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Abnormal brainstem auditory evoked responses in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): Evidence of delayed central conduction time

Josep Gamez [a,*], Teresa Minoves [b]

[a] *Department of Neurology, Hospital Universitari Vall d'Hebron, UAB, Barcelona, Spain*
[b] *Department of Neurophysiology, Hospital Universitari Vall d'Hebron, UAB, Barcelona, Spain*

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Abstract

Objective: To assess the usefulness of brain auditory evoked potentials (BAEPs) in the study of asymptomatic white matter alterations in brain MRI observed in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) patients.
Methods: The authors studied the neurophysiological characteristics of the BAEPs in four genetically confirmed MNGIE patients who presented varying degrees of leukoencephalopathy in brain MRI.
Results: Prolonged I–III and I–V interpeak latencies were the most common abnormalities found, with a correlation between the extent of brain MRI lesions and BAEPs.
Conclusions: The findings suggest a delayed central conduction time along the brainstem. BAEPs may be useful in the neurophysiological evaluation of central white matter lesions in MNGIE. Similar neurophysiological findings have been reported in other myelin disorders in the central nervous system.
Significance: The BAEPs abnormalities identified should be interpreted as an indirect sign of CNS involvement in MNGIE patients and provide comprehensive and integrated information concerning brainstem dysfunction. Further studies are necessary in order to identify whether there is a correlation between BAEPs and the clinical progression of the disease.

Keywords: MNGIE; BAEPs; Mitochondrial encephalomyopathies; Leukoencephalopathy; Central conduction time

1. Introduction

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an autosomal recessive multisystem disorder, characterized by gastrointestinal and extraocular muscle involvement, mitochondrial myopathy, sensorimotor demyelinating polyneuropathy (SMDP), and leukoencephalopathy. While neurological and gastrointestinal features are uniformly present in MNGIE patients, visceral neuropathy and myopathy are the disease's most prominent and debilitating manifestations (Hirano et al., 1994; Nishino et al., 1999; Nishino et al., 2000; DiMauro and Schon, 2003; Gamez and Garcés-Garmendia, 2005). MNGIE patients consequently complain of chronic pseudo-obstruction symptomatology rapidly leading to a cachexic appearance. Prognosis is related to the effects of gastrointestinal involvement on nutritional status. Information on fewer than 80 genetically confirmed MNGIE patients shows that they often die due to peritonitis, septicemia, intestinal perforation, esophageal bleeding, and bronchoaspiration before 40 years of age (Hirano et al., 1994; Nishino et al., 2000; Gamez et al., 2002; Kocaefe et al., 2003; Hirano et al., 2004; Martin et al., 2004; Szigeti et al., 2004; Gamez et al., 2005; Hirano et al., 2005; Slama et al., 2005).

Unlike the striking gastrointestinal manifestations, the symptoms associated with neurological involvement are

* Corresponding author. Tel.: + 34 93 274 61 41; fax: +34 93 417 27 42.
E-mail address: 12784jgc@comb.es (J. Gamez).

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mild, and despite progressive muscular wasting, patients rarely complain of weakness. Only ptosis and ophthalmoparesis are evident upon physical examination, although they may be absent. However, laboratory examinations have shown both leukoencephalopathy and slow peripheral nerve conduction velocities (NCV) resembling an SMDP (Hirano et al., 1994; Hirano et al., 2004; Bedlack et al., 2004; Gamez and Garcés-Garmendia, 2005; Said et al., 2005).

A typical MRI finding is an abnormally high signal in T_2-weighted sequences in the white matter, involving both hemispheres and the brainstem. In some cases, the characteristics of this leukoencephalopathy mimic those found in leukodystrophies (Hirano et al., 1994; Nishino et al., 2000; Hirano et al., 2004). Pathological studies performed on only four patients showed a reduction in the number of myelinated fibers, but no gliosis, spongy degeneration, necrosis, or significant astrocytosis (Bardosi et al., 1987; Simon et al., 1990; Uncini et al., 1994). The less specific term "leukoencephalopathy" was therefore initially used, because of doubts about whether the primary event is axonal atrophy or demyelination. Despite this severe leukoencephalopathy, patients do not present cognitive alterations or symptoms suggesting brainstem involvement (Simon et al., 1990; Hirano et al., 2004).

Little is known about the effect of white matter involvement on the neurophysiological function of central pathways. BAEPs are an accurate indicator for assessing the integrity of the auditory brainstem pathway. The neuroradiological findings in our MNGIE patients led us to investigate the possible alterations in efferent pathways of the olivo-cochlear bundle.

In this study, we report on abnormal BAEP responses in three of our MNGIE patients. To our knowledge, no previous studies have documented BAEP abnormalities in MNGIE.

2. Patients and methods

2.1. Patients

Four genetically confirmed MNGIE patients between 25 and 34 years old were studied. All showed MRI findings of leukoencephalopathy and features of SMDP in nerve conduction studies (NCS). Informed consent was obtained for this study under an IRB-approved protocol.

2.1.1. Case 1

A 29-year-old man born to healthy non-consanguineous parents, referred for study of a chronic intestinal pseudo-obstruction syndrome associated with severe weight loss and hypoalbuminemia.

Examination showed mild bilateral external ophthalmoparesis and sunken eyes, but no ptosis. He weighed 44 kg and was 1.78 m tall, with marked cachexia and mild muscle weakness affecting the deltoids, biceps, and iliopsoas. Tendon reflexes were absent. Mild bilateral sensorineural hearing loss was present (Table 1).

Table 1
Clinical features and laboratory investigations in the four patients

	Patient 1	Patient 2	Patient 3	Patient 4
Clinical features				
Sex/age	M/29	W/25	W/34	W/27
Age at onset (years)	4	1	18	3
Height/weight	178 cm/44.0 kg	166 cm/32.8 kg	150 cm/45 kg	150 cm/23.3 kg
First symptom	Poor weight gain, abdominal pain	Recurrent abdominal pain	Bilateral ptosis	Abdominal pain
Current involvement	GI/NL/C	GI/NL/C	NL	GI/NL/C
Clinical neurological findings	O/S/HL	Pt/O/S/HL/W	Pt/O/W	Pt/O
Reflexes	A	A	D	D
Laboratory investigations				
EMG	SMDP/MP	SMDP/MP	SMDP	SMDP
R. median MCV:	36 m/s	25 m/s	35 m/s	38 m/s
R. peroneal MCV:	27 m/s	NR	23 m/s	35 m/s
R. sural SCV:	NR	NR	NR	30 m/s
Resting lactate	2.0 mmol/L	1.2 mmol/L	1.9 mmol/L	2.94 mmol/L
Resting pyruvate	0.25 mmol/L	0.26 mmol/L	0.12 mmol/L	0.18 mmol/L
ALT	25 U/L	32 U/L	35 U/L	76 U/L
CK	147 U/L	72 U/L	20 U/L	231 U/L
Proteins	5.2 g/dL	6.42 g/dL	7.7 g/dL	5.66 g/dL
Thymidine	3.2 μM	9.1 μM	3.3 μM	5.4 μM
TP activity	3 nmol/h/mg	8 nmol/h/mg	Undetectable	Undetectable
Brain MRI	DLK	DLK	PLK	DLK
Genotype	dup 18 pb/dup 18 bp	L371P/L371P	R44Q/R44Q	R44Q/R44Q

Abbreviations: A, abolished; C, cachexia; D, diminished; DLK, diffuse leukoencephalopathy; GI, gastrointestinal; HL, hearing loss; L, left; MCV, motor conduction velocities; MP, myopathic pattern; N, neuropathy; NL, neurological; NR, No response; O, ophthalmoparesis; PLK, patchy leukoencephalopathy; Pt, Ptosis; TP, thymidine phosphorylase; R, right; S, sensory impairment; SCV, sensory conduction velocities; SMDP, sensory motor demyelinating polyneuropathy; W, weakness. Normal values: CK, 55–195 IU/L; ALT, 12–40 IU/L; Lactate, 0.3–2.1 mmo/L; Pyruvate, 0.02–0.19 mmo/L; Protein, 6.67–8.3 g/dL; Thymidine, <0.05 μM; TP activity, >544 nmol/h/mg protein.