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ScienceDirect

Neuromuscular Disorders 25 (2015) 161–164

www.elsevier.com/locate/nmd

Case report

Clinical and electrophysiological features in a French family presenting with seipinopathy

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Received 7 August 2014; accepted 16 October 2014

Abstract

Seipinopathies are a group of inherited diseases affecting upper and lower motor neurons due to mutations in the *Berardinelli–Seip congenital lipodystrophy 2* gene (*BSCL2)*. We report a French family carrying the N88S mutation in the *BSCL2* gene. A 12-yr-old girl complained of bilateral asymmetrical *pes cavus* with right hand motor deficit and amyotrophy, asymmetrical leg amyotrophy and pyramidal signs. Electrophysiological examination showed axonal asymmetrical motor neuropathy with distal predominance. Her father complained of right hand rest tremor with bilateral hand weakness. Physical examination revealed left leg, hand and forearm amyotrophy, akinesia and right arm rigidity, brisk reflexes in the lower limbs and bilateral Babinski sign. Nerve conduction studies showed distal asymmetrical axonal neuropathy with slight sensitive impairment with moderate decrease of nerve conduction velocity in some nerves. DNA sequencing revealed the presence of the known N88S mutation in the *BSCL2* gene (dideoxy-nucleotide method on a 3730 DNA Analyzer, Life Technologies). *BSCL2* gene mutations are associated with a wide spectrum of clinical and electrophysiological phenotypes and should be suspected in cases of distal hereditary motor neuropathy with pyramidal signs or early hand involvement. There may also be associated mild demyelination which may vary in severity within the same family. Clinical diagnosis was more difficult in this particular case due to the association with Parkinson symptoms.

Keywords: Distal hereditary motor neuropathy; Seipinopathy; *BSCL2* gene; Parkinson disease

1. Introduction

BSCL2 is a gene encoding a protein named Seipin, first identified in 2001 as a candidate gene for the Berardinelli–Seip syndrome or Congenital Generalized Lipodystrophy type 2 (CGL2) [1], a rare autosomal recessive disease with lipoatrophy, insulin resistance, hypertriglyceridemia and mental retardation. Seipinopathies are a group of rare inherited autosomal dominant diseases, recently described, affecting upper and lower motor neurons, due to two different mutations in the *BSCL2* gene [2]. Both mutations are associated with a wide phenotype spectrum including Silver syndrome, complicated form of hereditary spastic paraplegia (SPG17) and distal hereditary motor neuropathy type V (dHMN-V) [3]. In 2009, Ito et al. [4] proposed using the generic term of "seipinopathy" to describe these different diseases. About 25 families have now been described in the literature. We report here a French family carrying the N88S mutation in the *BSCL2* gene, initial diagnosis being difficult due to extrapyramidal symptoms in the father.

2. Methods

Two patients were included in the study: a 46-year-old man and his 17-year-old daughter (familial pedigree presented in Fig. 1). They underwent clinical examination, electrophysiological testing using standard techniques (nerve conduction velocities, needle EMG and somato-sensory and motor evoked potentials, Nicolet Viking, Madison, WI, USA). The coding sequence of *BSCL2* was sequenced by the dideoxy-nucleotide method on a 3730 DNA Analyzer (Life Technologies).

3. Case reports

Both patients have given their informed consent for publication.

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http://dx.doi.org/10.1016/j.nmd.2014.10.006
0960-8966/

Patient 1 was a 46-year-old patient complaining of rest tremor in the right hand associated with hand weakness. At the same time he had noticed some wasting of the interosseous muscles of the left hand. His medical history revealed trauma to the right peroneal tendon at the age of 6 years, surgically treated twice, at the ages of 17 and 30 (right ankle arthrodesis). From the time of the second surgery, he had presented a complete palsy of the flexion and extension of the foot with right leg amyotrophy. Interestingly, physical exam also revealed lower left leg involvement with distal amyotrophy and ankle dorsiflexion defect (Fig. 1). In the upper limbs muscle wasting was observed in the left first dorsal interosseous and thenar muscles, both forearm muscles together with motor weakness. It was associated with akinesia and rigidity of the right arm. Gait examination showed a loss of arm swing and the patient was amimic. Tendon reflexes were unusually brisk in the lower limbs, normal in the upper limbs and bilateral Babinski sign was found. No cranial nerve involvement, sensory or cognitive impairment or fasciculation were observed. General examination was normal.

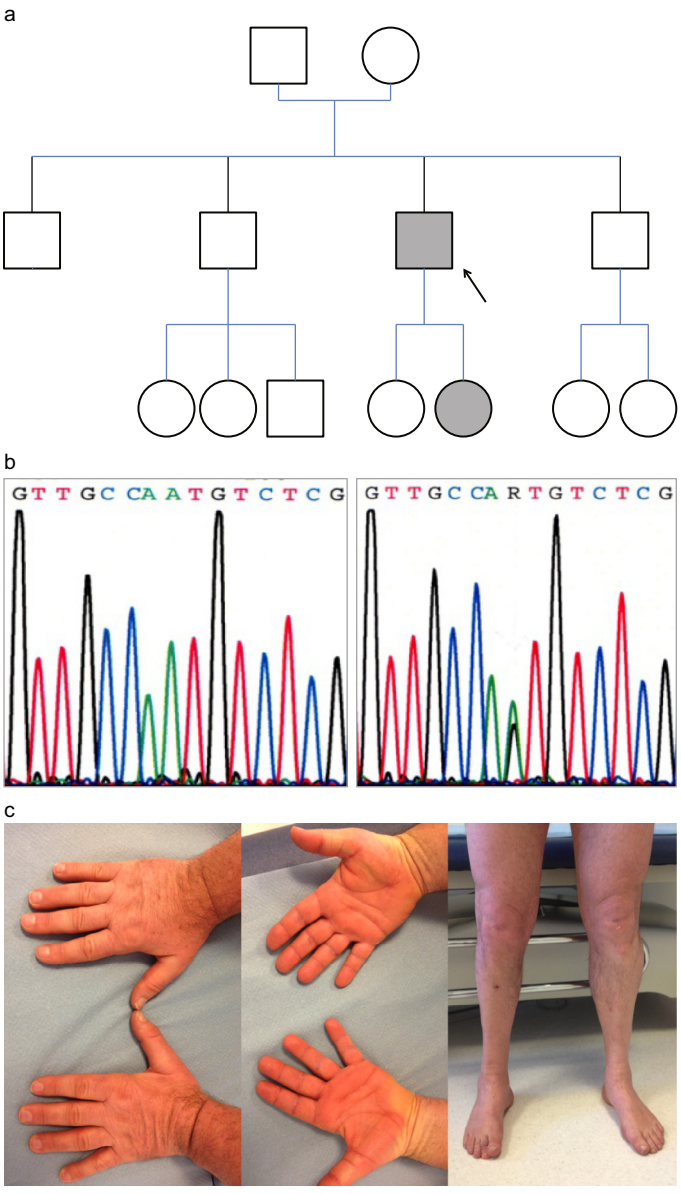

Fig. 1. (a) Familial pedigree. (b) Sequences for the codons 86–90 of *BSCL2* (nucleotides 256–270). Nucleotide numbering is according to the cDNA RefSeq number NM_032667. Left: Control sequence. Right: Sequence for the proband showing the mutation p.Asn88Ser (c.263A > G). (c) Asymmetrical amyotrophia of the left hand with interosseous and thenar muscle wasting. Asymmetrical amyotrophia of the legs.

The electrophysiological study showed heterogeneous axonal loss on several nerve trunks, with distal predominance. There was a marked reduction of nerve conduction velocity in some nerves suggesting a possible additional demyelination process. Severe signs of motor chronic denervation affecting distal muscles of the lower and upper limbs were observed. Sensitive impairment remained slight (Table 1).

At that time, Parkinson disease (PD) was considered as likely, possibly associated with amyotrophic lateral sclerosis (ALS). There was no past familial history of PD or ALS, and no additional specific investigation was performed in this area.

Patient 2 was the daughter of patient 1. She was actually seen 5 years earlier by paediatricians, independently of her father. At that time, aged 12, she complained of gait fatigability and bilateral asymmetrical pes cavus. During her childhood she had had several bilateral ankle sprains. She had no history of hypotonia or delay in walking. Her cognitive development was normal. Physical examination revealed a motor deficit of the extension of the first two digits of the right hand, with amyotrophy affecting the thenar and the interosseus muscles. She also had asymmetrical leg amyotrophy (right > left). Tetrapyramidal syndrome with brisk reflexes of the four limbs and bilateral Babinski sign were also observed. No cranial nerve involvement, sensory impairment or fasciculation was observed. General examination was normal.

The first electrophysiological examination was curtailed due to the patient's unwillingness. It showed an axonal asymmetrical motor neuropathy, affecting the upper and the lower limbs, with a distal predominance. Sensory potentials were normal (Table 1). Motor evoked potentials confirmed the bilateral upper neuron impairment. Somatosensory evoked potentials, cerebrospinal fluid analysis, cerebral and spinal cord MRI were normal, as well as ophthalmological and abdominal ultrasound examination. Blood and urine chromatography of amino acids were normal, as well as the glycosaminidase dosage. The search for a mutation in SCA3, frataxine and SMN1 genes was negative.

Five years later, at the age of 17, she could be examined together with her father. Her clinical and EDX examination remained stable as compared with initial examinations. Familial pedigree was completed: brother and father of patient 2 supposedly had gait impairment but this could not be seen. New genetic testing was considered in the field of dHMN. Sequence analysis of exon 3 in *BSCL2* gene was performed, and the known heterozygous mutation c.263A > G (p.Asn88Ser; N88S) was found in the proband and her father. The mutation was not found in the mother. Final diagnosis was seipinopathy in both patients, the father presenting in addition with PD.