

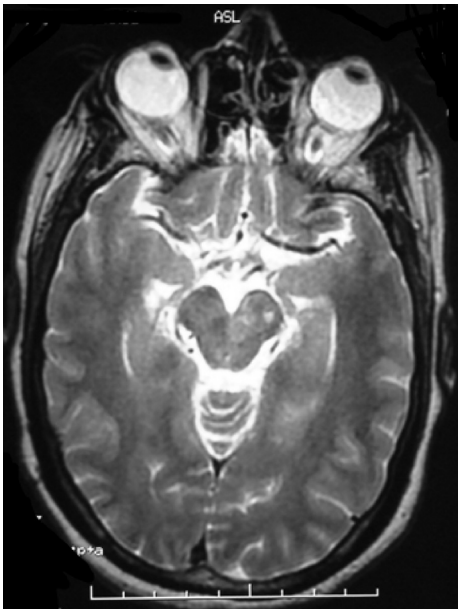

Fig. 2 – Axial T2-weighted magnetic resonance imaging (MRI) shows an abnormal, hyperintense signal involving the right side of the midbrain.

No patient died during the hospital stay, and none of those with cerebellar infarction developed hydrocephalus or pressure on the brain stem, a known life-threatening complication. Twelve patients (22.6%) were capable of performing activities independently at the time of hospital discharge, 29 (54.7%) had partially recovered, and only seven (13.2%) still presented with severe sequelae. Ten patients were seen 6 months later and showed continuing improvement after neurological assessment.

4. Discussion

Stroke is a well-known complication of neurosyphilis, and MVS can arise as a unique subset of neurosyphilis. However, with the widespread use of penicillin, neurosyphilis has considerably decreased in recent years, although the acquired immunodeficiency syndrome (AIDS) epidemic has led to a reemergence of the disease worldwide, and especially atypical forms such as MVS.

While specific epidemiological data for MVS are still unavailable, numerous reports from HIV-infected patients suggest that atypical presentations of neurosyphilis might be a marker of HIV infection in asymptomatic patients [8,11]. In addition, many authors have described cases of MVS in immunocompetent patients even after appropriate treatment of primary syphilis [12,13].

In our present report, HIV serology tests were negative in all the patients who underwent it, confirming the fact that neurosyphilis is still a health problem in some developing countries independently of AIDS [13].

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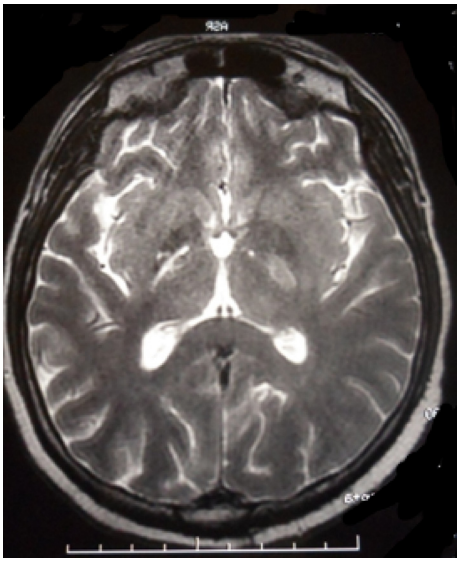

Fig. 3 – Axial T2-weighted MRI shows an abnormal hyperintense signal involving the right posterior limb of the internal capsule.

The frequency of seroconversion (SCV) is variously described in the literature as representing 11–14.9% of cases [3,4,14], compared with 10.3% of all our present neurosyphilis cases. Most of the cases described in the literature were younger than typical stroke patients [7,9,10] and, indeed, 50% of our patients were aged < 40 years.

Our results are consistent with those described in the literature. SCV occurs in the tertiary and, occasionally, secondary stages of untreated syphilis within the first few months to several years after infection, with a peak occurrence at 7 years after the initial infection [15]. However, the possibility of atypical symptoms and presentations, rapid progression to tertiary syphilis and treatment failures of this 'great imitator' should still be borne in mind.

High-risk sexual behaviors were reported in only 7.5% of our cases, which may be explained by the strong taboo surrounding sexual activity in our culture, and 17% of our patients had genital ulcers. According to several series, this condition is found in 12–56% of cases [16,17].

Many reports suggest that previous therapy for primary syphilis often involves concentrations of penicillin in CSF that are inadequate for eradicating *T. pallidum* [18,19]. Also, Moskovitz et al. [12] reported cases of HIV-infected patients with neurosyphilis who developed MVS despite high-dose intravenous penicillin G treatment. In our present series, four patients who received therapy for early syphilis developed recurrent infections of the CNS regardless of HIV infection.

The pathophysiology of MVS is a perivascular lymphoplasmocytic infiltration around small blood vessels in the thickened meninges combined with a focal endarteritis known as 'Heubner arteritis', which most of the time involves the medium and large vessels. This type of arteritis is characterized by fibroblastic proliferation of the intima and thinning of the media, causing narrowing of the arterial lumen. Moreover, other small blood vessels called 'lenticulostriate arteries' may also be damaged by endothelial and adventitial proliferation. All these lesions lead to progressive stenosis, which can result in multiple small areas of infarction [6].

However, vascular syphilis can cause cerebral infarction regardless of CNS arteritis. It has been reported that aortic aneurysms arise in syphilis and can also lead to cerebral infarction [20]. The MCA is the most commonly involved artery, with a frequency of 66% [15] while, less frequently, the anterior and posterior cerebral arteries or branches of the basilar artery are affected.

In our present series, 28 patients (52.8%) suffered a stroke of the MCA territory. However, what was particularly striking was the high frequency of rare vascular forms. Indeed, 14 cases (26.4%) were diagnosed with striatitis related to the lenticulostriate arteries, leading to a unilateral parkinsonian syndrome, whereas 11 patients (20.8%) had cerebellitis suggestive of vertebrobasilar obliterans arteritis, causing a cerebellar hemisyndrome, a condition rarely reported in the literature [21–23].

As described in other studies [24], cerebral or medullary venous, deep venous system or venous sinus are rarely affected. In our series, one patient had a deep cerebral venous thrombosis of the Rosenthal vein. Clinical symptoms depend on the arterial territory involved. It is a combination of various subacute or chronic, diffuse encephalitic signs and focal features in young people.

The appearance of a prodromal syndrome before acute transitory or permanently ischemic incidents should suggest a syphilitic diagnosis even if it affects only 25% of cases [3]. These prodromes can appear a few weeks to several months before the appearance of clinical signs, and may include headaches, personality changes, emotional lability, insomnia, decreased visual acuity and vertigo, seemingly as a result of leptomeningeal inflammation. In our series, 50% of patients reported a prodromal syndrome before acute or subacute neurological events either spontaneously or after direct questioning.

In addition to clinical signs, the diagnosis of MVS requires non-treponemal and specific treponemal testing of CSF samples. Specific treponemal tests include fluorescent treponemal antibody absorption (FTA-ABS) and TPHA, which have a sensitivity of 97–100% and remain positive even after successful treatment [25]. Non-treponemal tests include the VDRL and rapid plasma reagin (RPR) tests, which are less sensitive than either the FTA-ABS or TPHA. These tests have a high specificity, but a sensitivity of only 30% and 70% in latent and late syphilis, respectively [25]. Non-treponemal CSF examination is the diagnostic test of choice for follow-ups.

In our department, a diagnosis of MVS is always suspected in young patients who have had a stroke. As in many centers, laboratory tests for syphilis, comprising TPHA and VDRL in blood and CSF, are included in our preliminary stroke laboratory examination. In addition, MVS is very often associated with lymphocytic pleocytosis [26]. All of the patients in our present series had syphilitic meningitis lying at the base of their vascular injuries.

Although radiological imaging is non-specific, CT can show ischemic infarctions in vascular territories that are enhanced with contrast [27], while MRI is useful for diagnosing acute

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infarcts in the vertebrobasilar territory or lacunar infarction related to diffuse and small-caliber-vessel injury. It can also more clearly demonstrate leptomeningeal enhancement with dural thickening and edema.

MR angiography using an axial three-dimensional time-of-flight technique can also reveal irregularities in cerebral artery trunks [22], although angiographic findings have been reported by only few authors [28]. Appearances may be normal or reveal arthritic lesions of the intracranial vessels, with concentric narrowing and ectasia of the supraclinoid carotid and basilar arteries. The proximal anterior and middle arteries, but only their distal branches, may also be affected [29]. Angiography can also detect concomitant atheromatous ulcerated stenosis of the extracranial carotid artery, which may be unrelated to the suspected neurosyphilis [28,29]. For our present study, it was not deemed necessary to perform cerebral angiography in all our patients, given the associated risks of the procedure.

Treatment protocols for neurosyphilis remain controversial. While a high-dose regimen of intravenous aqueous penicillin G has been considered effective against neurosyphilis, there have been several reports in the literature of penicillin treatment failure, with progression or recurrence of neurosyphilis in both HIV-infected and non-HIV-infected patients [12,30]. Several studies have recommended 18–24 MU/day of penicillin G administered intravenously for 10–14 days. Efficacy of this treatment is assessed by cell counts and serological conversion of CSF, although there are no established guidelines to define an adequate rate of resolution of such CSF abnormalities [11,30].

In 1999, our department performed a comparative study of two protocols as first-line treatments in two groups of neurosyphilitic patients. Each group included eight patients. Treatment for group A consisted of a 4-h intravenous infusion of 20 MU/day of penicillin G for 3 weeks, whereas treatment for group B was a 6-h intravenous infusion of 30 MU/day of penicillin G for 10 days. It was concluded that the B therapy was more efficient than A in terms of patient recovery time, normalization of inflammatory signs and negative VDRL test results. Our department also adopted the regimen of four courses of penicillin therapy at the time of diagnosis rather than at 3, 6 or 9 months earlier, regardless of CSF analysis results and type of neurosyphilis. In addition, as with stroke management, the treatment also involves antiplatelet or anticoagulation agents according to the vascular injury related to neurosyphilis [2].

In our present retrospective study, laboratory parameters were not studied after the course of penicillin, and follow-up was based on clinical criteria only. A larger prospective study and a well-controlled study with adequate analyses of CSF parameters, including monitoring of penicillin concentrations, is now needed to verify these results and to validate the superiority of protocol B.

Our study was limited by its retrospective nature especially concerning serological and biological follow-up following the four courses of penicillin. However, despite CSF analyses, our patients received penicillin infusions every 3 months over the course of 1 year, whereas the US Centers for Disease Control and Prevention (CDC) have recommended, in 2002, another course of penicillin 6 months after the initial treatment in cases of persistent CSF perturbations [31].

To our knowledge, the strength of our study is that this was the largest published series of MVS, which is also seen in immunocompetent patients who differ from most of the cases described in the literature.

5. Conclusion

The diagnosis of neurosyphilis remains a challenge that requires syphilis screening tests, especially in young patients presenting with stroke.

Disclosure of interest

The authors declare that they have no competing interest.

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