Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/pjnns

Case report

Heterogeneous phenotypic manifestations of maternally inherited deafness associated with the mitochondrial A3243G mutation. Case report

Magdalena Hoptasz [a], *Adam Szczuciński* [a,b,*], *Jacek Losy* [a,c,d]

[a] *Department of Clinical Neurology, Clinical Hospital of H. Święcicki by University of Medical Sciences, Poznań, Poland*
[b] *Department of Neurochemistry and Neuropathology, University of Medical Sciences, Poznań, Poland*
[c] *Department of Clinical Neuroimmunology, Chair of Neurology, University of Medical Sciences, Poznań, Poland*
[d] *Neuroimmunological Unit, Institute of Experimental and Clinical Medicine, Polish Academy of Sciences, Poznań, Poland*

ARTICLE INFO

Article history:
Received 16 April 2013
Accepted 23 December 2013
Available online 23 January 2014

Keywords:
Mitochondrial disorder
A3243G mutation
Maternally inherited deafness
Mitochondrial encephalomyopathy, lactic acidosis and strokelike episodes

ABSTRACT

The A3243G mutation is one of the most frequent mutations of mitochondrial DNA. The phenotypic expression of the A3243G mutation is variable and causes a wide range of syndromic and non-syndromic clinical disorders. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome is the most frequent syndromic manifestation of the A3243G mutation. Stroke-like episodes seem to be the dominant feature of MELAS. We have investigated the case of a family with A3243G mutation, in which a dominant symptom in three generations was the maternally inherited hearing loss with absence of stroke-like episodes. Besides deafness, we found also other clinical features such as myopathy, neuropathy, migraine, ataxia, short stature, diabetes mellitus, and cardiomyopathy.

1. Introduction

The maternally inherited point mutation of A3243G in the mtDNA is the most frequent cause of mitochondrial multisystem disorder with a variable clinical phenotype [1]. The prevalence of A3243G mtDNA was estimated to be 0.95–16.3 per 100,000 – much higher than previously reported [2,3]. In 80% of cases, mtDNA A3243G mutation is associated with a mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS). The same mutation may cause clinically well-defined combinations of symptoms such as maternally inherited diabetes and deafness (MIDD), myoclonus epilepsy with ragged red fibres (MERRF), progressive external ophthalmoplegia (PEO) and Leigh syndrome (LS) [4,5]. However, the phenotype of many A3243G mutants does not comply with any of these syndromes (non-syndromic manifestations).

2. Case presentation

A 48-year-old woman (Fig. 1IVA) was admitted to our clinic for progressive hearing loss, generalized muscle weakness and gait difficulties. She had a history of normal birth and development.

* *Corresponding author at*: Zakład Neurochemii i Neuropatologii, UM im. K. Marcinkowskiego w Poznaniu, ul. Przybyszewskiego 49, 60-355 Poznań, Poland.
E-mail address: adamszczucinski@poczta.onet.pl (A. Szczuciński).
0028-3843/$ – see front matter
http://dx.doi.org/10.1016/j.pjnns.2013.12.007

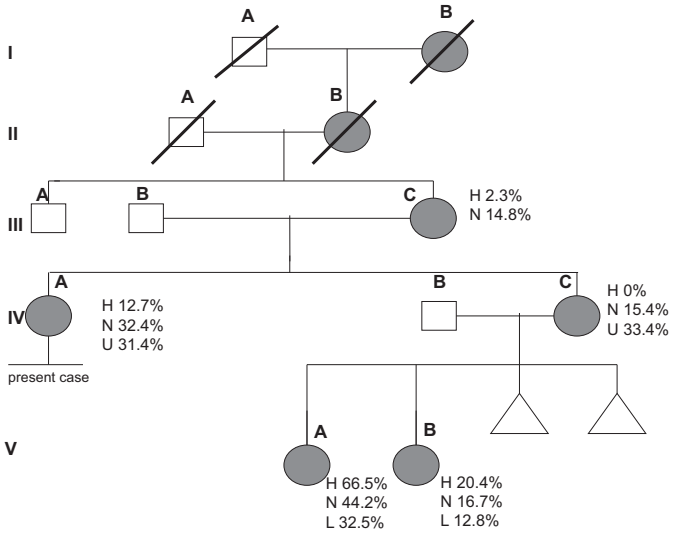

Fig. 1 – The pedigree of family with A3243G mutation. The proportion of mutant mtDNA in hair follicles (H), nail (N), urinary sediment (U) and peripheral blood leukocytes (L).

She was intellectually normal, able to finish high school and start working as an office worker. She had been healthy until the age of 33 when she developed bilateral hypoacusis. One year later she was diagnosed with diabetes and started insulin therapy. Until the age of 45, she had a slow progression of hearing impairment. Since then, she has experienced a rapidly progressing deafness. She was assessed for a cochlear implant. Besides the hearing loss, she also noticed weakness of the lower extremities, fatigability, and imbalance. One year before admission, she had been diagnosed as having hypertrophic cardiomyopathy and polycythemia vera. She had not suffered from stroke-like episodes, seizures, dementia or recurring headache.

Physical examination revealed her to be emaciated, with a weight of 46 kg and a height of 165 cm; body mass index was 17. Her pulse was 62 beats/min and blood pressure 118/62 mm Hg. Fundoscopic examination revealed no diabetic retinopathy. Visual acuity was normal in both eyes. Examination of the cranial nerves showed bilateral severe deafness. She had generalized muscle weakness and atrophy, but more severe in the proximal limb muscles. The deep tendon reflexes were decreased. Her gait was broad-based, and she was unable to walk a straight line. The coordination was impaired by mild ataxia and dysdiadochokinesia. The Romberg test was positive. Her sensory examination was normal.

Results of routine laboratory tests on admission are shown in Table 1. An audiogram showed profound (>100 dB) sensorineural hearing loss on her left and severe (75 dB) deficit on right ear. Echocardiography indicated left ventricular hypertrophy with moderate mitral regurgitation and left ventricular systolic dysfunction with decreased ejection fraction (35–40%). Twenty-four-hour ECG showed no cardiac rhythm disorder. Electromyography and nerve conduction studies revealed a length-dependent sensorimotor axonal polyneuropathy. Magnetic resonance imaging (MRI) demonstrated mild vermis atrophy, notable cortical atrophy, and subcortical lesions of increased signal intensity in the parietal regions (Fig. 2). Magnetic resonance angiography was normal.

Table 1 – Patient's laboratory test results.

Lab tests		Normal range
White blood cell count	$11.2 \times 10^3/\mu L$	3.9–11.0
Red blood cell count	$7 \times 10^6/\mu L$	3.5–5.2
Hematocrit	52.6%	33.0–46.0
Haemoglobin	18.9 g/dL	12.0–15.6
Mean corpuscular volume	78.9 fL	88.0–99.0
Platelet count	$477 \times 10^3/\mu L$	120–400
Glucose (fasting)	155 mmol/L	60–99
Glycosylated haemoglobin (HbA_{1c})	9.2%	4.0–5.6
Sodium	128 mmol/L	136–145
Potassium	5.3 mmol/L	3.5–5.1
Calcium	9.3 mg/dL	8.8–10.2
Phosphorus	4.5 mg/dL	2.7–4.5
Calcium	9.3 mg/dL	8.8–10.2
Phosphorus	4.5 mg/dL	2.7–4.5
Urea	31 mg/dL	17–50
Creatinine	0.6 mg/dL	0.5–0.9
Creatine kinase	67 U/L	26–140
Serum lactate	3.0 mmol/L	0.5–2.2
Cerebrospinal fluid lactate	4.7 mmol/L	1.2–2.4
Aspartate transaminase	21 U/L	10–31
TSH	0.6 μIU/mL	0.28–4.6
Cortisol at 09:00 am	594 nmol/L	171–536
Adrenocorticotropic hormone	17.7 pg/mL	<60
Aldosterone	96 pg/mL	10–160
Plasma renin activity	<0.15 ng/mL/h	0.5–1.9
Capillary blood gasometry		
pH	7.4	7.35–7.45
$PvCO_2$	26.9 mm Hg	32–45
PvO_2	94.8 mm Hg	75–100
HCO_3	16.2 mmol/L	21–27
SO_2	94.7%	95–95%

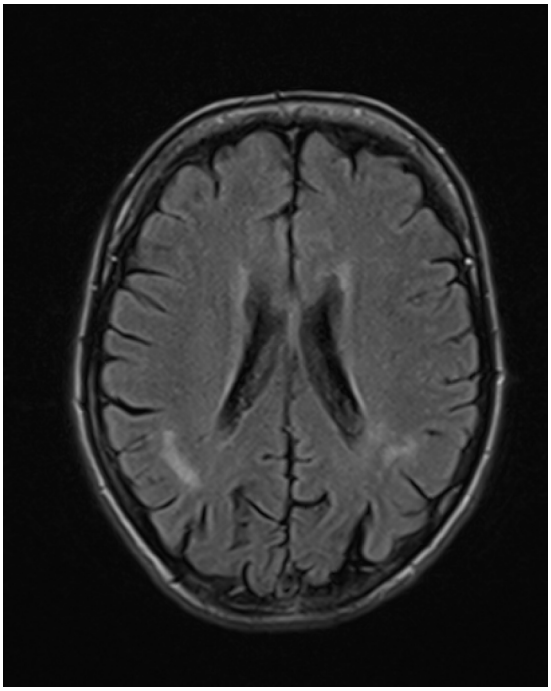

Fig. 2 – Brain magnetic resonance image scan showing ischaemic lesions in the parietal regions.

Table 2 – Family with A3243G mutation.

	IB	IIB	IIIC	IVA	IVC	VA	VB
Age of onset (years)	?	?	57	33	31	4	4
Hearing loss	+	+	+	+	+	+	+
Short stature	–	–	–	–	+	+	+
Neuropathy	–	–	+	+	–	–	–
Muscle weakness	–	–	+	+	–	–	–
Ataxia	–	–	+	+	–	–	–
Migraine	–	–	–	–	+	–	–
Stroke	–	–	–	–	–	–	–
Seizure	–	–	–	–	–	–	–
Lactic acidosis	–	–	–	+	–	–	–
Diabetes	–	–	–	+	–	–	–
Cardiomyopathy	–	–	–	+	–	–	–
Polycythemia vera	–	–	–	+	–	–	–

DNA was isolated from hair follicles, nail and urinary sediment and the A3243G mutation was identified by polymerase chain reaction (PCR). The heteroplasmy rates were 12.7%, 32.4% and 31.4%, respectively. She declined to undergo a muscle biopsy.

A detailed clinical examination was carried out on the mother of our patient (Fig. 1IIIC). The 72-year-old woman presented with a 4-year history of progressive weakness in her right upper extremity and both lower extremities resulting in frequent falls and difficulty standing from a chair, climbing stairs and carrying objects. Additionally, she complained of dysarthria and dizziness, as well as gait disturbance. Since the age 57, she has been suffering from progressive hearing impairment. She was underweight with a weight of 44 kg and a height of 166 cm.

On examination, she was intellectually normal, but she had moderate dysarthria. The cranial nerve examination was normal except for bilateral sensorineuronal hearing loss. The physical examination demonstrated atrophy and wasting of the proximal limb muscles. The neurologic examination revealed significant muscle weakness in the four extremities and muscle hypotonia. The deep tendon reflexes were decreased in both legs and arms. Her gait was wide-based with marked ataxia. The sensory examination was normal. A Romberg sign was present. Her Mini-Mental Status Examination (MMSE) score was normal (28/30 points).

Her extensive laboratory studies were normal, including a normal blood glucose and a normal glycosylated haemoglobin level. The concentration of lactate in blood was normal. Brain MRI revealed notable cortical atrophy, ventricular dilatation and cortical hyperintensity of the frontal and parietal lobes with restricted diffusion.

Electromyography and nerve conduction study confirmed a length-dependent sensory axonal polyneuropathy. The mitochondrial DNA A3243G point mutation was detected in both hair follicles and nail, and the degree of mutated DNA was 14.8% and 2.3%, respectively.

A 43-year-old sister of our patient (IVC) had been suffering migraine headache for 12 years. She and her two daughters – 10-year old (Fig. 1VA) and 5-year old (Fig. 1VB) – had short stature and mild bilateral hypoacusis. They carried the mitochondrial A3243G mutation and had previously been diagnosed as having MELAS syndrome. They had no history of stroke-like episodes (brain MRI scans revealed no focal abnormality) or lactic acidosis and had no other symptoms. We did not have opportunity to examine them.

The maternal grandmother (Fig. 1IIB) and the maternal great-grandmother (Fig. 1IB) both had bilateral deafness as the only symptom. However, they had never been admitted for any detailed examination. Various symptoms and diseases that have been found in members of the family with A3243G mutation are presented in Table 2.

3. Discussion

We have investigated the case of one family with A3243G mutation, in which a dominant symptom in four generations was the maternally inherited sensorineural hearing loss. The clinical picture of our 48-year-old patient typically fits that observed in patients with the maternally inherited diabetes and deafness (MIDD) syndrome. However, it is not an appropriate acronym for our case due to the absence of diabetes and the presence of variable other symptoms in the maternal family members. Our patient had clinical, neuroradiological and metabolic features of mitochondrial encephalomyopathy (ataxia, severe deafness, generalized muscle weakness and atrophy, cardiomyopathy, brain and cerebellar atrophy, diffuse white-matter lesions, lactate increase in cerebrospinal fluid). Additionally, she was diagnosed with polycythemia vera – this association with mtDNA A3243G mutation has not been reported in the literature. To our knowledge, however, mitochondrial disorders predominantly manifest in tissues with high-energy requirements, such as the central nervous system, peripheral nervous system, heart, muscle, endocrine glands, kidneys, eyes, inner ears and also bone marrow [6]. The mutation causes respiratory chain deficiency with impaired oxidative phosporylation and ATP production [2].

Regarding the family history, the mother (Fig. 1IIIC) of our patient had clinical features of muscle weakness, peripheral sensory neuropathy, cerebellar ataxia and hearing loss which occurred in the fifth decade. The younger sister (Fig. 1IVC) of our patient and her two daughters had mild hypoacusis and short stature and also had the A3243G point mutation. They had previously been diagnosed with MELAS syndrome. The characteristic clinical features of MELAS syndrome are

encephalopathy manifesting as dementia and seizures, stroke-like episodes at young age (usually < 40 years), lactic acidosis and myopathy with ragged-red fibres [7,8]. However, none of the family members have ever experienced any of the typical clinical features of MELAS. Their condition should be classified as non-syndromic mitochondrial disorder. MELAS is the commonest of the mitochondrial disorders but the mitochondrial A3243G mutation does not necessarily imply MELAS. Other frequent clinical manifestations of A3243G mutation include: sensorineural deafness, progressive external ophthalmoplegia, dementia, ataxia, diabetes, pigmentary retinopathy, myoclonic, hypoparathyroidism, peripheral neuropathy and cardiomyopathy in various combinations [4,9,10].

The phenotypic heterogeneity observed in investigated family may be the consequence of variable percentage of mutation load (cellular content of the A3243G mutation) among various tissues – a phenomenon called heteroplasmy [11]. Level of heteroplasmy is usually higher in muscles (up to 92%), but mutation may be also detected in hair follicles, blood lymphocytes or urinary sediments [10]. Several studies have shown that levels of heteroplasmy for the A3243G mutation decrease with age in most tissues [12]. On the contrary, a high degree of heteroplasmy is associated with an earlier age of onset of the disease and severity of the phenotype [10,13,14]. The varied clinical expression of mtDNA mutation in one family often makes appropriate diagnosis a considerable challenge.

In conclusion, we reported the case of a family with A3243G mtDNA mutation with a dominant symptom of maternally inherited sensorineural hearing loss. A3243G mtDNA mutation should be considered as a potential cause of various neurological disorders even in patients without any classic clinical features of MELAS syndrome.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES

[1] Yatsuga S, Povalko N, Nishioka J, Katayama K, Kakimoto N, Matsuishi T, et al., for MELAS Study Group in Japan. MELAS: a nationwide prospective cohort study of 96 patients in Japan. Biochim Biophys Acta 2012;1820:619–24.
[2] Frederiksen AL, Jeppesen TD, Vissing J, Schwartz M, Kyvik KO, Schmitz O, et al. High prevalence of impaired glucose homeostasis and myopathy in asymptomatic and oligosymptomatic 3243A>G mitochondrial DNA mutation-positive subjects. J Clin Endocrinol Metab 2009;94:2872–9.
[3] Chinnery PF. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. Mitochondrial disorders overview. GeneReviews. Seattle: University of Washington; 2010, http://www.ncbi.nlm.nih.gov/books/NBK1224/.
[4] Blum S, Robertson T, Klingberg S, Henderson RD, McCombe P. Atypical clinical presentations of the A3243G mutation, usually associated with MELAS. Intern Med J 2011;41:199–202.
[5] Donovan LE, Severin NE. Maternally inherited diabetes and deafness in a North American kindred: tips for making the diagnosis and review of unique management issues. J Clin Endocrinol Metab 2006;91:4737–42.
[6] Finsterer J. Manifestations of the mitochondrial A3243G mutation. Int J Cardiol 2009;137:60–2.
[7] Finsterer J. Stroke and stroke-like episodes in muscle disease. Open Neurol J 2012;6:26–36.
[8] DiMauro S, Hirano M. MELAS. GeneReviews. Seattle: University of Washington; 2012, http://www.ncbi.nlm.nih.gov/books/NBK1233/.
[9] Koga Y, Akita Y, Takane N, Sato Y, Kato H. Heterogeneous presentation in A3243G mutation in the mitochondrial tRNA(Leu(UUR)) gene. Arch Dis Child 2000;82:407–11.
[10] Finsterer J. Genetic, pathogenetic, and phenotypic implications of the mitochondrial A3243G tRNALeu(UUR) mutation. Acta Neurol Scand 2007;116:1–14.
[11] Laloi-Michelin M, Meas T, Ambonville C, Bellanne-Chantelot C, Beaufils S, Massin P, et al., Mitochondrial Diabetes French Study Group. The clinical variability of maternally inherited diabetes and deafness is associated with the degree of heteroplasmy in blood leukocytes. J Clin Endocrinol Metab 2009;94:3025–30.
[12] Liou CW, Huang CC, Wei YH. Molecular analysis of diabetes mellitus-associated A3243G mitochondrial DNA mutation in Taiwanese cases. Diabetes Res Clin Pract 2001;54(Suppl. 2):S39–43.
[13] Olsson C, Zethelius B, Lagerström-Fermér M, Asplund J, Berne C, Landegren U. Level of heteroplasmy for the mitochondrial mutation A3243G correlates with age at onset of diabetes and deafness. Hum Mutat 1998;12:52–8.
[14] Hammans SR, Sweeney MG, Hanna MG, Brockington M, Morgan-Hughes JA, Harding AE. The mitochondrial DNA transfer RNALeu(UUR) A → G(3243) mutation. A clinical and genetic study. Brain 1995;118:721–34.