Clinical Neurology and Neurosurgery 177 (2019) 92–96

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Ataxia with novel compound heterozygous *PEX10* mutations and a literature review of *PEX10*-related peroxisome biogenesis disorders

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ARTICLE INFO

Keywords:
Peroxisome biogenesis disorders (PBD)
Peroxisome biogenesis factor 10 (*PEX10*)
Ataxia

ABSTRACT

Objectives: To describe the clinical and genetic features of a Chinese peroxisome biogenesis disorder 6B patient with *PEX10* mutations and review *PEX10*–related peroxisomal disorders.

Patients and methods: The proband is a 7-year-old boy with mild mental retardation and gait instability, intention tremor and nystagmus. An extensive clinical and laboratory evaluation including molecular genetic studies was performed. Genomic DNA was extracted from peripheral blood using the standardized phenol/chloroform extraction method, and the coding region of the *PEX10* gene was sequenced in three family members.

Results: Cerebral MRI showed cerebellar atrophy. Magnetic resonance spectroscopy revealed a decreased N-acetyl aspartate peak in the cerebellum. Nerve conduction velocity examination found prolonged motor and sensory nerve potential latencies (proximal obvious), decreased potential amplitude, and slow nerve conduction velocity. Routine blood tests and biochemistries were abnormal. The *PEX10* gene test showed compound heterozygous mutations (c.209 G > A, p. G70E and c.830 T > C, p. L277 P). The mutation c.830 T > C, p. L277 P has been previously reported, whereas c.209 G > A, p. G70E is novel.

Conclusion: We identified an ataxia case of peroxisome biogenesis disorder 6B caused by novel compound heterozygous mutations of the *PEX10* gene. Peroxisome biogenesis disorders should be considered in the differential diagnosis of autosomal recessive ataxia, especially cases with early onset.

1. Introduction

Human peroxisome biogenesis disorders (PBDs) refer to a huge, genetically heterogeneous group of autosomal recessive disorders with clinical significance. They can be divided into the following two distinct subtypes based on clinical manifestations: the Zellweger syndrome spectrum (ZSS) disorders and rhizomelic chondrodysplasia punctata (RCDP) type 1 [1]. The former consists of three overlapping clinical phenotypes: Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD), in order of decreasing severity [1–3]. Patients with ZSS show neurodevelopmental features of psychomotor retardation, facial dysmorphisms, and multisystem involvement (retina, liver and kidney) [2,4]; death occurs in infancy or early childhood. Atypical phenotypes, both more severe and milder, have been described [5]. With elevated biological blood metabolites, such as very long chain fatty acids (C26:0/C22:0 and C24:0/C22:0 ratios) and increased phytanic, pristanic, and pipecolic acid levels, bile acid supplements or dietary restriction of phytanic acid may play a therapeutic role to a certain extent [6].

There are 16 *PEX* genes that encode proteins called peroxins, which are associated with peroxisome biogenesis and/or protein import. Defects in 14 of these genes have now been shown to cause PBDs (including *PEX1, 2, 3, 5, 6, 10, 11β, 12, 13, 14, 16, 19, 26* and *7*); the exceptions are *PEX11α* and *PEX11*γ [5]. Among them, peroxisome biogenesis factor 10, which is coded by the *PEX10* gene and located at the peroxisomal membrane, is involved in importing the peroxisome matrix protein [7]. *PEX10* mutations are included under ZSS disorders, and several have been previously reported. Here, we describe a 7-year-old Chinese boy with the ataxic form of PBD with compound heterozygous mutations (c.209 G > A, p.G70E and c.830 T > C, p.L277 P) in *PEX10* and review *PEX10*–related peroxisomal disorders.

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https://doi.org/10.1016/j.clineuro.2019.01.004
Received 30 May 2018; Received in revised form 3 January 2019; Accepted 5 January 2019
Available online 07 January 2019
0303-8467/

2. Patients and methods

2.1. Patient

The proband is a 7-year-old boy with an early onset ataxia with intentional tremor and mild mental retardation. After an informed consent, the patient was extensively clinical and laboratory evaluation.

2.2. Genetic analysis

Blood samples were collected from the patient and his parents after obtaining informed consent. Unaffected individuals (n = 200) of matched geographic ancestry were included as healthy controls. The protocols were all approved by the Ruijin Hospital Ethics Committee, Shanghai Jiao Tong University School of Medicine. Genomic DNA was extracted from peripheral blood using the standardized phenol/chloroform extraction method, whole exome sequencing was performed, and Sanger sequence of the *PEX10* gene was confirmed in three family members.

3. Results

3.1. Clinical features

The proband is a 7-year-old boy from a family with no consanguineous relationships. Neither parent is clinically affected. The boy was a G1P1 product of a full term, spontaneous vaginal delivery with no neonatal problems. Motor development was normal immediately after birth, and he could walk alone at 14 months of age. However, at that time, his parents noted greater walking instability and balance problems compared with same-age peers. By 3 years, the proband's walking instability had progressed, and he could not jump and often fell when walking unsupported, with an average frequency of 4–5 times per day. He could not walk independently. At the same time, the boy began to lose motor control of both hands. He also had evidence of mild mental retardation, but showed normal understanding of colors, size and numbers.

Physical examination revealed binocular horizontal nystagmus, knee flexion, bipedal eversion, ataxic gait with the right side postural and intention tremor. Limb muscle strength was normal, but muscle tension was slightly decreased with hyporeflexia. Bilateral Babinski signs were not elicited. He did poorly on finger-to-nose and heel-knee-tibia tests. Patient showed significant balance dysfunction when opening and closing eyes, indicating that the patient had cerebellar ataxia without posterior column dysfunction. On International Cooperative Ataxia Rating Scale (ICARS) assessment, the patient scored a total of 52 points, consistent with severe ataxia; the posture and gait static score was 26 points, the gesture and gait dynamic score was 21 points, the verbal disorder score was 2 points and the oculomotor disorder score was 3 points.

It is a pity that we didn't perform peroxisomal functional studies including very long chain fatty acid levels. Electromyography showed roughly normal findings in bilateral tibialis anterior and interosseous muscles. Nerve conduction velocity examination of the bilateral median nerve, tibial nerve and common peroneal nerve revealed prolonged motor and sensory nerve action potential latency (proximal obvious), decreased potential amplitude, and slowed nerve conduction velocity. Bilateral ulnar motor nerve testing was normal, but latency of sensory nerve action potentials was prolonged (proximal obvious), potential amplitude was decreased, and nerve conduction velocity was slowed. Cerebral MRI showed cerebellar atrophy with widened sulci (Fig. 1A). Magnetic resonance spectroscopy (MRS) showed a decreased N-acetyl aspartate peak (arrow) in the cerebellum, but was normal in other brain areas (Fig. 1B and C). Laboratory tests revealed increased creatine kinase (360 U/L; reference range: 24–195 U/L) and decreased hemoglobin (108 g/L; reference range: 120–160 g/L), mean corpuscular volume (76.4 fL; reference range: 83.9–99.1 fL) and mean corpuscular hemoglobin (26.0 pg; reference range: 27.8–33.8 pg). Urinalysis showed 2+ ketone bodies, 1+ bilirubin and 1+ occult blood test.

3.2. Genetic analysis

Whole exome sequencing revealed compound heterozygous mutations in *PEX10* (NM_002617) exon 3 c.209 G > A (p. G70E) and exon 5 c.830 T > C (p. L277 P). Direct polymerase chain reaction and Sanger sequencing of *PEX10* exon 3 and exon 5 revealed a heterozygous carrier state for c.209 G > A in the father and heterozygous carrier state for c.830 T > C in the mother (Fig. 1D and 1E; primer information is found in Table 1). c.830 T > C is included in the Human Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/index.php as ID, CM090797) [8]. c.209 G > A is a novel mutation, not previously reported, and was not found in the Exome Aggregation Consortium (ExAC), 1000 Genome Project or in the 200 healthy controls. However, another substitution of the same amino acid (c.208 G > C, p. G70R) was reported by Ebberink et al. in 2011 [8,9]. The pathogenicity prediction of the two mutations was disease-causing for both by Mutation Taster. In addition, in PolyPhen2, both mutations were predicted to be possibly damaging (probability score 1.000, sensitivity: 0, specificity: 1.000 for both). Pathogenicity assessment according to the American College of Medical Genetics and Genomics (ACMG) revealed that c.209 G > A is likely pathogenic and c.830 T > C is pathogenic [10].

4. Discussion

Human PBDs in the Zellweger syndrome spectrum (PBDs-ZSS) are a heterogeneous group of genetic disorders resulting from mutations in the *PEX* genes, which encode peroxin proteins involved in normal peroxisome assembly and functions [1,3]. The main features of these diseases are neuronal, hepatic and renal multisystem involvement, and includes severe mental retardation. In the most severe cases, children die within the first year of life [5]. *PEX10* gene mutations account for about 3.4% of all PBD patients [11]. Through genetic testing and assessing the pathogenicity and co-segregation of pedigrees, we identified a Chinese 7 year-old boy with ataxic form of autosomal recessive PBD 6B (phenotype MIM number, 614871), which caused by compound heterozygous mutations of the *PEX10* gene. The heterozygous mutations include a known mutation and a novel. PBDs caused by pathogenic mutations of the *PEX10* gene can be divided into two subtypes based on clinical phenotype, PBD 6 A (phenotype MIM number, 614870) and PBD 6B. PBD 6 A (also known as Zellweger's syndrome) is an autosomal recessive syndrome of multiple congenital anomalies. Affected children present with profound dystonia, seizures, and inability to feed during the newborn period. There are characteristic craniofacial abnormalities, abnormal eyes, neuronal migration defects, hepatomegaly and achondroplasia. This phenotype is so severe that children usually do not survive for more than one year [12]. Clinical symptoms of PBD 6B are milder than those of 6 A [11,13]. Patients are usually affected by childhood or early adolescence. The main clinical features are slowly progressive cerebellar ataxia and lower limb hypo or areflexia. Partial patients also companied with mental retardation, tremors, dysarthria, and sensorimotor axonal neuropathy. Decreased N-acetyl aspartate peak in the cerebellum on MRS, include the present case, suggesting neuronal loss [8,14,15]. Currently, medical management of any manifestations of PBD-ZSD focuses largely on symptomatic or supportive therapies [3]. Bile acid supplements or dietary interventions have been reported some extent effective [3,6].

The *PEX10* gene encodes the peroxisomal membrane protein; it has 6 exons (coding 326 amino acids), two putative transmembrane domains and a RING finger domain (Fig. 2) which helps form the PEX2–PEX10–PEX12 ubiquitin ligase complex. This complex is involved in releasing the transport receptor and importing the matrix protein [11,13]. By using the alternative splice acceptor site at the 3′

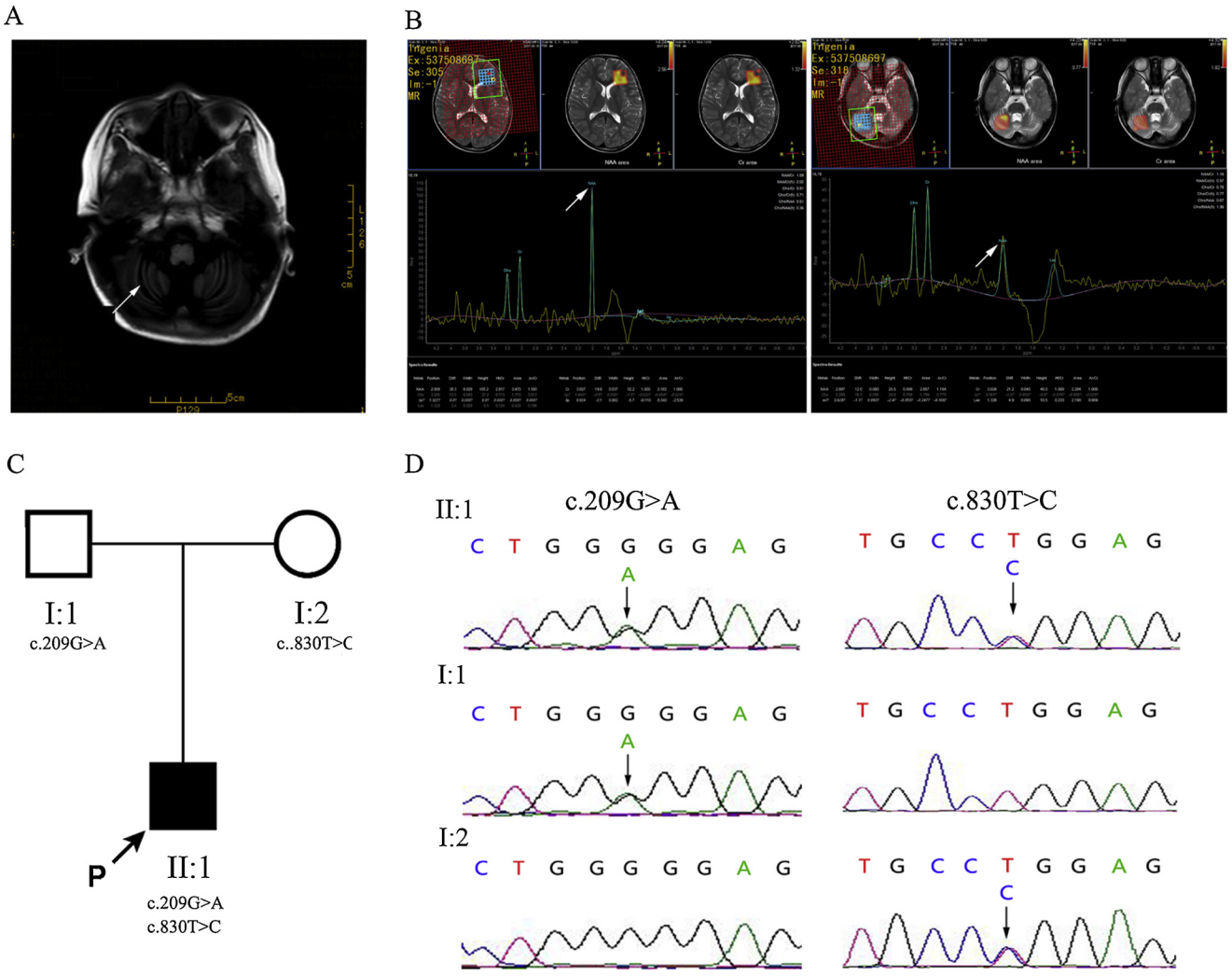

Fig. 1. Cerebral MRI showed cerebellar atrophy and widened sulci (Fig. 1A). MRS showed a decreased N-acetyl aspartate peak (arrow) in the cerebellum, but was normal in other areas (Fig. 1B and C). Whole exome sequencing revealed two compound heterozygous mutations in *PEX10* (NM_002617) exon 3 c.209 G > A (p.G70E) and exon 5 c.830 T > C (p.L277 P). Direct polymerase chain reaction sequencing of *PEX10* gene exon 3 and exon 5 revealed that the father is a heterozygous carrier for the mutation c.209 G > A (p.G70E) and the mother is heterozygous for c.890 T > C (p.L297 P); arrows show mutated nucleotides (Fig. 1D and 1E).

Table 1
PEX10 gene primer information.

Primer	Sequence (5' > 3')	Tm (°C)	Amplicon (bp)
PEX10-3F	GACAAGATGGGGCTGTTGAC	60	675bp
PEX10-3R	AAGCAGAGGATTTGGGTTCC		
PEX10-5F	GCAGCTGTACGGTTTCAGG	60	422bp
PEX10-5R	CTCAAAACTGGAGGGTGCTC		

end of intron 3, two different lengths of PEX10 mRNA transcripts (NM_002617 and NM_153818) are generated; the longer one (NM_153818) accounts for 10% of the intracellular PEX10 mRNA and seems to be slightly less functional [7–9]. To date, about 31 various mutations have been reported in *PEX10*, the mutations are distributed in all the exons, and RING finger domain seems to be more affected [8,9,13–19] (Fig. 2). Among them, there are 10 homozygous mutations and 23 heterozygous mutations (both types were reported in c.814_815del and c.704_705insA). Mutation types include missense,

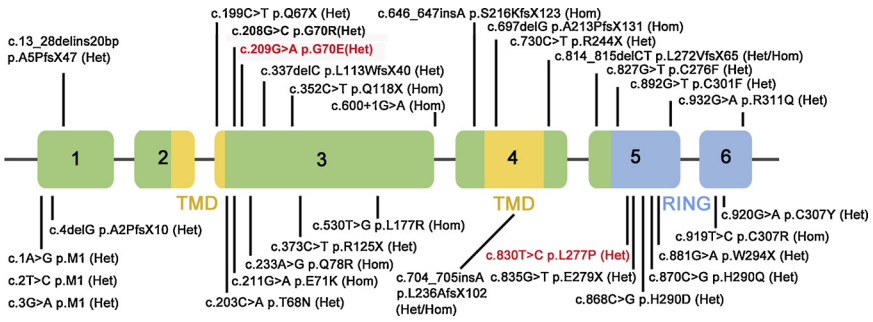

Fig. 2. PEX10 is a peroxisomal membrane protein with 6 exons coding 326 amino acids and 2 putative transmembrane domains and a RING finger domain. To date, about 31 various mutations have been reported in *PEX10*, which include missense, nonsense, deletion, insertion, splice-site and disruptions of the start codon mutations.

Table 2
Reference ataxia genes list.

ABCB7	ABHD12	ADCK3	AFG3L2	AHI1	AMPD2
ANGPTL3	ANO10	APOB	APTX	ARG1	ARL13B
ASL	ASS1	ATCAY	ATM	ATN1	ATP1A3
ATP2B3	ATP7B	ATP8A2	ATXN1	ATXN10	ATXN2
ATXN3	ATXN7	B9D1	BCKDHA	BCKDHB	BEAN1
BTD	C10orf2	C5orf42	CA8	CABC1	CACNA1A
CACNA1G	CACNB4	CAMTA1	CASK	CC2D2A	CCDC88C
CEP104	CEP290	CEP41	CHMP1A	CLCN2	CLP1
COL18A1	COQ2	CPS1	CSPP1	CSTB	CUL4B
CWF19L1	CYP27A1	DAGLA	DARS2	DBT	DLD
DNAJC19	DNMT1	EEF2	EIF2B1	EIF2B2	EIF2B3
EIF2B4	EIF2B5	ELOVL4	ELOVL5	ERCC6	ERCC8
EXOSC3	EXOSC8	FGF14	FLVCR1	FMR1	FXN
GCLC	GFAP	GOSR2	GRID2	GRM1	HEXA
HLCS	IFRD1	INPP5E	ITM2B	ITPR1	JPH3
KATNIP	KCNA1	KCNC3	KCND3	KCNJ10	KCTD7
KIAA0586	KIF1C	KIF7	L2HGDH	MARS2	MCCC1
MECP2	MKS1	MME	MRE11A	MTPAP	MTTP
NAGS	NOL3	NOP56	NPC1	NPC2	NPHP1
OFD1	OPA1	OPHN1	OR5J2	OTC	PAX6
PC	PCCA	PCCB	PCLO	PDE6D	PDYN
PEX1	PEX10	PEX2	PEX26	PEX3	PEX5
PEX7	PHYH	PIK3R5	PLA2G6	PLEKHG4	PMPCA
PNKP	POLG	POLR3A	PPP2R2B	PRICKLE1	PRKCG
PRPS1	PTEN	PTF1A	RARS2	RELN	RNF170
RNF216	RPGRIP1L	RUBCN	SACS	SCARB2	SCN1A
SCYL1	SEPSECS	SETX	SIL1	SLC17A5	SLC1A3
SLC25A1	SLC25A15	SLC2A1	SLC6A19	SLC9A1	SLC9A6
SMPD1	SNX14	SPTBN2	SSRP1	STUB1	SYNE1
SYT14	TBP	TCTN1	TCTN2	TCTN3	TDP1
TDP2	TECT1	TGM6	TK2	TMEM138	TMEM216
TMEM231	TMEM237	TMEM240	TMEM67	TP1A3	TPP1
TRPC3	TSEN2	TSEN34	TSEN54	TTBK2	TTC21B
TTPA	TUBB4A	UBA5	VAMP1	VHL	VLDLR
VPS13A	VRK1	VWA3B	WDR81	WWOX	XK
ZIC1	ZIC4	ZNF423	ZNF592		

nonsense, deletion, insertion and splice-site mutations as well as disruption of the start codon, most of which result in removing large portions of the *PEX10* coding region, suggesting that a loss-of-function mechanism may be involved [7]. A genotype-phenotype correlation study for *PEX10* deficiency showed that nonsense and frameshift mutations seem to be associated with severe clinical and cellular phenotypes, and missense mutations with milder phenotypes [7,8]. The fact that missense mutations were identified in the patient with milder form of PBD is consistent with the description (Tables 2 and 3).

Similar *PEX10*-related cases presented with early onset progressive cerebellar ataxia, abnormal biological data, obvious cerebellar atrophy, with or without axonal motor neuropathy have been described [8,14,15]. One Japanese family with three affected siblings not only had ataxia and mild mental retardation, but also experienced mydriasis, hyperreflexia and involuntary head movements [17], suggesting that multiple parts of the nervous system might be involved. Cultured fibroblasts from the patients compared with controls showed abnormal catalase distribution in a mosaic pattern, which could be restored by co-transfection or overexpression of wild type *PEX10* cDNA, suggesting a partial loss-of-function mechanism [15,17]. All these cases and ours share an early onset (5–15 years) and with compound heterozygous mutations of *PEX10*, one of the mutations was located in the highly conserved RING finger domain, as was the present case (c.830 T > C p. L277 P), suggesting a critical role for the RING finger domain in PEX10 function. In addition, homozygous mutations destroying the RING finger domain have been reported to cause a more severe phenotype of the Zellweger spectrum; of these, c.814_815delCT is the most common mutation in the Japanese population [20]. However, the mechanism by which the mutations affect RING finger domain function remains unknown. Another mutation in our proband, c.209 G > A, p. G70E, is close to the first transmembrane domain and may have an impact on import of the matrix protein.

Table 3
Nerve Conduction Studies.

	Latency (ms) Left/Right	Amplitude (mv) Left/Right	NCV (m/s) Left/Right
Ulnar nerve (motor)			
Wrist-ADM	2.33/2.26	10.4/10.8	–
(Normal value: $\bar{x}\bar{x}$, limit)	(2.4, 2.9)	(19.0, 8.0)	–
Elbow –Wrist	4.38/4.32	9.7/10.2	58.5/58.3
(Normal value: $\bar{x}\bar{x}$, limit)	–	(17.0, 8.0)	(65.0, 58.0)
Ulnar nerve (sensory)			
	Latency (ms) Left/Right	Amplitude (uv) Left/Right	NCV (m/s) Left/Right
Finger V-Wrist	2.16/2.13	8.0/8.1	49.3/49.6
(Normal value: $\bar{x}\bar{x}$, limit)	–	(19.6, 7.20)	(59.3, 47.4)
Median nerve (motor)			
	Latency (ms) Left/Right	Amplitude (mv) Left/Right	NCV (m/s) Left/Right
Wrist-APB	2.51/2.54	9.8/9.7	–
(Normal value: $\bar{x}\bar{x}$, limit)	(3.0, 3.70)	(22.0, 9.0)	–
Elbow –Wrist	5.42/5.48	9.3/9.4	44.7/44.2
(Normal value: $\bar{x}\bar{x}$, limit)	–	(18.0, 8.0)	(65.0, 56.0)
Median nerve (sensory)			
	Latency (ms) Left/Right	Amplitude (uv) Left/Right	NCV (m/s) Left/Right
Finger II-Wrist	2.23/2.24	5.9/4.8	49.4/49.4
(Normal value: $\bar{x}\bar{x}$, limit)	–	(34.0, 11.3)	(61.9, 49.5)
Tibial nerve (motor)			
	Latency (ms) Left/Right	Amplitude (mv) Left/Right	NCV (m/s) Left/Right
Ankle-AH	3.88/3.79	1.84/3.6	–
(Normal value: $\bar{x}\bar{x}$, limit)	(4.8, 6.0)	(13.0, 4.0)	–
Knee – Ankle	9.83/9.78	1.54/1.44	35.3/35.1
(Normal value: $\bar{x}\bar{x}$, limit)	–	(5.8, 3.9)	(48.5, 44.9)
Tibial nerve (sensory)			
	Latency (ms) Left/Right	Amplitude (uv) Left/Right	NCV (m/s) Left/Right
Toe I-Ankle	4.06/4.04	2.0/2.1	39.8/39.8
(Normal value: $\bar{x}\bar{x}$, limit)	–	(4.0, 0.9)	(43.9, 35.1)
Common peroneal nerve (motor)			
	Latency (ms) Left/Right	Amplitude (mv) Left/Right	NCV (m/s) Left/Right
Ankle-EDB	2.92/2.93	1.09/2.3	–
(Normal value: $\bar{x}\bar{x}$, limit)	(4.1, 5.0)	(10.0, 3.0)	–
Knee – Ankle	7.46/7.45	0.89/1.68	39.6/39.8
(Normal value: $\bar{x}\bar{x}$, limit)	–	(8.0, 3.0)	(51.0, 45.0)
Common peroneal nerve(sensory)			
	Latency (ms) Left/Right	Amplitude (uv) Left/Right	NCV (m/s) Left/Right
Stim 1-Rec 1	5.05/4.70	4.3/4.2	45.6/48.2
(Normal value: $\bar{x}\bar{x}$, limit)	–	(4.5, 0.9)	(60.9, 48.7)

$\bar{x}\bar{x}$:mean, limit : upper or lower limit.

Above all the discussed characteristics: unexplained early-onset ataxic form, companioned with or without other central or peripheral neuropathy or other systems involvement, prompting us to consider the possibility of PBD and the differential diagnosis with early-onset autosomal recessive ataxia. If we attach more importance to the early atypical symptom with more advanced molecular genetics technology (for instance, whole exome sequencing), which not only improve our early diagnosis, but also early intervention, and enhance the quality of life for these patients.

5. Conclusion

Our study suggests that mild phenotype PBD-ZSS-related mutations should be considered in patients with early-onset, slowly progressive autosomal recessive ataxia, with or without multiple affected systems, because early diagnosis of this partially treatable disease may improve symptoms. By studying this pedigree, we have expanded the phenotype and genotype spectrum of PBD.

Conflicts of interest statement

The authors declare that they have no conflict of interests.

Acknowledgements

This project is supported by National Natural Science Foundation of China (81571086); Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant Support (20161401); Interdisciplinary Project of Shanghai Jiao Tong University (YG2016MS64). The authors want to thank patients and their family members for their generous participation in this study.

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