Leigh disease: 9 years follow up of a Polish family harboring T8993C mitochondrial DNA mutation

Łukasz A. Małek, Bartłomiej Kisiel, Lech Korniszewski

Section of Pediatric Diabetology, Neonate Pathology and Birth Defects, 2nd Department of Paediatrics, Medical University of Warsaw, Poland. Head of Department and Tutor: Lech Korniszewski, MD PhD

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Corresponding author:
Łukasz A. Małek
Kazury 1/13
02-795 Warsaw, Poland
Phone: +48 501 034 090
Phone/fax: +48 22 648 32 23
E-mail: lamalek@amwaw.edu.pl

Abstract

Leigh disease (LD) or subacute necrotizing encephalomyelopathy (SNE) is a mitochondrial dysfunction. It can be caused by either mitochondrial or nuclear DNA mutations, which impair communication of the complexes of the human electron transporting chain (ETC) directly or by interfering with nucleus-mitochondrion. Leigh disease is characterized by psychomotor retardation, muscle weakness, pyramidal signs, lactic acidosis, hypotonia, dysphagia, symmetric basal ganglia and brainstem lesions. Due to a relatively small number of published cases and multisystemic involvement of LD there is no clear definition of symptoms and definite diagnosis can be based only on the genetic analyses. In our study we describe a Polish family harboring T8993C mutation in one of the subunits of ETC complex V (ATPase). We present the differential diagnosis of LD and observations of the described family performed 9 years from the diagnosis of Leigh disease. We suggest that the results of the neurophysiologic examinations in LD patients are characteristic both for neuronal and muscular lesions. Apart from that we assessed physical or psychological state of the family members measured by self-constructed LD-specific quality of life questionnaire.

Key words: mitochondrial myopathy, Leigh disease, case study, quality of life

Introduction

Leigh syndrome (LD) or subacute necrotizing encephalopathy (SNE) was first described in 1951 and belongs to a growing number of diseases called mitochondrial myopathies [1, 2]. There are 3 major causes of Leigh syndrome, each transmitted by a different mode of inheritance: X-linked recessive, autosomal recessive and maternal [1, 3, 4]. All of the causes lead to the impairment of the mitochondrial function. The studied family harbors a common T8993C Leigh mutation in the ATP6 subunit of the ATP synthase (complex V of the electron transporting chain). Some of the complex V subunits as well as some subunits of all the other ETC complexes except the second one are encoded by 16,5 kb mitochondrial DNA (mtDNA). Coexistence of normal and mutated DNA copies within one cell is known as heteroplasmy, but its degree (percentage of mutated mtDNA) only partially correlates with severity of symptoms. What is more, all three general types of inheritance may present different phenotypes. The onset symptoms of Leigh disease usually include neurogenic muscle weakness, but classification of LS symptoms varies from case to case

Table I. Symptoms of Leigh disease by frequency of appearance

	Rahman [7]	Jiang [1]	Savasta [6]	Jacobs [5]	Together
Number of cases	10	8	3	3	24
Psychomotor retardation	10	6	3	2	21 (88%)
Muscle weakness	8	8	3	2	21 (88%)
Pyramidal signs	9	8	0	3	20 (83%)
Lactic acidosis					
at rest	9*	6	1	2	18 (75%)
after glucose stimulation	0	1	2	0	3 (12,5%)
Dysfagia	8	7	2	0	17 (71%)
Hypotonia	7	5	3	2	17 (71%)
Apneas	8	4	3	1	16 (67%)
Nystagmus	4	5	2	3	14 (58%)
Focal changes on CT/MRI***	2*	6	3	0	11 (46%)
Vision and hearing impairment	4	5	0	1	10 (42%)
Ataxia	5	2*	0	2	9 (37,5%)
Peripheral neuropathy***	?	?	?	3	?

** – some cases where not studied*

*** – MRI changes in T_2 imaging can be present in periventricular regions, globus pallidus, caudate nuclei, putamen, thalamus and in the mid-brain [1, 6, 7, 11]. On the other hand CT changes can disclose enlargment of the brain ventriculi and/or bilateral atrophy of the brain cortex [11].*

**** – peripheral neuropathy in LD of mitochondrial origin appears in 30% of cases [3]*

which is provoked by a small number of patients studied and published. Most common clinical manifestations found in literature are presented in Table I [1, 5-7].

Subjects and methods

Subjects

The study included three patients: a 50-year-old white woman (case 1) and her 18-year-old twin daughters (cases 2 and 3) all harboring T8993C mutation in ATP6ase gene of mtDNA.

Quality of life questionnaire (QOL)

To assess the quality of life a questionnaire specific for Leigh disease was constructed. It consisted of two parts, part A concentrating on the physical state and part B describing the psychological condition of the patients. Part A included questions about the distance of walking without fatigue, severity and frequency of equilibration problems, the intensity of pain in the lower limbs while walking, sensation loss and general weakness. Part B was based on the Beck scale in Polish adaptation [8]. To compare the results of both tests first – filled retrospectively for the time of the first approach and second – done on our check-up we used one to ten scale adding negative points from each question.

Case reports

Case 1

M.K., a 50-year-old white woman, first presented in February 1994 with 9-year history of progressive troubles in walking which started after pregnancy and made her resign from work as a shopping assistant. The proband complained of a burning pain in the lower limbs while moving even small distances (500 meters), balance problems and tripping. Neurological examination at that time apart from lower limbs paresis showed weakness in the upper limbs and various degrees of superficial and deep sensation impairment at trunk and lower limbs.

Preliminary diagnosis included sclerosis multiplex, but cerebrospinal fluid examination excluded that suspicion. At this point myelosis funicularis was taken into consideration, but vitamin B12 and folium acid concentrations demonstrated only small variations from the average.

EMG studies in 1994 and 1995 demonstrated a neurogenic process with deficit of sensory and motor fibers and signs of reinnervation.

Ophthalmologic consultation revealed rarefied arteries and pigment regrouping. ECG and EEG showed no appreciable changes, but MRI disclosed mild enlargement of lateral ventricles and signs of spinal atrophy.

Before the genetic studies were performed in Sweden in 1997 the diagnosis remained unclear. As

described above hypertrophic, demyelinization processes and microelements deficiency were excluded. In Sweden proband's nephew started to present symptoms of LD which led to genetic examination of the whole family. It revealed a high degree of T8993C DNA heteroplasmy in proband's vastus muscle and lymphocyte samples (Table II).

Biopsy and histopathological examination of quadriceps muscle done soon after genetic examinations disclosed mixed neurogenic and metabolic muscle impairment with various fiber size, lipid accumulation and signs of reinnervation [8].

On our examination in 2003 patient complained of stiffness in both lower limbs which made her stay at home and walk only with a support. She admitted that balance problems worsened especially at rest.

These findings were not present or less expressed 9 years ago. EMG revealed markedly increased dennervation changes. QOL test results showed progression of the disease presenting an increased number of negative points checked off by the patient in both parts (Table III).

Case 2

A.K., a 18-year-old woman, was born in 1985 with 10 pts Apgar followed by transient respiratory failure. She started to present slight fatigue and troubles at school in the age of 12 with psychological examination of mild mental deficiency.

Laboratory examinations from that time demonstrated borderline concentration of lactate in blood and muscle histologic studies showed some onset changes in fiber lipid content. EMG disclosed neurogenic type changes, while MRI and ophthalmologic examinations did not disclose any LD specific alterations.

In the anamnesis from 2003 proband complained of the pain in the lower limbs while walking present even after short physical efforts. Symptoms were accompanied by problems with keeping balance, tripping and bruising knees. Needle EMG of the right brachial biceps performed at time of control disclosed myopathy type changes. Genetic studies of the proband are presented in Table II.

In the assessment of quality of life the patient checked off approximately the same number of negative points in 1996 and in 2003 (Table III).

Table II. Results of the genetic studies for the mitochondria DNA T8993C mutation heteroplasmy in studied patients

Sample type	Case 1	Case 2	Case 3
Muscle	99%	97%	87%
Lymphocyte	91%	92%	71%

Case 3

M.K., twin sister of the patient presented in case 2, was born with 9 pts Apgar and body mass 2200 g showing signs of dystrophy. She never presented any clinical symptoms of LD. In 1996 she underwent the same examinations as her sister which disclosed paragon able results despite the different clinical phenotype of two sisters. Genetic studies of the proband are presented in Table II.

Because at the time of control in 2003 she did not have any clinical symptoms we decided to limit our investigations to quality of life questionnaire (Table III).

Discussion

Apart from Leigh disease T8993C mutation can be found in other mitochondrial myopathies like NARP (neurogenic ataxia and retinitis pigmentosa) or Leber disease [3, 10].

We excluded the alternate diagnosis because of the lack of eye fundus alterations and absence of the optic nerve atrophy in studied cases.

We suggest that neurological lesions can coexist with muscle impairment which is a reason why both types of electrophysiological abnormalities can be found in LD patients at a different time from the onset. An argument sustaining that theory could be modifications found on muscle histological examinations.

Neurophysiological examinations seem to be very sensitive even in an early state of the disease but they are unspecific and do not present a good prognostic value for LD. The „gold standard" of diagnosis and prognosis are genetic studies though on the other hand they cannot specify the symptoms onset time and the velocity of disease progression. It is important in LD to study muscles and nerves which present most severe symptoms because the results of neurophysiological studies can vary from one to another segment of the patients organism with the

Table III. Quality of life assessment in the studied group

Lear/*	Case 1			Case 2			Case 3		
	A	B	A+B	A	B	A+B	A	B	A+B
1994 or 1996	69	55	**124**	62	75	**137**	20	44	**64**
2003	83	73	**156**	58	75	**133**	21	46	**67**

** part of the QOL questionaire*

variations of heteroplasmy among one or different tissues. It should be emphasized that examinations aimed at other neuromuscular segments in the studied probands could have disclosed more alterations.

The results of EMG examinations were very similar in two sisters in 1996 despite their different clinical state. The similarity of changes can derive from the fact that we studied two heterozygotic twins. There are not any published cases about twins with LD. The psychomotor retardation in case 2 could have been caused by transient neonatal respiratory failure characteristic of LD. The difference in the clinical state among two twin daughters may be also explained with genetic studies. In case 2 heteroplasmy in muscle and blood samples were higher then in case 3. That concentration difference in mutated mtDNA among both sisters might be responsible for the early onset of the disease in one of them and only small abnormalities present in the other which may eventually lead to a fully expressed disease in the future.

Onset of the symptoms after a pregnancy period in case 1 supports the thesis that oxygen demanding stress events with genetic background can all together lead to clinical demonstration or progression of the disease11. For this reason all our patients were advised to limit exercise to a necessary minimum and avoid stress situations. The risk which cannot be mathematically measured. persists for both daughters in case of their pregnancy.

Conclusions

In Leigh disease we must consider to events which are nerve and muscle impairment. LD is a progressive disorder which exacerbates in stress situations such us respiratory failure, pregnancy or infection. Neurophysiological examinations are a sensitive but an unspecific diagnostic method in Leigh disease and correlate well with progression of the disorder, but they do not assess the clinical state of the patient. We introduce the quality of life questionnaires to the LD examinations as a good marker of the clinical state in these patients.

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