

Neurosyphilis Presenting with a Stroke-Like Syndrome

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Abstract

Objectives: Syphilis is still a public health problem in the world. Israel is a country with high immigration rates, some of the new immigrants coming from countries with a high prevalence of syphilis.

Patients: We want to report a series of 7 patients admitted to the neurology ward at the Kaplan Medical Center in Rehovot, Israel with acute strokes which ultimately were attributed to meningo-vascular syphilis.

Methods: Retrospective observational study.

Results: Six patients are presented with acute ischemic stroke and 1 with intra parenchymal hematoma. There were 6 male patients and one female. The mean age of the patients was younger than that of stroke patients in Israel. There were 6 patients of Ethiopian origin and one born in Israel. All the patients had positive VDRL and TPHA serology in the blood and all the patients that had LP performed had positive syphilis ELISA in the liver.

Conclusion: Neurosyphilis should be considered among patients with stroke and the presence of more "traditional" cardiovascular risk factors should not prevent us from considering it.

Keywords: Neurosyphilis; Stroke; Vascular risk factor

Introduction

Syphilis is still a public health problem in the world. The World Health Organization estimated that approximately 12 million new cases are reported each year in the world with More than 90 percent from developing countries [1-3]. Moreover, syphilis has acquired a higher potential of morbidity and mortality with the increasing prevalence of HIV infection. If syphilis is rare in developed countries, it is much more common in developing countries where prevalence can reach 25% amongst blood donors.

Israel is a country that absorbs Jewish immigrants from all over the world. In particular, from 1990 to 2001 more than 900,000 immigrants came to the country (13% of the total Israeli population), mostly from the former Soviet Union and from Africa.

A study that tested serological evidence of syphilis among blood samples from volunteer blood donors in Israel showed that the new immigrants from Africa and from Eastern Europe who arrived in Israel after 1990 had a 19-fold and 10.8-fold (resp.) higher risk for syphilis seropositivity than donors born in Israel [4]. The findings were similar to the prevalence in their countries of origin, as reported by the Israeli Ministry of Health and the 2001 WHO European Health database. These results are in accordance with the high incidence of syphilis in the former communist countries of Eastern Europe, with rates of 262, 245, and 150 cases per 100,000 in the Russian Federation, Kazakhstan and Ukraine, respectively, and with data published from Africa in 2001, with infection rates of 1000, 300-400, and 100-200 cases per 100,000 found in Zambia, Kenya, and Benin, respectively.

A high rate of syphilis co-infection has been reported in HIV-positive patients residing in northern Israel [5].

Lately the Israeli Health Ministry reported that there has been an increase in the number of cases of syphilis in the Tel Aviv district in the last two years, primarily among refugees and foreign workers. The number of reported cases rose significantly from 38 in 2012 to 112 last year [6].

We will follow up a series of seven patients admitted to the neurology ward at the Kaplan Medical Center in Rehovot, Israel with acute strokes which ultimately were attributed to meningo-vascular syphilis.

Our goal is to draw attention to the clinical and radiologic features of stroke in patients with neuro-syphilis. Even in stroke patients with vascular risk factors we should bear in mind the possibility of syphilis as the cause of the stroke and test for it when appropriate. Serological tests for syphilis as a screening method are quite simple and we should use them in appropriate stroke patients.

Patients and Methods

All patients were admitted to our department between 08/2014 and 08/2015 due to acute onset of neurological impairment consistent with acute cerebro-vascular disease.

The cohort for this study consisted of six consecutive acute stroke patients who were found to have positive antibodies to VDRL and TPHA in the serum. Antibodies were detected in the hospital immunologic laboratory.

Each acute stroke patient at our department undergoes a thorough battery of investigations for determining the type and localization of

stroke, vascular and cardiac risk factors. Concordantly all patients underwent an unenhanced CT scan, vascular imaging of cervical arteries by US-Doppler or CTA and cardiac evaluation with cardiac echography and 24 hours cardiac rhythm holter.

Syphilis can be diagnosed by different serological laboratory tests, which are also useful in establishing the disease stage, in conjunction with other clinical tests. Serological diagnosis is generally established using a standard non-treponemal antibody screening test, the Venereal Disease Research Laboratory test (VDRL) or the Rapid Plasma Reagin test (RPR) are most commonly used, in combination with a specific treponemal antibody test such as the *Treponema pallidum* haemagglutination test (TPHA) for confirmation. ELISA (Trinity, biotech) is tested on the ETI-Max 3000 analyzer.

All patients found to have positive antibodies to VDRL (BBL) or TPHA (Axis-Shield) in the serum underwent lumbar puncture which measured the opening pressure, presence of inflammatory cells, content of protein and glucose in the liver and VDRL (BBL), TPHA (Axis-Shield) and syphilis ELISA. CSF antibodies were detected at the National Reference Center for Syphilis, Abu Kabir, Israel. None of our patients had HIV co-infection.

Six of our patients were treated with IV crystalline penicillin, 24 million units/day, for 14 days.

Case 1

A 69-year-old man, born in Ethiopia, suffering of type II DM, hyperlipidemia and hypertension, presented to the ER with right mild hemiparesis and dysarthria that started 3 hours before his arrival. Non-enhanced brain CT and brain and neck arteries CTA were reported normal. The patient was treated with I.V recombinant T.P.A but subsequently his condition deteriorated and he became almost hemiplegic. A follow up CT one week later disclosed a new hypo-dense region in the pons, not seen in the previous studies, consistent with an acute stroke.

Cardiac Echo (TTE) was normal and so was cardiac rhythm 24 hours monitoring.

Serum VDRL was positive 1:1, TPHA was positive.

LP - Normal opening pressure, 6WBC, CSF protein – 230 mg/dL, CSF glucose - 84 mg/dL.

In the C.S.F -Syphilis ELISA was positive, VDRL was negative, TPHA was positive

The patient was treated with IV penicillin crystalline 24 million IU/day for two weeks. During hospitalization, there was only minimal improvement in his condition and he was transferred to a rehabilitation facility.

Case 2

A 60-year-old man, born in Ethiopia, suffering of hypertension and ischemic heart disease. One month before the present admission he was hospitalized in our institution after a cardiac event (M.I) and underwent percutaneous cardiac angiography and stenting of the L.A.D and diagonal artery. Afterwards he was treated with anti-aggregate therapy –efficient.

The day he was admitted he experienced weakness of the right limbs. He presented within one hour to the E.R. Brain C.T without enhancement showed several small hypo-dense areas in the supra-

tentorial white matter. CTA of brain and neck arteries didn't show any hemo-dynamically significant vascular. He was treated with I.V recombinant T.P.A with significant improvement in the limb weakness. During the hospital stay a heart echography was normal and so was 24 hours heart rhythm holter.

During his stay, a blood test showed positive VDRL, positive TPHA

L.P – Normal opening pressure, normal content in terms of protein and glucose, 5 – white blood cells.

In the C.S.F -Syphilis ELISA was positive, VDRL was negative, TPHA was positive.

The patient was treated with IV penicillin crystalline 24 million IU/day for two weeks. During hospitalization, there was significant improvement in his condition.

Case 3

A 55-year-old male, born in Ethiopia, with a past medical history of hypertension, hyperlipidemia and mild diabetes, was admitted due to left limbs paresthesia and mild weakness that started an hour before. He was treated with I.V recombinant T.P.A and made a partial recovery. C.T.A performed several days later showed a new hypo-dense area in the right centrum semi ovale consistent with a new ischemic stroke and marked irregularity of the right M.C.A

Cardiac echography and 24 hours cardiac rhythm monitoring were normal.

Blood VDRL and TPHA were positive.

Lumbar puncture was performed. The C.S.F content was in normal limits except for increased protein content – 63 mg/dL (normal up to 45 mg/dL).

In the C.S.F -Syphilis ELISA was positive, VDRL was negative, TPHA was positive

The patient was treated with a course of I.V penicillin. He was discharged with anti-aggregate treatment.

Case 4

A 58-year-old female, born in Ethiopia, with a past medical history of hypertension, hyperlipidemia and diabetes, was admitted due to right limbs weakness and speech impairment that started the day before she was admitted in the hospital. Brain C.T. was interpreted as normal. Neck and brain C.T.A. performed the day after her admission showed a hypo-dense non-enhancing region in the left parietal lobe, that wasn't seen in the previous C.T. scan. Another new hypo-dense region was seen in the cerebellum. Both represent acute ischemic strokes most probably.

Cardiac echography (T.T.E.) and 24 hours cardiac rhythm holter were normal. The patient refused T.E.E. (trans-esophageal echography)

A blood test showed positive VDRL and TPHA. Lumbar puncture was performed. The C.S.F content was in normal limits except for increased protein content – 64 mg/dL (normal up to 45 mg/dL).

In the C.S.F -Syphilis ELISA was positive, VDRL was positive, TPHA was negative.

The patient was treated with a course of I.V penicillin. She was discharged to a rehabilitation facility.

Case 5

A 49-year-old male, born in Ethiopia, with a past medical history of hypertension, diabetes and heavy smoking, was admitted due to left limbs and face paresthesia that started several hours before.

His chronic medications included aspirin, which was interrupted several days previously as he was scheduled to a minor surgical cosmetic procedure.

Brain unenhanced C.T. was interpreted as normal. Cervical arteries duplex, cardiac echography (T.T.E.) and 24 hours cardiac rhythm monitoring were normal.

A blood test showed positive VDRL and TPHA.

Lumbar puncture was performed. The C.S.F content was in normal limits.

In the C.S.F -Syphilis ELISA was positive, VDRL was positive, TPHA was negative.

The patient was treated with a course of I.V penicillin.

Case 6

A 49-year-old male, born in Ethiopia, with a past medical history of hypertension was admitted due to acute left limbs weakness that appeared suddenly the day of his admission.

Brain C.T. showed a large acute parenchymal hematoma, 2.9 × 4.6 cm originating from the right basal ganglia region. Another small lacunar hypo-dense region representing an old infarct was seen in the left basal ganglia.

During the following days, several brain C.T scans were performed showing gradual shrinkage of the hematoma size.

A blood test showed positive TPHA, positive syphilis ELISA and VDRL.

Lumber puncture was not performed due to mass effect of the parenchymal hematoma and the patient was transferred to a rehabilitation facility.

Unfortunately, he was later lost to follow up.

Case 7

A 57-year-old male, born in Israel, with a past medical history of hypertension, hypercholesterolemia, diabetes mellitus and prior ischemic stroke was admitted due to sudden onset of dizziness and blurred vision which started the day before his admission. Neurological examination disclosed gaze paresis to the left and truncal and limbs ataxia.

Unenhanced brain CT showed bilateral old supra tentorial lacunar strokes. Cervical and brain arteries CT angiography, cardiac echography (T.T.E.) and 24 hours cardiac rhythm monitoring were normal.

A blood test showed positive TPHA and syphilis ELISA.

Lumbar puncture was performed. The C.S.F content was in normal limits.

In the C.S.F-Syphilis ELISA was positive, VDRL was positive, TPHA was negative.

The patient was treated with a course of I.V penicillin.

Results

The results are summarized in Table 1.

We describe a series of seven consecutive patients, who presented with acute neurological deficiency. Six of them were found to have acute ischemic stroke and one had a hemorrhagic stroke. There were six males and one female.

Mean age was 49.7- younger than the mean age of patients with acute stroke in Israel [7].

Six of them were new immigrants from Ethiopia and one was born in Israel.

All of them had also one or more "classical" vascular risk factors: hypertension, hyperlipidemia, diabetes or smoking.

Mean NIHSS score was 7.3.

Six of the patients had ischemic strokes, all of them consistent clinically and radiologically with lacunar strokes. 3 were supra-tentorial and 3 infra-tentorial. One patient had an intra-parenchymal hematoma.

CSF content: 6 out of 7 patients had increased protein content in the CSF. No pleocytosis was found. In 6 of the patients VDRL was positive in the liver and negative in one patient. ELISA was positive in all of them.

Discussion

Despite effective treatment and promising new diagnostics syphilis incidence continues to rise in low income countries and also in certain populations at risk in high income countries.

Israel is a country with high immigration rates, some of the new immigrants coming from countries with a high prevalence of syphilis.

We describe here a series of seven consecutive patients that presented along one year with acute neurological deficit, attributed to acute stroke.

As reported in previous series the majority of the patients are men. In our series, there was one woman only.

The clinical manifestations of neuro-syphilis are highly variable and patients with meningo-vascular syphilis may present with symptoms and signs that indistinguishable from stroke due to atheromatous disease [8-10]. According to former series ischemic stroke was the most common presentation. Occlusion of small vessels was found more frequently than that of large vessels. There seems to be the same incidence of posterior circulation stroke as those found in the carotid territory.

The clinical entity found in most of the patients in our series was ischemic stroke and this is in accordance with previously reported case series that analyzed clinical and imaging findings in patients with neurovascular syphilis. Only one patient had an intra-parenchymal hemorrhage [11-16].

Patient info/Gender/Age	Neurological Complaints and finding	Brain C. T	Blood Serology	C.S.F content	C.S.F Serology
Male, 69 yrs	Rt hemiparesis and dysarthria	Pontine acute stroke	VDRL+ TPHA+	6 WBC, glucose-normal, protein-high	VDRL-
					TPHA+
					ELISA+
Male, 60 yrs	Rt hemiparesis	Multiple lacunar strokes	VDRL+ TPHA+	5 WBC, glucose-normal, protein-normal	VDRL-
					TPHA+
					ELISA+
Male, 55 yrs	Lt hemiparesis	Rt acute lacunar stroke	VDRL+ TPHA+	2 WBC, glucose-normal, protein-high	VDRL-
					TPHA+
					ELISA+
Female, 58 yrs	Rt hemiparesis	Lt acute parietal and cerebellar strokes	VDRL+ TPHA+	1 WBC, glucose-normal, protein-high	VDRL+
					TPHA-
					ELISA+
Male, 49 yrs	Lt paresthesia	Normal	VDRL+ TPHA+	3 WBC, glucose-normal, protein-normal	VDRL+
					TPHA-
					ELISA+
Male, 49 yrs	Lt hemiplegia	Rt basal ganglia hematoma with mass effect	VDRL+ TPHA+	Not done	Not done
Male, 57 yrs	Truncal and limbs ataxia, gaze paresis	Bilateral old supra tentorial lacunar infarcts	VDRL+ TPHA+	2 WBC, glucose-normal, protein-normal	VDRL+
					TPHA-
					ELISA+

Table 1: Test results.

Most of the patients had multiple supra tentorial lacunar strokes but we cannot exclude missed infra tentorial strokes as the main imaging modality was CT.

Previous studies showed no difference in the incidence of more “classical” cardiovascular risk factors in stroke patients with and without neuro-syphilis. Such was the case in our series of patients. The occurrence of cardiovascular risk factors should not prevent testing for the occurrence of syphilis serology in cases with a high index of suspicion.

All the patients had positive serum serology as this was the inclusion criteria. Half of them had normal CSF content. Only 2 patients had very mild pleocytosis and two had high protein content.

All of them had positive TPHA and ELISA for syphilis in the CSF.

The major drawback of the present series is that the tested patients were not orderly chosen from all the stroke patients that were admitted at our department during that period.

Stroke patients less than 50-year-old are tested for syphilis serology in the serum. As for older patients with vascular risk factors we tested only the ones for whom there was a higher index of suspicion. We intend to plan a larger scale prospective study that will include testing

all stroke patients in order to better estimate the true prevalence of neurosyphilis among stroke patients and determine their clinical and radiological features.

Conclusion

The neurologic manifestations observed among patients with syphilis have evolved over time; the meningeal and vascular forms of syphilis are more commonly observed. In clinical practice, stroke patients should undergo blood serum screening for syphilis. When serology proves positive, all patients should undergo CSF examination. Neurosyphilis should be considered among patients with stroke, especially immigrants from countries with a high prevalence of syphilis and the presence of more “traditional” cardiovascular risk factors should not prevent us from considering it.

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Conflicts of Interest

There are no conflicts of interest to declare.

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