Neurosyphilis in a young Indian expatriate

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ABSTRACT

Neurosyphilis is the infection of the central nervous system with treponema pallidum species, and true to its reputation as the old mimic, can present with a multitude of clinical scenarios, one of which is stroke in the young. Rare in developed countries, except for an at-risk population of drug abusers and HIV infected patients; it is still common in the rest of the world. We describe the case of a young Indian male, his presentation, diagnosis and treatment, and remarkable recovery on aqueous penicillin G therapy following his presentation with a stroke.

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Wars, migration, and sexual promiscuity have prepared the ground for the return of neurosyphilis, also known as dementia paralytica, as an important cause of neurological and psychiatric syndromes.[1] While rare in developed countries, it remains a serious public health problem in the third world.[2] In one major study from South Africa, the average age of presentation ranged from 35.9-42.6 years.[3] In our case report, we present the unusual occurrence of this old mimic in an Indian male of only 20 years of age, his presentation, diagnosis and treatment, and subsequent remarkable recovery.

Case report. A 23-year-old Indian male gardener, single, presented to Riyadh Medical Complex, Riyadh, Saudi Arabia, accident and emergency department, complaining of back pain and neck stiffness for 10 days, fever and burning micturition for 3 days, followed by sudden loss of power of the right side of the body of 12 hours duration. He had worked as a farmer in his home country and had not been outside the Kingdom for the last 3 years. He had an unremarkable past medical and surgical history. His parents and 4 siblings were alive and well with no family history of chronic illnesses. Having a low-income job, he shared an apartment with 3 other co-workers. All his friends were well. He admitted to heavy smoking for the last 10 years, with one packet per day, and to occasional unprotected heterosexual intercourse. On examination, his vital signs showed a temperature of 37ºC, a blood pressure of 150/90 mm Hg, a pulse rate of 68 per minute and a respiratory rate of 22 per minute. General exam revealed a conscious and oriented young male with no skin rash, no lymphadenopathy, neck tenderness but no stiffness. A 1 x 1 cm ulcer with granulation tissue was noted on the anterior aspect of his right leg. Gastrointestinal system examination revealed a distended urinary bladder. Examination of the rectum and genitalia was categorically refused by the patient. Examination of the cardiovascular and respiratory systems was normal. Central nervous system examination showed a right upper motor neuron facial palsy; lateral gaze paralysis of the right eye was noted. Pupils were normal. Tone of both upper and lower limbs was normal. Reflexes were generally exaggerated, but while power on the left side was normal, power of the right upper limb was 4/5, and of the right lower limb

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2/5. There was no clonus and the plantar responses were equivocal. No cerebellar signs were noted, and sensation was intact. The patient was admitted with the working diagnosis of left dominant hemisphere stroke in the young. A Foley's catheter was inserted to relieve the bladder distension, and a lumber puncture performed after the CT scan of the brain with contrast revealed a radiolucent lesion of the left hemisphere not taking contrast with absence of any brain edema (**Figure 1**). Laboratory investigations revealed a white blood cell count of 8.9 x 10^9, with neutrophil count of 68%, lymphocyte count of 22%, monocytes of 8%, eosinophil count of 2%, hemoglobin of 13.5 g/dl, and platelet count of 231. Erythrocyte sedimentation rate was 41 mm/hrs. Urea and electrolytes showed a glucose level of 7.4 mmol/l, urea 4.1 mmol/l, creatinine 65 μmol/l, sodium 139 mmol/l, potassium 4.3 mmol/l, and chloride 108 mmol/l. Cardiac enzymes showed a lactate dehydrogenase level of 310 u/l and creatinine kinase level of 234 u/l. Liver function test showed an aspartate transferase level of 30 u/l, an alanine transferase level of 31 u/l and an alkaline phosphatase level of 265 u/l, total protein 70.9 g/l, albumin 47.6 g/l, total bilirubin 6.47 μmol/l. Coagulation profile showed a prothrombin time of 19 seconds, an international normalized ratio of 1.23, and an activated partial thromboplastin time of 27.4 seconds. Protein C activity was normal at 114.94%, anti-thrombin III activity was normal at 172.26%, protein S activity was normal at 120%. Serology revealed rheumatoid factor, anti nuclear antibody and anti ds DNA to be negative. Brucella titer for abortus and melitensis was negative. Widal test was negative. Malaria films thin and thick were negative. Blood and urine cultures were negative. Screens for human immunodeficiency virus 1 and 2 were negative. Electrocardiogram was within normal limits. Trans-thoracic echocardiogram was normal with an ejection fraction of 67%. Chest radiograph was normal. Ultrasound of the abdomen was normal. Cerebrospinal fluid (CSF) analysis showed a total leukocyte count of 1300 with 96% lymphocytes and 4% monocytes. The CSF glucose was 74.16 mg%, CSF protein was 250 mg%, and LDH 54 u/l. With the finding of lymphocytic meningitis, the patient was commenced on anti-tuberculous medication in the form of isoniazid 300 mgs per os per day, rifampicin 600 mgs per os per day, pyrazinamide 1.5 gms per os per day and ethambutol 800 mgs per os per day with pyridoxine 40 mgs per os per day and dexamethasone 4 mgs intravenously every 6 hours. On day 11 of hospitalization, while on treatment, he developed left lower limb weakness 3/5 with normal tone and reflexes. A sensory level appeared around T10. The Mantoux test had been negative and MRI of the brain and cervical spine showed multiple hypo-intense lesions on T1 weighted images and hyper-intense on T2 weighted images with patchy enhancement distributed mainly in the left para-ventricular area and posterior part of the left putamen, and along the posterior border of the right cerebellar tonsil, in the left temporal lobe, and upper medulla, and posterior to the M2 segment of the left middle cerebral artery (**Figure 2**). There was no meningeal enhancement. The whole of the cord showed an altered signal and was swollen and hyper-intense on T2 and showed patchy nodular enhancement along the anterior and posterior dural surfaces (**Figure 3**). These features were suggestive of a disseminated encephalomyelitis. Eventually, the diagnosis was reached on day 17 of hospitalization by serology, when the results of the syphilis screen were as follows: reactive plasma reagin (RPR) test was reactive >1/16 and treponema pallidum hemagglutination test was positive with a titer of >1/1280. The CSF Venereal Disease Research Laboratory test (VDRL) was positive. The patient suffered from neurosyphilis. The anti-tuberculous medication and dexamethasone were stopped, and he was started on aqueous penicillin G 4 million units intravenously every 4 hours, probenecid 500 mgs 4 times daily, and prednisone 40 mgs per day. This was continued for 16 days. He was evaluated by the ophthalmologist, but no lesions characteristic of syphilis were found. A dermatologist took a biopsy from the leg ulcer, but only normal granulation tissue was reported. Meanwhile, the patient improved markedly, regaining power of his upper limbs to 5/5 and return of power to the lower limbs right side 5/5 and left side 4/5. Repeat CSF analysis a week later showed total leukocyte count of 20 with 98% lymphocytes and 2% neutrophils, CSF glucose was 22 mg%, and CSF protein 100 mg%. The CSF stain and culture for tuberculosis were negative. The patient was eventually discharged on the 38th day of hospitalization able to walk unaided and with only a mild 4/5 weakness in the right side of his body.

Discussion. The study of a disease like syphilis is complicated by decade old terms that confuse more than they enable one to grasp the subject. A recent effort to categorize patients in a more clinically oriented way has been put forward by Timmermans and Carr;[3] according to their classification our patient, having presented as a stroke, belongs in category 2 of patients diagnosed to have neurosyphilis. Affliction of the brain in syphilis indicates contraction of infection many years before presentation, and even though treponema pallidum, the causative organism invades

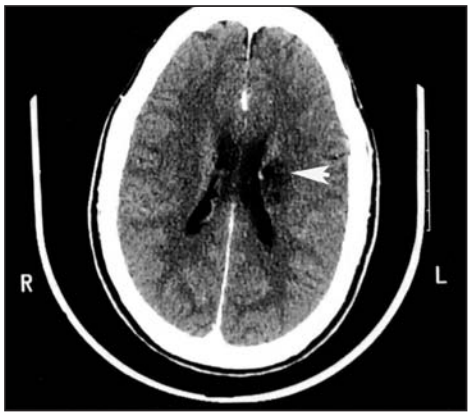

Figure 1 - Brain CT showing a hypodense area in the left internal capsule.

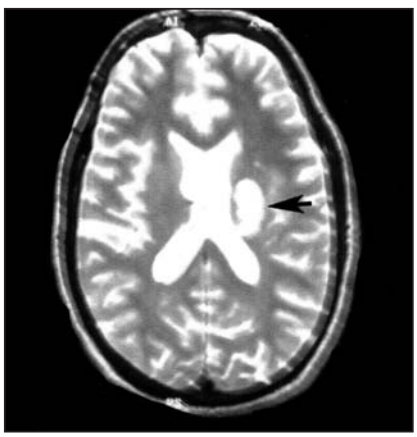

Figure 2 - Brain MRI (T2 weighted) showing a hyperintense lesion in the left internal capsule.

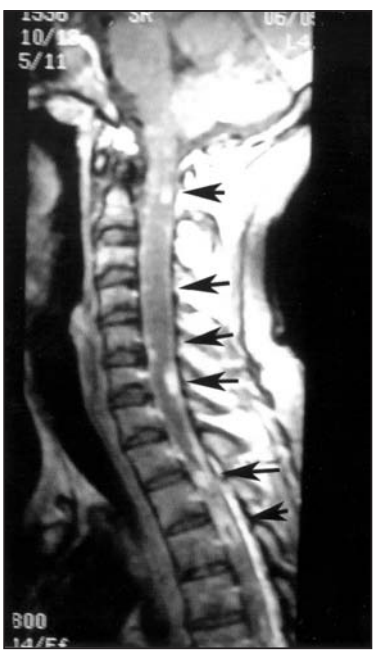

Figure 3 - Spinal cord MRI (T2 weighted) showing multiple hyperintense lesions along the cord.

the central nervous system early in the disease it persists in only a subset of infected persons.[3,4] Another reason for early presentation with neurosyphilis is the co-infection with the acquired immunodeficiency virus which increases the chances of progression from primary syphilis to neurosyphilis.[5] The average age of presentation appears to be around 35 years of age in different studies from around the world.[3,5,6] One patient was as young as 24-years-old and presented with a psychiatric disorder.[5] We believe that our patient acquired the illness at a young age from possible sexual abuse considering his reluctance to undergo examination of his rectal and genital areas, and since he was negative for the presence of human immunodeficiency virus.

When physical examination is unrevealing as to the presence of a syphilitic affliction, diagnosis becomes challenging. It is further complicated by incidental partial treatment with antibiotics given for other disorders.[7] The initial step is to think of it, and stroke in the young is the first indication to embark on the quest to prove its absence.[6] The diagnosis of neurosyphilis is a combination of an appropriate clinical presentation as in Timmermans and Carr's classification: Category 1 - Neuropsychiatric disorders, Category 2 - Cerebrovascular accident, Category 3 - Ocular, Category 4 - Myelopathy, Category 5 - Seizure, Category 6 -Brain stem/Cranial nerves, (with the caveat that patients sometimes fall in more than one category), in conjunction with serum markers, neuro-imaging abnormalities and CSF examination by VDRL testing, cell count and protein.[3] The serum diagnosis of syphilis includes a reactive serum plasma reagin, VDRL, fluorescent treponema absorbent antibodies (FTA) and treponema pallidum hemagglutination.[8] Both the RPR and VDRL were positive in high titers in our patient. The use of VDRL positivity in the cerebrospinal fluid as a sole criterion for diagnosis of neurosyphilis is nowadays to be taken with caution, since false positive results can occur and in one of the largest examined series by Al-Semari et al, 207 examined specimens of CSF of neurosyphilis cases had a negative VDRL.[3,9] Even though the FTA might be positive in VDRL negative cases, the test is highly sensitive and false positive results may occur.[3] To increase the reliability of treponema antibody tests in the CSF, one can use the ratio of serum-to-CSF albumin content to assess the intra-thecal production of treponema antibodies, especially the TPHA assay (index).[10] The high initial CSF lymphocytic predominant pleocytosis and increased protein as in our patient, decreases with treatment and can be used as a clinical guide for re-treatment.[10] This improvement also occurs in

patients with underlying HIV infection except for the VDRL test which might continue to remain positive in these patients, bringing up the question of whether or not a more extensive course of therapy is indicated in this sub-group.[11] Neuroradiologically, there is an enhancement of affected brain structures after intravenous administration of gadolinium, as can be seen in the MRI of our patient and the meninges as well as the CSF itself, while the CT scan brain is rather non-specific.[12]

We conclude that diagnosis will most likely remain a combination of clinico-laboratory and radiological features. The treatment of choice for neurosyphilis remains penicillin.[13] Doxycycline and ceftriaxone remain alternatives for those with an allergy to penicillin.[13] The optimal dose and duration is an ongoing subject of trials with a Moroccan group proposing a higher dose for a shorter period of time, namely, infusion of 30 million units of penicillin G over 6 hours daily for 10 days, instead of 20 million units daily for 21 days.[2] The Centers for Disease Control and Prevention guidelines recommend 18-24 million units of aqueous penicillin G per day intravenously in divided doses every 4 hours for 14 days.[14] Our patient received 24 million units of aqueous penicillin G a day for a total duration of 16 days, and in retrospect the additional probenecid was found to be not necessary. Clinical improvement was remarkable and was reflected in the results of the CSF analysis. Neurosyphilis is rare and remains a diagnosis of exclusion in patients presenting with a cerebrovascular accident. It should be considered in patients from third world countries, those with risk factors of drug abuse, HIV infection, and stroke in the young.

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