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Title : Sensory neuronopathy as a major clinical feature of mitochondrial trifunctional protein
deficiency in adults

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Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

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Title : Sensory neuropathy as a major clinical feature of mitochondrial trifunctional protein deficiency in adults

Abstract:

INTRODUCTION: Mitochondrial trifunctional protein deficiency (MTPD) is a long-chain fatty acid oxidation disorder characterized by co-existence of rhabdomyolysis episodes and peripheral neuropathy. Two phenotypes are described: generalized mitochondrial trifunctional protein deficiency (gMTPD) and isolated long-chain-3-hydroxyacyl-CoA dehydrogenase deficiency (iLCHADD) that is always associated with the c.1528G>C mutation. Peripheral neuropathy of MTPD is commonly described in children as axonal, length-dependent and sensorimotor.

OBJECTIVES: To report clinical and electrophysiological features of four independent adult MTPD patients with peripheral neuropathy.

RESULTS: Onset of the disease was characterized in all patients by rhabdomyolysis episodes occurring during childhood preceded by severe hypoglycemic episodes in three patients. Peripheral nerve involvement manifesting as sensory ataxia appeared later, during adolescence or adulthood. In all cases, electroneuromyogram showed no length-dependent sensory potentials decrease characteristic of sensory neuropathy ("ganglionopathy"). All patients harbored at least one c.1528G>C mutation.

DISCUSSION: We describe MTPD as a newly hereditary etiology of sensory neuropathy in adults, specifically in patients with c.1528G>C mutation. MTPD should be screened for by performing plasma acylcarnitines in patients with chronic sensory neuropathy and additional suggestive features such as exercise intolerance or retinopathy.

5 Key words: LCHAD deficiency, MTP deficiency, ganglionopathy, sensory neuronopathy, rhabdomyolysis.

Abbreviations :

CPT 2: Carnitine-Palmitoyl-Transferase 2

FAOD: Fatty acid Oxidation disorder

HADHA: HADHA gene

HADHB: HADHB gene

EMG: Electromyography

iLCHADD: Isolated Long Chain Acyl-CoA dehydrogenase deficiency

MADD: Multiple acyl-CoA dehydrogenase deficiency

gMTPD: Generalized Mitochondrial Trifunctional Protein deficiency

NCS: Nerve Conduction Study

PR : Pigmentary Retinopathy VLCADD: Very Long Chain Acyl-CoA dehydrogenase deficiency

INTRODUCTION

Long-chain fatty acid oxidation disorders (LCFAODs) are a group of autosomal recessive diseases that have some shared manifestations usually beginning in childhood (non-ketotic hypoglycemia, hepatomegaly, cardiomyopathy, rhabdomyolysis). In some late onset patients, muscle symptoms may be prominent, with exercise, fasting or fever-induced rhabdomyolysis crisis. These diseases chiefly comprise CPT2 deficiency, VLCAD deficiency, and mitochondrial trifunctional protein deficiency (MTPD) encompassing two entities, isolated long-chain-3-hydroxyacyl-CoA dehydrogenase

deficiency (iLCHADD) and generalized mitochondrial trifunctional protein deficiency (gMTPD). Among LCFAODs, only MTPD has been associated with peripheral neuropathy.

MTP is a hetero-octamer composed of four α - and four β -subunits and contains three different enzyme activities that catalyze the final three chain-shortening reactions in long-chain fatty acids β -oxidation. *HADHA* gene encodes the α -subunit, which has both long-chain enoyl-CoA hydratase (LCEH, EC4.2.1.17) and LCHAD (EC 1.1.1.211) activities, whereas *HADHB* gene encodes the β -subunit, which has only long-chain 3-ketoacyl-CoA thiolase (LCKT, EC 2.3.1.16) activity. Mutations in *HADHA* or *HADHB* usually cause a gMTPD, with decreased activity and levels of all three enzymes because of the failure to form a hetero-octamer. Homozygosity for the *HADHA* mutation c.1528G>C has been reported to cause iLCHADD. Compound heterozygous *HADHA* mutations with one c.1528G>C mutation may be associated with either iLCHADD or gMTPD[1]. In this case, only enzymatic activity measurements may determine whether patients have iLCHADD or gMTPD. We will use the term MTPD to encompass both entities if needed, notably if distinguishing iLCHADD from gMTPD is not possible.

Even though gMTPD and iLCHADD patients have close clinical phenotypes, they are clearly distinct [2]. For example, pigmentary retinopathy (PR) is a common feature only in iLCHADD patients, whereas adult-onset rhabdomyolysis without previous pediatric manifestations has only been described in gMTPD [3]. Measurement of plasma acylcarnitines is essential as a screening diagnostic test for MTPD, showing increased long-chain hydroxyacylcarnitines [4]. Definite diagnosis relies on enzymatic and/or molecular tests. Peripheral nerve involvement in MTPD patients is classically described as a progressive axonal length-dependent and sensorimotor neuropathy [5,6]. Here we report four adult patients, all harboring at least one c.1528G>C mutation, presenting with pure sensory non-length-dependent neuropathy (i.e., sensory neuronopathy or ganglionopathy) as a major clinical feature, which has not been previously described.

CASES REPORT

See Table 1 (clinical data), 2 (biochemical and genetic data) and 3 (electrophysiological data).

Patient 1:

A 47-year-old woman experienced recurrent episodes of myalgia and myoglobinuria triggered by exercise, fasting, intercurrent cold and intercurrent infection, since the age of 4 years. Creatinine kinase levels during bouts rose up to 10 000 U/L. She suffered from acute muscle pain once a week and she interrupted sport practice at the age of 13 years because of exercise intolerance. Clinical symptoms insidiously worsened during the fourth decade with frequent falls, upper limb clumsiness, cramps, constrictive pain and distal paresthesia in all four limbs. Clinical examination revealed severe proprioceptive ataxia, distal tactile hypoesthesia and bilateral pes cavus, without motor impairment. Reflexes were abolished in all four limbs. Nerve conduction studies (NCS) at 44 years revealed decreased amplitudes and low velocity conduction in median sensory nerves, and complete abolition of other sensory potentials. Motor potentials were only slightly decreased in median nerves and tibial posterior nerves with normal conduction. Electromyography (EMG) showed neuropathic process in the lower limbs, without any myopathic feature. Treatment introduced at diagnosis in adulthood, with low-fat diet, medium chain triglycerides, carnitine and synthetic ketone bodies (sodium DL,3-hydroxybutyrate) led to a reduction of muscle pain episodes and seemed to improve her endurance, but rhabdomyolysis episodes persisted approximately once a year.

Patient 2:

This 25-year-old female patient was born prematurely due to acute fatty liver of pregnancy. At ages 8 and 13 months, she presented with acute episodes of vomiting and hypoglycemia with loss of consciousness associated with hepatomegaly and liver failure. These acute manifestations

resolved after treatment with low-fat diet, L-carnitine and riboflavin; the diagnosis of MTPD was achieved. During childhood she displayed recurrent episodes of rhabdomyolysis triggered by intense exercise, with creatine kinase levels up to 30 000 UI/l. PR was observed when she was 8, and a balance disorder occurred insidiously from the age of 11 years, associated with frequent falls. Physical examination revealed sensory ataxia, reduced distal pallesthesia in the lower limbs, no tactile hypoesthesia and absent reflexes in all four limbs. Her visual acuity was 1/10. Sensory NCS showed low amplitudes (asymmetric only for radial nerves) with moderately decreased velocities, or abolished potentials in all four limbs, and a normal motor NCS (Table 2). A mild myopathic pattern was detected on EMG. Visual loss progressively worsened as did ataxia despite treatment, contrasting with a decrease in the frequency of rhabdomyolysis episodes.

Patient 3:

This 30-year-old male presented several hypoketotic hypoglycemia events since age 2 and suffered from exercise intolerance and episodes of rhabdomyolysis (peak creatine kinase levels=44200 U/L) triggered by exercise or fasting since age 7. Despite treatment with low-fat diet, medium chain triglycerides and L-carnitine, which improved hypoglycemia and muscle symptoms, balance disorders occurred insidiously from age 22 and progressively worsened. He also suffered from PR leading to blindness at age 28. Physical examination showed sensory ataxia, tactile sensory loss affecting the hands and feet, decreased lower limb pallesthesia and generalized areflexia. NCS showed decreased amplitudes of sensory potentials, predominantly in the upper limbs, with asymmetrical distribution. Motor amplitudes were mildly decreased in the lower limbs. EMG was normal.

Patient 4:

This 20-year-old female presented a hypoglycemic coma with hepatomegaly and liver failure at age 7 months. At onset of treatment (7 months) with low-fat diet, medium chain triglycerides and carnitine, she had normal deep tendon reflexes and visual acuity. During childhood she complained about episodic muscle pain during febrile illness and physical exertion, and had one or two minor rhabdomyolysis episodes per year since 7 years of age. She exhibited decreased visual acuity since 9 years of age that slowly worsened. PR was confirmed on electroretinogram. At last follow-up she did not complain about balance and/or gait disorders or sensory signs but all her reflexes were abolished and she had minor clinical signs of a sensory disorder. NCS showed severely decreased amplitudes of sensory potentials in the four limbs without length-dependent pattern. Motor amplitudes were all normal.

Biochemical and Molecular Investigations:

In all four patients, measurement of plasma acylcarnitines showed increased long-chain acylcarnitines suggesting MTPD, and two *HADHA* mutations including at least one c.1528 G>C mutation were detected (Table 3). Patient 2 was then diagnosed iLCHADD on a genetic basis (homozygous c.1528 G>C), as was patient 4 on enzymatic assays performed on cultured skin fibroblasts. Patients 1 and 3 were diagnosed either iLCHADD or gMTPD, as no enzymatic activities were measured whereas mutations were equivocal of either phenotype.

Blood tests performed in order to rule out alternative causes of sensory neuronopathies were negative for all four patients, and included immunological (serum protein electrophoresis with immunofixation, antinuclear factor, anti-DNA antibodies, anti-SSA and anti-SSB antibodies, anti-gangliosides antibodies, onconeural antibodies), infectious (human immunodeficiency virus, hepatitis, and Lyme serologies), and metabolic markers (vitamins B9, B12, E, and homocysteine).

DISCUSSION

We report herein the first observations of sensory neuropathy in four MTPD patients, all harboring at least one c.1528 G>C mutation in the *HADHA* gene, manifesting as a progressive sensory ataxia with onset in adolescence or adulthood.

Sensory neuropathy, or "ganglionopathy" corresponds to a primary degeneration of sensory neurons in dorsal root ganglia. The clinically pure sensory neuropathy described in the reported four patients fulfill diagnostic criteria for sensory neuropathy, even though NCS showed patients 1 and 3 had slightly decreased motor potentials in the lower limbs [7]. Mild motor nerve abnormalities have been previously reported in sensory neuropathy with paraneoplastic disorders, discussed as a possible diffusion of the pathological process beyond sensory ganglia into the peripheral nerves [8]. In our patients, we noted that the median nerve was less affected than the ulnar and radial nerves, a recently reported observed feature arguing in favor of this diagnosis [9]. Characterization of a clinically pure sensory neuropathy as a neuronopathy is essential in the diagnostic approach, as sensory neuronopathies have specific etiologies. Acquired sensory neuropathy is associated with paraneoplastic syndromes, human immunodeficiency virus infection, Goujerot-Sjögren syndrome and toxics (cisplatin, high doses of vitamin B6) [7]. The broad laboratory investigations performed in our four patients ruled out these major acquired causes of sensory neuropathy especially for patient 1 diagnosed with MTPD in adulthood. Genetic etiologies are dominated by Friedreich ataxia and mitochondrial disorders, notably caused by polymerase gamma mutations [10–12].

MTPD-associated peripheral neuropathy was mainly described in the gMTPD late-onset neuromuscular form, where it is present in 80% of cases [13]. Neuropathy often precedes rhabdomyolysis [5,6,14]. The neuropathy is described as an axonal length-dependent mixed sensory and motor neuropathy [6,14]. Patients usually present with motor weakness, with lower limbs

impaired earlier than upper limbs, that may be severe, some patients requiring a wheelchair in their early teens [5,15]. Patients also suffer from sensory impairment with proprioceptive disorders and paresthesia [6]. NCS shows a sensorimotor impairment more severe in the lower than upper limbs [6]. Interestingly, gMTPD-associated peripheral neuropathy may be first diagnosed as Charcot-Marie-Tooth disease when muscle symptoms are absent [3,16]. None of the patients with sensorimotor neuropathy and gMTPD described in the literature have harbored the c.1528 G>C mutation.

iLCHADD-associated peripheral neuropathy (as in our patients 2 and 4) has been less often described. Frequency was initially reported to be low, but this is true only for very young patients [17]. Since metabolic therapies allowed patients to live longer, peripheral neuropathy was most often observed later on during patient follow-up. Tuuli et al. recently reported that 8/12 treated iLCHADD patients (with homozygous c.1528 G>C mutation) developed a peripheral neuropathy detected by NCS between 6 and 12 years of age [18]. Interestingly, no patients complained of any weakness, as peripheral neuropathy was mainly sensory with decreased sensory potentials in all four limbs, and no decreased motor potential except in one patient. Data about sensorial NCS were not comprehensive enough to assess potential compatibility with sensory neuronopathy. Other patients with MTPD associated with the c.1528 G>C mutation and peripheral neuropathy have been described, although there is no way of knowing if they had gMTPD or iLCHADD (as in our patients 1 and 3) [19,20]. They all had a purely sensory peripheral neuropathy that was considered to be length-dependent axonal type. Therefore, it seems that MTPD with presence of the homozygous or heterozygous c.1528 G>C mutation is associated with a purely sensory peripheral neuropathy that we were able to fully characterize in our patients as a sensory neuronopathy. Despite treatment, peripheral neuropathy, such as PR, was still progressing in our patients, confirming data previously reported [13,18].

To conclude, our data suggest that the type of peripheral neuropathy may be a new feature that differentially characterizes MTPD with or without c.1528G>C mutation, in addition to PR.

Presence or not of this mutation may be a more accessible and clinically relevant feature than enzymatic activities (i.e., gMTPD vs iLCHADD) to dichotomize MTPD patients into two different clinical phenotypes. Indeed, enzymatic analysis is less often performed now that genetic testing is widely available, and enzyme testing may still be equivocal because of mild decrease of LCEH and LKAT activity [19]. MTPD with c.1528G>C mutation is a new genetic etiology of sensory neuropathy, always preceded by other MTPD manifestations in our patients, that must be added to the list of genetic causes. Plasma acylcarnitines followed by confirmatory molecular analysis of genes *HADHA* and *HADHB* (starting from the frequent c.1528 G>C mutation on *HADHA*) should be performed in chronic sensory neuropathies of unknown diagnosis especially when associated with exercise intolerance, high creatine kinase levels, or other multiple-system features (cardiomyopathy, liver disease with episodic hypoglycemia, and pigmentary retinopathy).

Disclosure of interest

[The authors declare no conflict of interest](#)

Table 1: Clinical findings in the four MTPD patients

Data	Patient 1	Patient 2	Patient 3	Patient 4
Age at last follow up	47	25	30	21
Age at disease onset	4	8 months	2	7 months
Time of diagnosis	adult	infantile	infantile	infantile
Initial clinical presentation	Rhabdomyolysis	Hypoglycemic coma	Hypoglycemic coma	Hypoglycemic coma
Hypoglycemia (age at onset)	-	+ (8 months)	+ (2)	+ (7 months)
Rhabdomyolysis (age at onset)	+ (4)	+ (4)	+ (7)	+ (7)
Retinopathy (age at onset)	-	+ (8)	+ (9)	+ (9)
Balance disorder (age at onset)	+ (40)	+ (11)	+ (22)	-
Paresthesia (age at onset)	+ (40)	+ (NA)	-	-
Hepatomegaly	-	+	NA	+
Ataxic gait	+	+	+	-
Romberg	NA	+ (oscillations)	+ (oscillations)	+ (oscillations)
Tactile sensory loss	+ (distal four limbs)	-	+ (distal four limbs)	-
Hypopallesthesia	NA	+ (four limbs)	+ (four limbs)	+ (four limbs)
Ataxic UL	+	NA	NA	-
Ataxic LL	+	NA	NA	+
Weakness	-	-	-	-
Amyotrophy	-	-	-	-
DTR	All absent	All absent	All absent	All absent
Pes cavus	+	-	-	-
Sensory Neuropathy Score*	7.9	7.9	7.9	7.9**

*: in favor of a probable sensory neuropathy if above 6.5, according to Camdessanché and al

[7]; **: without considering item e (motor conduction) due to numerous non available data; NA : Not

Available; LL : lower limbs; UL : upper limbs; DTR : deep tendon reflexes

Table2: Metabolic and genetic findings in the four MTPD patients

Investigations	Patient 1	Patient 2	Patient 3	Patient 4
Plasmatic creatine kinase level at rest (U/l) (norm: 25 – 160 U/l)	110	263	1130	64
Urinary organic acids	Important excretion of 3-hydroxybutyric acid, 2-ketoglutaric acid, adipic acid, suberic acid	Important excretion of hydroxydicarboxylic acids	NA	Important excretion of dicarboxylic and hydroxydicarboxylic acids
Plasmatic acylcarnitine profile	Increase of C12, C14, C14:1, C14-OH, C16, C16:1, C16:1OH, C16OH, C18 and C18:1-OH	Increase of C10 to C18: OH acylcarnitines	Increase of C16 :1-OH : 3-OH and C18 : 1-OH- 3-OH	Increase of C8-OH, C14-OH and C16-OH
Fatty acid Oxidation Assay on cultured fibroblasts	NA	NA	Significant decrease of long chain fatty acid oxidation and moderate decreased of medium chain fatty acid oxidation	NA
3 hydroxy acyl-CoA dehydrogenase activity measured on cultured fibroblasts	NA	LCHAD deficiency (11.6 Units; N :69,5 - 94,3)	NA	LCHAD deficiency
Mutations of HADHA gene	c.914T>A (Ht) c.1528G>C (Ht)	c.1528 G>C (Hm)	c.1058-9delAinsT (Ht) c.1528G>C (Ht)	c.914T>A (Ht) c.1528 G>C (Ht)

NA : Not Available; Ht : Heterozygous; Hm : Homozygous

Table3: Electrophysiological features of the four MTPD patients

NCS data	Case 1		Case 2		Case 3		Case 4		Normal values
NR	Left	Right	Left	Right	Left	Right	Left	Right	NR
Age at examination	44 years		25 years		28 years		20 years		NR
	MOTOR CONDUCTION								
	MEDIAN NERVE								
Amplitude (mV)	3.17	2.72	15	16.02	6.51	9.69	7.5	NA	>6
Terminal latency (ms)	3.8	3.2	2.9	3.3	2.9	2.9	3.1	NA	<3.7
Velocity (m/s)	57	54	53	52	54	53	46.2	NA	>48
F – wave (ms)	28.3	27.1	22.8	22.5	NA	23.9	30.1	NA	
	ULNAR NERVE								
Amplitude (mV)	9.49	9.56	11.48	10.38	13.57	12.38	NA	NA	>6
Terminal latency (ms)	2.9	2.7	3	2.8	2.3	2.6	NA	NA	<3
Velocity (m/s)	51	54	50	56	51	52	NA	NA	>48
F – wave (ms)	27.5	26	28	27.6	ND	31.2	NA	NA	
	PERONEAL NERVE								
Amplitude (mV)	2.81	3.14	7.67	7.01	1.17	4.20	3.8	NA	>3
Terminal latency (ms)	4.7	3.9	3.9	3.6	5.5	4.5	3.85	NA	<5
Velocity (m/s)	55	39	40	41	40	41	41.7	NA	>42
F – wave (ms)	43	42.3	40.9	38.1	42.4	45.9	55.4	NA	
	POSTERIOR TIBIAL NERVE								
Amplitude (mV)	3.92	2.26	9.35	9.59	2.42	2.32	NA	NA	>6
Terminal latency (ms)	3.3	5.4	3.5	6.6	4.4	3.6	NA	NA	<5.5

Velocity (m/s)	NA	NA	NA	NA	NA	NA	NA	NA	>42
F – wave (ms)	60.7	62.3	51.7	54.2	56.4	51.5	NA	NA	
	SENSORY CONDUCTION								
	MEDIAN NERVE								
Amplitude (μV)	5.1	3.1	13.4	9.1	11.4	5.6	0.97	0.95	>15
Velocity (m/s)	NA	25	32	35	39	42	41.1	NA	>45
	ULNAR NERVE								
Amplitude (μV)	No	No	No	No	0.6	NA	No	NA	>8
Velocity (m/s)			response	response	NA	NA		NA	>45
	RADIAL NERVE								
Amplitude (μV)	No	No	NA	2.4	2.2	2.4	No	2.5	>15
Velocity (m/s)			NA	NA	30	32		NA	>45
	SURAL NERVE								
Amplitude (μV)	No	No	2.4	2.1	5.1	4.5	NA	1.99	> 10
Velocity (m/s)			NA	NA	31	36	NA	33.9	>40
	SUPERFICIAL SENSORY PERONEAL NERVE								
Amplitude (μV)	No	No	No	No	2.1	2.1	No	NA	>10
Velocity (m/s)					35	32		NA	>40

NA : Not Available. Abnormal values are in bold; No : no obtained potential;

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