

Antimony-induced cerebellar ataxia

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ABSTRACT

Visceral leishmaniasis (VL), caused by *Leishmania donovani* is endemic over several parts of Sudan. The disease is fatal if not treated. Although sodium stibogluconate (Pentostam®), a pentavalent antimonial is not free from toxicity, it has been in use for treatment of VL for the last 50 years. Like other infectious diseases, neurological manifestations of VL and sodium stibogluconate have been documented. In this report, we present 2 cases of cerebellar ataxia most likely induced by Pentostam®, and explain the probable cause.

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Visceral leishmaniasis (VL), caused by *Leishmania donovani* (*L. donovani*), is endemic over several parts of Sudan. The disease is a major cause of morbidity and mortality and is fatal if not treated.¹ Sodium stibogluconate (Pentostam®), a pentavalent antimonial drug is the mainstay of treatment. Side effects of Pentostam range from reversible electrocardiogram change, myalgia, reversible peripheral neuropathy, and liver dysfunction to pancreatitis and pancreatic necrosis.²⁻⁴ Recently, neurological manifestations in VL, such as burning sensation of the feet to multiple cranial nerves palsies have been documented.⁵ Cerebellar ataxia and other neurological complications have been reported with infections (malaria, varicella) and as a toxic effect of some drugs such as non-steroidal anti-inflammatory drugs.⁶⁻⁹ In this report, we present 2 cases of cerebellar ataxia that followed administration of sodium stibogluconate and we explained the probable cause.

Case Report. *Patient 1.* A 30-year-old male was seen at a field treatment center for VL with a short history of fever, productive cough, and loss of appetite. The findings of the physical examination revealed

a generally ill patient with a pale conjunctivae with no jaundice or cyanosis. Liver and spleen were not palpable. Thick blood film was negative for malaria parasites, lymph node aspirate was negative for *L. donovani* but the direct agglutination test (DAT) titre was reported as suggestive of VL. He was started on sodium stibogluconate (Pentostam®, Wellcome, England) at a dose of 20 mg/kg body weight/day. On day 17th of treatment he developed severe right hypochondrial pain and vomiting. Sodium stibogluconate was stopped and was given tinidazole and chloramphenicol on clinical suspicion of amebic liver abscess and typhoid enteritis. Five days later, his condition did not improve and he was put back on sodium stibogluconate for more than 3 injections, after which he developed marked generalized tremors and unstable gait. The abdominal ultrasound showed no evidence of amebic liver abscess. He was then referred to Soba University Hospital, Khartoum for further management. On admission he was emaciated, pale and febrile, axillary temperature was 39°C. He had generalized abdominal pain, but

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the liver and spleen were not palpable. There was a widespread coarse crackles on the chest examination. Cardiovascular examination revealed no abnormality. Nervous system examination showed that he was oriented to the place, time and person. Cranial nerves were intact including funduscopy, and his speech was normal. Upper and lower limbs examination showed marked intention tremors and in-coordination that was confirmed by the finger-nose and heel-shin tests. The muscle power was normal with increased tone and markedly exaggerated reflexes. Sensory examination was normal, and the plantar reflex was going down. He had an unsteady gait. His chemical and hematological investigations were normal apart from low hemoglobin of 6.0 grams/dl and an erythrocyte sedimentation rate of >150 mm first hour. Lymph node aspirate was negative for *L. donovani* amastigotes. Chest x-ray was suggestive of broncho-pneumonia. He was treated with antibiotics for his chest infection with an excellent response. The DAT titre was negative (<200). His leishmanin skin test was positive with an induration of 15 mm. An electroencephalogram (EEG) examination showed generalized epileptiform spikes. A provisional diagnosis of pentostam-induced cerebellar ataxia was made, possibly as part of a widespread brain insult. Chest x-ray 2 weeks after admission showed no abnormal findings. He continued to improve, and by 4 weeks the tremors disappeared and his coordination was back to normal but the reflexes remained exaggerated. A repeat EEG showed persistence of widespread spikes. He was discharged in good condition. At 2 years follow up he reported no episodes of convulsions. No EEG was carried out.

Patient 2. A 27-year-old female with parasitologically confirmed VL, who received 126 injections of Pentostam without clinical or parasitological response. While on Pentostam, she developed abnormal movements of both upper and lower limbs. On admission, she was wasted, febrile, pale but oriented in time, place and person. She had hepatosplenomegaly with palpable epitrochlear and inguinal nodes. Central nervous system examination showed intact cranial nerves, with abnormal head movement (titubation). Upper limbs showed normal tone, power, reflexes and intact sensations. Abnormal movement (myoclonus) of the upper limbs was noted. Lower limbs were wasted with abnormal movements, but with normal tone, power, reflexes and sensations. Impaired coordination of upper and lower limbs was confirmed by the finger-nose and heel-shin tests. Her gait was wide-based. Lymph node aspirate was positive for Leishman Donovan bodies, and the parasite was successfully grown in culture. Her leishmanin skin test was non-reactive

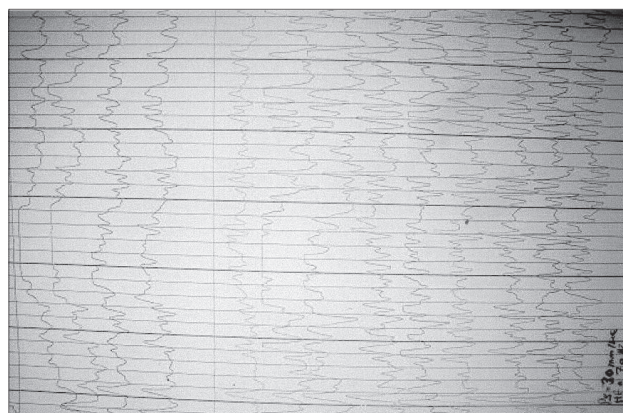


Figure 1 - Electroencephalogram tracing showing generalized epileptiform spikes.

and her DAT titre was strongly positive with high reciprocal titre of >102 400. An EEG examination showed generalized epileptiform spikes and she was diagnosed as Pentostam-unresponsive VL with pentostam-induced cerebellar ataxia (**Figure 1**). She responded clinically and parasitologically to AmBisome® (liposomal amphotericin B; Gilead Science International, Cambridge, UK) at a dose of 2 mg/kg body weight/day for 14 days. Her neurological symptoms and signs improved dramatically with the treatment.

Discussion. Visceral leishmaniasis is an inevitably fatal condition if not treated. Under field conditions, some patients may exhibit the classical symptoms and signs of VL with no parasite in the lymph node/bone marrow aspirate. Empirical Pentostam treatment may have to be given on DAT results only. The DAT has some limitations especially in endemic areas where some healthy individuals may have anti-leishmania antibodies, which are usually taken as an indicator of subclinical infection. Cured VL patients may continue to have a positive DAT for many years. Therefore, interpretation of the DAT titres should be carried out very carefully in the endemic areas, where other diseases, such as malaria may have a similar clinical picture to VL. The leishmanin skin test is a simple test, which is always negative in patients with active VL, and changes to positivity after approximately 6 months of successful treatment. We have previously shown that individuals with a positive leishmanin test are protected from the disease.¹⁰ Our 14 years experience showed that Pentostam is a fairly safe drug that can be given under field conditions without the need to monitor liver functions. Visceral leishmaniasis endemic area in Sudan is also endemic for malaria.

The first patient most probably had an acute Pentostam toxicity that resulted in widespread brain insult an assumption that can be supported by absence of history of seizures and the accompanying hypertonia, hyper-reflexa, myoclonus and the abnormal EEG. The improvement of symptoms while in the hospital probably indicate clearance of Pentostam from the body.

The second patient received large amounts of Pentostam without parasitological or clinical response. Investigations were carried out, it was ruled-out that failure of response was not due to an underlying disease (HIV/AIDS; tuberculosis), which probably indicate that the parasite was primarily Pentostam-unresponsive. She responded to a second line drug, AmBisome (liposomal amphotericin B; Gilead Science International, Cambridge, UK). Her cerebellar symptoms and signs improved while on the AmBisome treatment, most probably due to the slow clearance of the Pentostam. In her case, VL-precipitated neurological manifestations cannot be ruled out. Her condition is probably due to a combination of the Pentostam toxicity and VL. Her condition was stable when she was seen 12 months post-treatment.

In conclusion, Pentostam can induce cerebellar ataxia as part of a widespread brain insult, which can be attributed to its nature as a heavy metal-containing drug.

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