NARP Syndrome: A 20-Year Follow-Up

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Key Words

NARP · Diagnosis · Follow-up · Disease course

Abstract

One member of a pedigree with NARP syndrome (neurogenic weakness, ataxia, and retinitis pigmentosa), a mitochondrial disorder due to a point mutation at position 8993 in the mitochondrial genome ATPase 6 gene, was reevaluated some 20 years after first being reported in the medical literature. Initially assessed at age 39 years, she had retinitis pigmentosa and a mild sensory axonal neuropathy, typical features of NARP, but was otherwise clinically normal. At age 59 years, she was registered blind, had sensorineural hearing impairment, had recently been diagnosed with diabetes mellitus, and may have had some mild cognitive impairment. This case shows that the clinical phenotype of NARP due to mitochondrial dysfunction may evolve over a period of decades.

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Introduction

Neurogenic weakness, ataxia, and retinitis pigmentosa, or NARP syndrome, is a mitochondrial disorder most commonly resulting from a point mutation at base pair 8993 of the mitochondrial genome in the ATPase 6 gene [1]. Besides the clinical features encapsulated in the name, the clinical phenotype may also include epileptic seizures, sensorineural hearing loss, cognitive impairment, diabetes mellitus, cardiomyopathy, and lactic acidosis. Mutations at the same position may also cause maternally inherited Leigh's syndrome [2–4].

In 1994, Fryer et al. [5] reported a family with the NARP mutation in which 7 children had a heterogeneous phenotype including Leigh's syndrome, retinitis pigmentosa, mental retardation, and developmental delay, the latter prompting diagnosis of cerebral palsy in

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some of the children. Their mother (case II.2 in Fryer et al. [5]) was also briefly described: aged 39 years, she had retinitis pigmentosa diagnosed at age 31 years when she presented with poor night vision. She was otherwise clinically normal. Nerve conduction studies showed evidence of a mild sensory axonal neuropathy. She was reported on quantitative mitochondrial DNA (mtDNA) analysis to have 78% mutant mtDNA, less than that found in all the affected children (range 86–93%) [5].

We recently had the opportunity to reevaluate 1 member of this pedigree some 20 years after the original publication.

Case Report

The patient (case II.2 in Fryer et al. [5]) was referred to the Neurology Clinic at age 59 years. Her complaint was of postural dizziness. Family members and friends noted her to be occasionally confused. One other member of the original pedigree (III.5; originally said to have mild developmental delay [5]), now aged 27 years, attended 1 consultation with his mother and contributed some collateral history, but he was not clinically assessed. The patient's vision had progressively deteriorated and she had been registered blind at age 53 years.

Hearing difficulties developed around the age of 53 years. Audiometry at the time of referral to the Neurology Clinic showed a 50–60-dB sensorineural hearing loss in both ears. On examination, there was no postural blood pressure drop: 160/80 mm Hg lying, 160/90 mm Hg after standing at 2 and 5 min.

Blood tests performed by the primary care physician immediately prior to referral included a random blood glucose of 9.8 mmol/l. A subsequent oral glucose tolerance test was consistent with diabetes mellitus (0 min: blood glucose 10 mmol/l; 120 min: 21 mmol/l). HbA1c was 55 mmol/mol, and therefore above the threshold (<53 mmol/mol) deemed good glycaemic control. Blood lactate (1.5 mmol/l; normal range 0.4–2.0 mmol/l), pyruvate (55 µmol/l; normal range 45–90 µmol/l), and blood creatine kinase (79 U/l; normal range 25–200 U/l) were normal.

Neurogenetic testing showed the m.8993T>G mutation associated with the NARP phenotype. The mutation was present in heteroplasmic form at an intermediate level (58%; low <30%, intermediate 30–70%, high >70%). ECG showed a sinus rhythm with a normal PR interval (145 ms). Transthoracic echocardiogram showed ventricular and valvular function within normal limits.

Detailed neuropsychological evaluation was not possible because of the patient's primary sensory deficits in the visual and auditory domains. The Six-Item Cognitive Impairment Test (6CIT), a purely verbal cognitive screening instrument [6], was administered, on which she scored 4/28, a score at the upper limit of the normal range [7]. On the AD8, an informant screening questionnaire for dementia [8], which was completed by a family friend who had known the patient for 3 years, she scored 4/8, above the recommended cutoff for dementia [9].

Neurophysiological studies included an EEG which was within normal limits, and EMG and nerve conduction studies which showed a purely sensory axonal length-dependent peripheral polyneuropathy (absent sural, superficial peroneal, and ulnar sensory responses; normal distal latency of median sensory response with reduced SNAP amplitude). MRI of the brain was normal, with no evidence of atrophy or cerebrovascular disease. Functional imaging with 99mTc-HMPAO-SPECT showed foci of mildly reduced perfusion in the right temporal and both parietal lobes with normal perfusion anteriorly.

Discussion

This report extends the clinical and genetic observations in 1 patient with NARP syndrome previously reported nearly 20 years earlier [5]. Although the initial description of the family reported the presence of the mtDNA 8993 mutation [5], it was not stated which of the 2 documented mutations (m.8993T>C and m.8993T>G) was responsible. Current neurogenetic testing showed that she had the T>G mutation. Heteroplasmy was confirmed, but with lower levels of mutant mtDNA in the blood than originally reported (58 vs. 78%), which might explain the mild clinical phenotype. The risk of developing severe functional disability is said to increase greatly beyond 60% blood heteroplasmy with the m.8993T>G mutation [10]. Nonetheless, there was clear evidence of clinical progression over the approximate 20-year period between assessments, with worsening of visual function to registered blindness, development of sensorineural hearing impairment (both at the beginning of the sixth decade), and onset of diabetes mellitus (end of the sixth decade). The possibility of some cognitive impairment could not be ruled out.

There are few reports in the literature of adult patients with NARP 8993 mutations, and none, as far as we have been able to ascertain, extending to the threshold of the seventh decade. As might be anticipated from the heterogeneous patterns of tissue injury in NARP [11], clinical heterogeneity is likely in older as well as younger patients. The index case in the original report by Holt et al. [1] was 47 years old, with retinitis pigmentosa diagnosed age 12 years and progressive visual impairment to blindness at age 30 years; besides ataxia no other clinical features were reported. Her asymptomatic 52-year-old sister had some clumps of retinal pigment and some proximal muscle weakness [1]. Uziel et al. [10] reported a 32-year-old woman (Ped FIII/10) with retinitis pigmentosa only, with 55% mutant mtDNA m.8993T>G in the blood. A 48-year-old female reported by Gelfand et al. [11] in a family with the m.8993T>C mutation had, in addition to visual impairment and peripheral neuropathy, evidence of depression but with no hearing loss or diabetes with 78% leukocyte heteroplasmy. A greater extent of blood heteroplasmy (>80%) may be required for increased risk of developing severe functional disability with the m.8993T>C mutation [10]. Slow disease progression over a 20-year follow-up has also been described in a patient with Leigh-like syndrome due to an m.8993T>G mutation with 72% blood heteroplasmy who presented with early onset encephalopathy [12].

Prior to referral, our patient was not under neurological follow-up. In view of the possibility of disease progression, as evidenced by the evolution to blindness, hearing impairment, diabetes mellitus, and possibly cognitive impairment in this case, it would seem desirable that NARP patients undergo regular follow-up, in the hope that with the advent of disease-modifying treatment the complications of evolving disease might be prevented. Monitoring for euglycaemia and cardiac complications might also be undertaken, as even without disease-modifying therapy these are two aspects of patient care which might be optimized with early detection.

References

- 1 Holt IJ, Harding AE, Petty RK, Morgan-Hughes JA: A new mitochondrial disease associated with mitochondrial DNA heteroplasmy. *Am J Hum Genet* 1990;46:428–433.
- 2 Tatuch Y, Christodoulou J, Feigenbaum A, et al: Heteroplasmic mtDNA mutation (T→G) at 8993 can cause Leigh disease when the percentage of abnormal mtDNA is high. *Am J Hum Genet* 1992;50:852–858.
- 3 Shoffner JM, Fernhoff PM, Krawiecki NS, et al: Subacute necrotizing encephalopathy oxidative phosphorylation defects and the ATPase 6 point mutation. *Neurology* 1992;42:2168–2174.

- 4 Sciacco M, Prella A, D'Adda E, et al: Familial mtDNA T8993C transition causing both the NARP and the MILS phenotype in the same generation. A morphological, genetic and spectroscopic study. *J Neurol* 2003;250:1498–1500.
- 5 Fryer A, Appleton R, Sweeney MG, Rosenbloom A, Harding AE: Mitochondrial DNA 8993 (NARP) mutation presenting with heterogeneous phenotype including 'cerebral palsy'. *Arch Dis Child* 1994;71:419–422.
- 6 Brooke P, Bullock R: Validation of a 6 item cognitive impairment test with a view to primary care usage. *Int J Geriatr Psychiatry* 1999;14:936–940.
- 7 Jefferies K, Gale TM: 6-CIT: Six-item cognitive impairment test; in Lerner AJ (ed): *Cognitive Screening Instruments: A Practical Approach*. London, Springer, 2013, pp 209–218.
- 8 Galvin JE, Roe CM, Powlishta KK, Coats MA, Muich SJ, Grant E, Miller JF, Storandt M, Morris JC: The AD8. A brief informant interview to detect dementia. *Neurology* 2005;65:559–564.
- 9 Galvin JE, Roe CM, Xiong C, Morris JE: Validity and reliability of the AD8 informant interview in dementia. *Neurology* 2006;67:1942–1948.
- 10 Uziel G, Moroni I, Lamantea E, et al: Mitochondrial disease associated with the T8993G mutation of the mitochondrial ATPase 6 gene: a clinical, biochemical, and molecular study in six families. *J Neurol Neurosurg Psychiatry* 1997;63:16–22.
- 11 Gelfand JM, Duncan JL, Racine CA, et al: Heterogeneous patterns of tissue injury in NARP syndrome. *J Neurol* 2011;258:440–448.
- 12 Sobreira C, Marques W Jr, Pontes Neto OM, et al: Leigh-like syndrome with the T8993G mutation in the mitochondrial ATPase 6 gene: long-term follow-up discloses a slowly progressive course. *J Neurol Sci* 2009;278:132–134.