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Case Report

Lafora Disease Case Report: A Classic Presentation of An Ultra-Rare Disease in Durban, South Africa

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Abstract:

Metabolic screen including thyroid function, vitamin B12 (340 pmol/L) and lipid profile were normal. His serum lactate was normal (1.5 mmol/L). Sodium valproate and carbamazepine levels were within therapeutic range. Inflammatory markers were normal, while an infective screen including HIV, syphilis, herpes simplex virus and hepatitis were negative. Lumbar puncture revealed normal chemistry and was negative for herpes simplex virus, varicella-zoster virus, GeneXpert, syphilis and cryptococcus.

Key words: skin; liver; cell layer; Lafora bodies

Introduction

Lafora disease (LD) is an autosomal recessive (AR) disorder of glycogen metabolism characterized by progressive myoclonus, refractory seizures and dementia [1-4]. It is a neurodegenerative condition beginning in adolescence and often fatal within ten years of onset [2-4]. It forms part of the group of disorders known as the progressive myoclonus epilepsies (PMEs) [2, 5]. Other causes of PME include Unverricht-Lundborg disease (ULD), neuronal ceroid lipofuscinosis (NCL), myoclonic epilepsy with ragged red fibres (MERRF), sialidosis and Gaucher disease, amongst others [2, 3]. Diagnosis of LD is made through the demonstration of pathognomonic polyglucosan inclusions (Lafora bodies) derived from skin, liver, muscle or brain biopsy [2, 3, 6], as well as genetics testing when available. We report a case of confirmed LD in a 28-year-old male at Inkosi Albert Luthuli Central Hospital in Durban, South Africa. To the authors' knowledge this is only the second reported case of LD in South Africa, with one previously published case report by de Graaf et al. in 1989 at Tygerberg Hospital, outside Cape Town.

Case Report

A 28-year-old male presented to the neurology unit at Inkosi Albert Luthuli Central Hospital with a ten-year history of progressively worsening bilateral tonic-clonic seizures, facial twitching, upper limb jerks and cognitive decline. He had a normal birth history and developmental milestones. He had been well prior to age 18, with no previous history of a hypoxic event or trauma. There was no family history of note. On social history, he had previously worked as a taxi driver and was a cigarette smoker with a 14 pack-year history. He drank alcohol on social occasions but did not have a history of illicit drug use. Despite being commenced on adequate doses of sodium valproate and carbamazepine by his district hospital, there was no improvement in seizure frequency. On examination he was noted to have mild cognitive impairment and a scanning dysarthria. Continuous focal movements of the right orbicularis oris and left orbicularis oculi were seen. He was observed to have stimulus-sensitive and action myoclonus of the right upper limb, as well as negative myoclonus. He was quadrispastic and had bilateral cerebellar dysfunction. His fundus examination was normal (with no cherry-red spot seen). Whilst in the ward, he was observed to have behavioural problems, having verbal and at times, physical, altercations with other patients in the neurology ward. In summary, this was a 28-year male patient who presented with features of a progressive myoclonic epilepsy (PME). On investigation his serological markers revealed normal urea and electrolytes, liver function and full blood count. Anti-nuclear factor and autoimmune encephalitis panel were negative. Metabolic screen including thyroid function, vitamin B12 (340 pmol/L) and lipid profile were normal. His serum lactate was normal (1.5 mmol/L). Sodium valproate and carbamazepine levels were within therapeutic range. Inflammatory markers were normal, while an infective screen including HIV, syphilis, herpes simplex virus and hepatitis were negative. Lumbar puncture revealed normal chemistry and was negative for herpes simplex virus, varicella-zoster virus, GeneXpert, syphilis and cryptococcus. His EEG revealed a slow background but no epileptiform activity. MRI brain showed multiple focal hyperintensities in the cortex as well as the thalami, midbrain and putamina (Figure 1). With no clear

aetiology established, an axillary skin biopsy was performed. Histology revealed pathognomonic Lafora bodies in the sweat gland luminal cell layer. These are illustrated in Figure 2 as violet inclusion bodies after periodic acid Schiff (PAS+) staining.

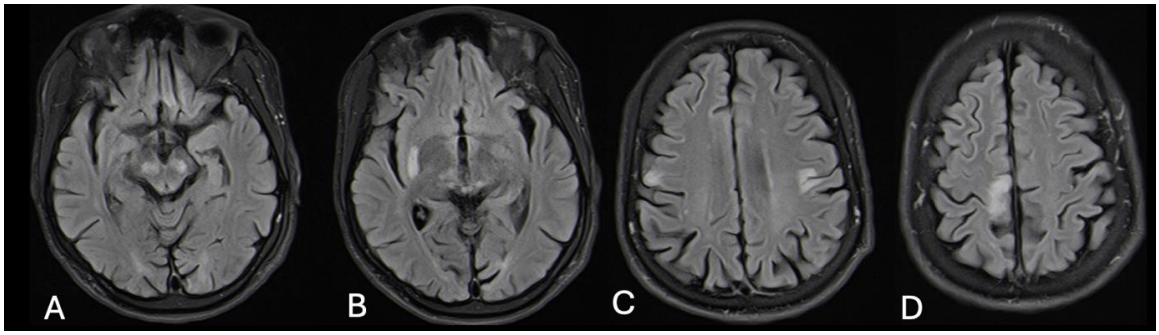

Figure 1: Note multiple focal hyperintensities in the midbrain (A), thalami (B), putamina (B) and cortical regions (C, D).

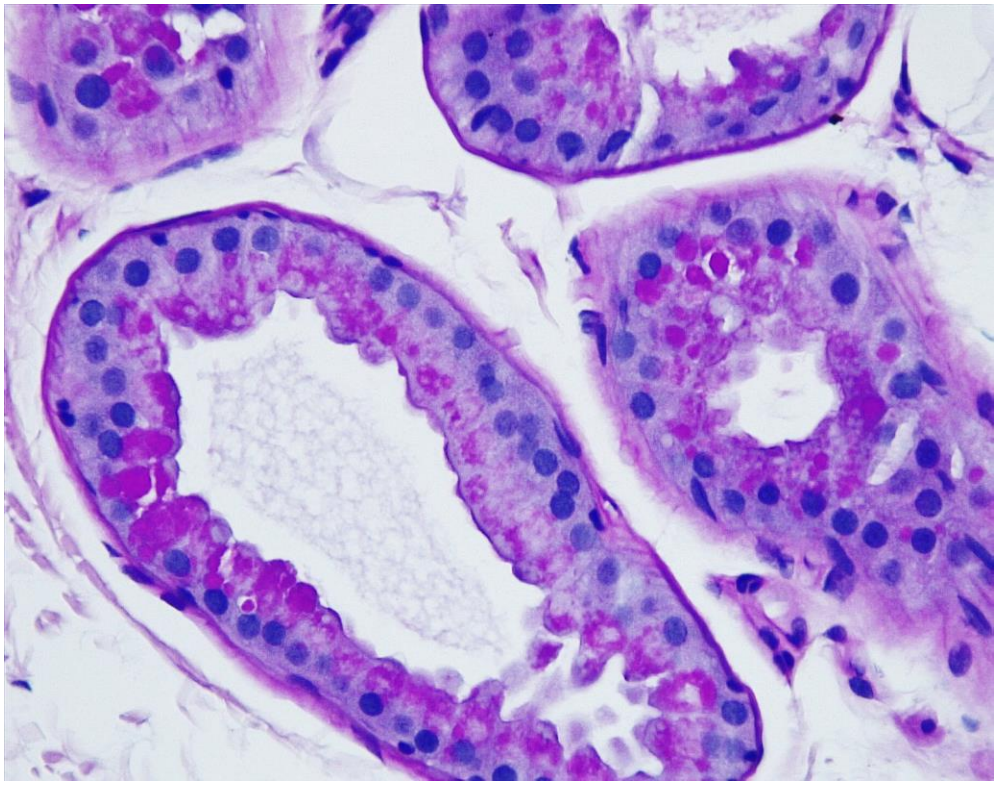

Figure 2: Axillary skin biopsy from the index patient stained with periodic acid Schiff (PAS+) demonstrates Lafora bodies (arrows) within the luminal cell layer of apocrine glands.

The patient's treatment was adjusted to include levetiracetam, topiramate and clonazepam - and carbamazepine was weaned off. This brought about a significant reduction in the frequency of his seizures and myoclonic jerks. Genetic counselling was given. He remains profoundly ataxic and spastic which renders him wheelchair-bound. He is fortunate to have been transferred and to receive constant supervision at a non-profit organization (NPO) care home.

Discussion

LD is an autosomal recessive disease caused by mutations in the EPM2A and EPM2B (or NHLRC1) genes, encoding for the proteins laforin and malin, respectively [2, 3, 7]. Normally, malin uses laforin as a scaffold to bind to poorly branched glycogen and aid in its clearance [7]. In LD, due to the absence of the malin or laforin proteins, poorly branched glycogen accumulates, which results in Lafora body formation via proteins like p62 [7]. Lafora bodies are typically found in the brain (neurons and astrocytes), liver, muscle and sweat glands [3-5, 7]. A patient with PME will usually present in adolescence with a combination of myoclonus, refractory seizures, dementia, ataxia, dysarthria or behavioural disturbance, usually following a normal childhood [2-4]. Most cases of PME cannot be distinguished from one another on history and exam alone [2, 3]. While the presence of a clinical finding such as a macular cherry red spot may point towards a diagnosis of sialidosis type I (or other storage disorders) [8], clinical exam alone often does not narrow the differential diagnosis in PMEs. Although it is encouraging that the genetic defects for most PMEs (ULD, LD, NCL, MERRF, sialidoses) have been identified [3], genetic testing is usually not available in resource-limited settings. In such settings it is therefore important to consider axillary skin biopsy as a means to diagnosing LD. With its high concentration of apocrine glands, axillary skin biopsy offers an effective, convenient and

relatively non-invasive means of establishing the diagnosis of LD [6]. While glycogen accumulation may occur in ageing and other neurodegenerative conditions such as Alzheimer's, Parkinson's, adult polyglucosan body disease and Pick's disease [7], the clinical characteristics of patients with PME are unlikely to overlap with these conditions. To the authors knowledge only one case of LD has been reported in South Africa, with none reported in the province of KwaZulu-Natal. A 1989 case report authored by de Graaf et al. at Tygerberg Hospital (Western Cape) [9] documented a 17-year-old male who presented with psychosis, seizures and myoclonus, in addition to optic atrophy, macular degeneration and cardiac failure, the latter features being unusual in the setting of LD. The diagnosis of LD was confirmed on biopsy of the brain, skin, skeletal muscle, peripheral nerve and liver. The patient died following complications of status epilepticus a few months after he was discharged [9]. In conclusion, LD, one of the PMEs, should be considered in the setting of a young patient presenting with myoclonus, seizures and cognitive decline. Diagnosis of LD through axillary skin biopsy, as in this case, allows for timeous diagnosis and appropriate intervention, especially in resource-constrained settings where genetic testing may not be available. Our case of confirmed LD is the second reported case in South Africa, and the first in the province of KwaZulu-Natal.

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