Truth is a daughter of time: a case of MELAS diagnosed 25 years after initial manifestation

Martin Windpessl1,*, Petra Müller2 and Manfred Wallner1

1Fourth Department of Medicine, Klinikum Wels-Grieskirchen, Wels, Austria and 2Department of Neurology, Landesnervenklinik Linz, Linz, Austria

*Correspondence address. Klinikum Wels-Grieskirchen, Grieskirchnerstrasse 42, 4600 Wels, Austria. Tel: +43-699-10200004; Fax: +43-7242-415-3993; E-mail: martin.windpessl@gmx.net

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The acronym MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes) belies the true scope of one of the most prevalent mitochondriopathies in adults. While the original description focused on neuromuscular symptoms, we now recognize this syndrome as genetically well defined but phenotypically profoundly heterogeneous, as exemplified by our experience. Here we report the case of a man who initially presented in 1986. In hindsight, his illness was a classic manifestation of MELAS, but the illness was ascribed to an ill-defined viral encephalitis. Over the years, diabetes and hearing impairment developed and his functional status deteriorated progressively. It took the quarter of a century to arrive at the correct diagnosis. It is worthwhile to keep an open mind when dealing with chronically ill patients with a seemingly clear-cut diagnosis.

INTRODUCTION

Mitochondriopathies are multi-system disorders affecting virtually all organs and cause significant morbidity. The 3243A>G mutation in the mitochondrial DNA is one of the most common and is associated with broad phenotypic diversity. In consequence, patients carrying this mutation may present to physicians in practically any medical speciality. Not surprisingly the diagnosis and management of this disorder remains a challenge.

CASE REPORT

In 1986, a previously healthy 18-year-old male presented to our hospital with a 1-week history of fever, headache and vomiting. Meningism, but no focal neurological signs, was noted on examination. Lumbar puncture was performed, revealing slight elevation of protein in the cerebrospinal fluid (CSF) but no increased cell count. Over the next few days, right-sided weakness developed. Electroencephalogram demonstrated left parieto-occipital focal slowing. Results of T1/T2-weighted brain magnetic resonance imaging were reported to be in keeping with an inflammatory process in the left occipital area. The patient was commenced on acyclovir, but herpes serology came back negative. When generalized tonic-clonic seizures ensued, anticonvulsant therapy with carbamazepine was established. The patient was finally discharged with a provisional diagnosis of viral encephalitis, although no causative agent was found. No residual neurological deficits persisted. In 1989, hearing impairment was first documented and ascribed to the previous encephalitis. The following years saw recurrent admissions for seizures, and sodium valproate was added. The patient’s functional status deteriorated progressively. In 1999, he was diagnosed with diabetes mellitus, requiring insulin straightaway.

The patient’s sister was admitted to our department in October 2010 with gross oedema of the legs. Her medical history included diabetes and sensorineural deafness. Advanced renal impairment was noted. In view of her phenotype, we suspected maternally inherited diabetes and deafness (MIDD). The 3243A>G mutation in the MT-TL1 gene of the mitochondrial DNA (mtDNA) was subsequently demonstrated in blood leucocytes, confirming the diagnosis.

When her brother was admitted in October 2011 for anorexia, we re-evaluated his past medical notes. In the initial CSF analysis, no lactate levels had been checked. Electrocardiogram showed Wolff–Parkinson–White syndrome. Macular dystrophy, but no signs of diabetic retinopathy, was found on
fundoscopy. CT scan of the brain showed diffuse cerebral atrophy, bilateral basal ganglia calcification and a left parieto-occipital hypodensity, likely representing a previous stroke-like event (Fig. 1). Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) was deemed a likely explanation for his multi-systemic disease and was confirmed by demonstration of the 3243A>G transition in blood and urine. The heteroplasmy rate (the mixture of normal and mutated mitochondrial DNA) was 50 and 90%, respectively. Anticonvulsant therapy was switched to levetiracetam and treatment with coenzyme Q10 was started. The patient now lives in a nursing home. Follow-up at our unit has been arranged.

DISCUSSION

The 3243A>G mtDNA mutation constitutes the most common cause of mitochondrial disease in adults, with a reported incidence of up to 200/100 000 [1]. The protean manifestations include asymptomatic carrier state, cardiac conduction defects, hearing impairment with or without diabetes, MIDD and MELAS [2]. As our case highlights, overlaps do occur. There is a significant variability in disease progression. Although no curative treatment is available to date, considerable progress has been made over the past decade in establishing diagnosis and aches for follow-up [3]. Characteristic radiological abnormalities, such as bilateral basal ganglia calcification, focal hypodensities, and generalized atrophy, can be detected on cerebral imaging [4]. Increased lactate levels in serum, and particularly in the CSF, are salient features in screening. ‘Ragged-red fibres’ are the hallmark feature in the muscle of most patients and are virtually thought synonymous with MELAS and other mitochondriopathies [5]. However, mutation load in urinary epithelial cells has been shown to correlate well with disease activity, obviating the need for muscle biopsy in many cases [6]. Coenzyme Q10 is commonly prescribed and benefit is anecdotally reported. Sodium valproate is best avoided, because it negatively interferes with mitochondrial function [7]. l-Arginine has emerged as a potentially helpful remedy in acute as well as chronic MELAS [8]. Although the syndrome was initially described as relentlessly progressive and usually fatal in early life, patients carrying this mutation may have lesser symptoms and a normal life span [9]. Regular assessment for other organ involvement, such as for cardiomyopathy, proteinuria or myopathy, is recommended. Family screening is advocated, and clinical presentation of relatives may aid diagnosis as in the present case. It is worthwhile to keep an open mind when dealing with chronically ill patients with a seemingly clear-cut diagnosis. In this patient, the ultimate cause for his debilitating illness was established 25 years after his initial presentation.

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