



Case report

SIL1-related Marinesco–Sjoegren syndrome (MSS) with associated motor neuronopathy and bradykinetic movement disorder

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Abstract

Marinesco–Sjoegren syndrome (MSS) is a recessively inherited multisystem disorder caused by mutations in *SIL1* and characterized by cerebellar atrophy with ataxia, cataracts, a skeletal muscle myopathy, and variable degrees of developmental delay. Pathogenic mechanisms implicated to date include mitochondrial, nuclear envelope and lysosomal–autophagic pathway abnormalities. Here we present a 5-year-old girl with *SIL1*-related MSS and additional unusual features of an associated motor neuronopathy and a bradykinetic movement disorder preceding the onset of ataxia. These findings suggest that an associated motor neuronopathy may be part of the phenotypical spectrum of *SIL1*-related MSS and should be actively investigated in genetically confirmed cases. The additional observation of a bradykinetic movement disorder suggests an intriguing continuum between neurodevelopmental and neurodegenerative multisystem disorders intricately linked in the same cellular pathways. © 2015 Elsevier B.V. All rights reserved.

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1. Introduction

Marinesco–Sjoegren syndrome (MSS) is a recessively inherited multisystem disorder caused by mutations in *SIL1* [1,2], encoding a nuclear exchange factor for the endoplasmic reticulum resident chaperone BiP. Precise pathogenic mechanisms are currently unknown but are likely to involve protein misfolding, activation of the UPS system and the lysosomal–autophagic pathway, as well as mitochondrial, and nuclear envelope abnormalities [3,4]. MSS is characterized by cerebellar atrophy with ataxia, cataracts, skeletal muscle myopathy and variable degrees of developmental delay. Here we present a case of *SIL1*-related MSS, with an associated motor neuronopathy and a bradykinetic movement disorder preceding the onset of ataxia.

2. Case report

This 5-year-old girl presented at the age of 6 months with global developmental delay, hypotonia, and weakness. She was the first child of a distantly related Chinese couple. She was born at 39 weeks in good condition, and weighed 2.97 kg (9–25th centile). Her gross motor milestones were delayed; at six months of age she had poor head control, and could not roll over. She sat unaided at 15 months, profound bradykinesia was noted at the age of two years, and she took steps with the support of a frame at three years. At four years she could walk short distances with the support of a Kaye-walker, however she remained very bradykinetic. Fine motor skills were also impaired. Speech development was delayed, however less significantly than gross and fine motor skills; at two years of age she had 20 words, continued to make significant progress and at the age of five years was bilingual. There were no concerns about her hearing. Concerns about her vision were raised at three years of age when she was found to have bilateral cataracts, which required surgical removal. She currently attends mainstream school with support.

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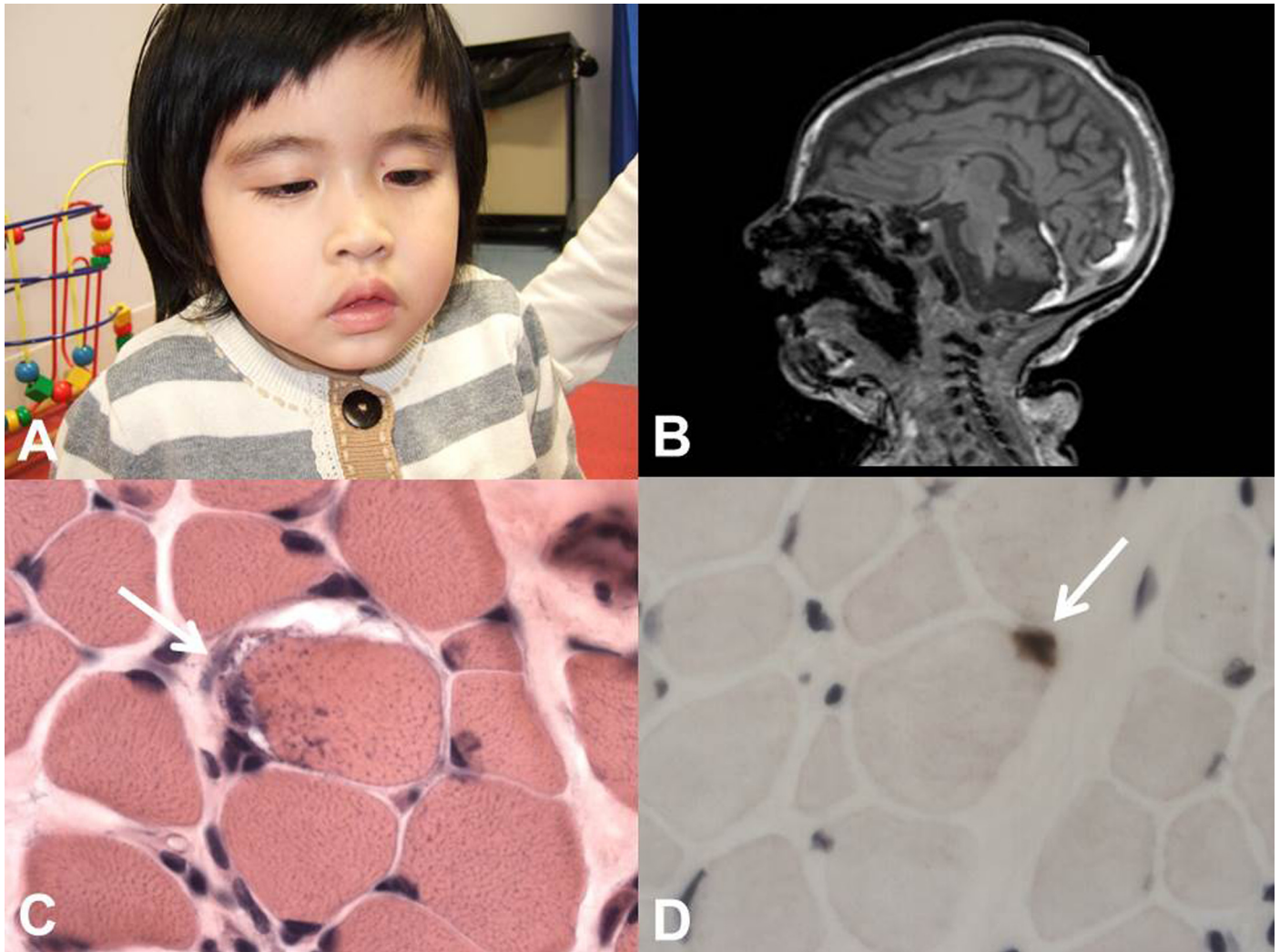


Fig. 1. A) Patient with *SIL1*-related MSS at 3 years of age. B) MRI of the brain, T1-weighted images, sagittal sections, showing marked cerebellar atrophy. C) Muscle biopsy from the quadriceps, transverse sections, H&E stain, showing a basophilic-rimmed subsarcolemmal vacuole (arrow) and D) staining positively with antibody to the ubiquitin-binding protein p62 (arrow).

On examination at 4 years of age (Fig. 1A, Video S1) height, weight and head circumference were all below the 0.4th centile. She was not dysmorphic and had a full range of eye movements. The most striking features were profound facial hypomimia, and marked generalized paucity of movement. There was also a degree of weakness, and mainly truncal ataxia, although this was not as prominent. There was no tremor. Reflexes were absent, and plantars were downgoing. On further examination at 4 years 6 months of age (Video S2), her ataxia had evolved but hypomimia and difficulties initiating and executing movements remained the most prominent neurological feature.

Laboratory investigations included mildly elevated CK levels ranging from 283 to 431 IU/l. Endocrine tests performed for her short stature and poor growth revealed growth hormone deficiency and low insulin-like growth factor levels, prompting initiation of growth hormone therapy. MRI of the brain revealed cerebellar atrophy (Fig. 1B). CSF neurotransmitter studies were normal.

Nerve conduction studies showed normal sensory and motor responses with appropriate velocities for age. Motor unit

duration estimation of the EMG showed an excess of long duration units in the tongue and, to a slightly lesser degree, tibialis anterior. This combination of findings was interpreted as indicating the presence of a motor neuronopathy with the cranial nuclei affected more than spinal neurones. Muscle biopsy featured an increase in endomysial connective tissue, abnormal variability in fibre size and occasional fibres with basophilic-rimmed vacuoles in the subsarcolemmal region, which appeared positive for p62 on immunohistochemical stains (Fig. 1C,D). Electron microscopy showed some small collections of membranous debris and mild myonuclear lobulation but no well-formed vacuoles (not shown).

Whole exome sequencing (WES) of the patient was performed within the NeuroGenics project (REC reference 13/EE/0398). The data analysis, using Clinical Sequence Miner tool (deCODE Genetics), revealed a homozygous frameshift mutation in *SIL1*, c.512_513delTT (p.Phe171Ter). The mutation was not present in Exome Variant Server (<http://evs.gs.washington.edu/EVS/>) or ExAC (<http://exac.broadinstitute.org/>) databases. Subsequent Sanger sequencing verified the *SIL1* mutation previously identified

on WES. With a view to the unusual clinical findings in our patient, we interrogated WES data for variants in genes known to be associated with inherited neuropathies and early-onset dyskinesia and Parkinsonism, and did not find any additional pathogenic variants. We only identified a not previously reported heterozygous missense variant in the neuralgic amyotrophy associated gene *SEPT9* [5], unlikely to be relevant considering asymptomatic consanguineous parents and a discordant clinical phenotype. Both parents were found to be heterozygous carriers of the homozygous *SIL1* mutation identified in their daughter.

3. Discussion

To date, more than 100 patients with *SIL1*-related Marinesco–Sjogren syndrome (MSS) have been reported in the literature, associated with a consistent phenotype of ataxia, myopathy, and cataracts with onset typically within the first decade of life [3,6]. Here we present a case of *SIL1*-related MSS, with an associated motor neuronopathy and a bradykinetic movement disorder preceding the onset of ataxia. This case expands the current spectrum of *SIL1*-related MSS and suggests a continuum with other early-onset multisystem disorders with overlapping clinico-pathological features and putatively linked in the same cellular pathways.

An associated motor neuronopathy to our knowledge has not been previously reported in *SIL1*-related MSS and is indeed considered an exclusion criterion by some authors [7]. Neuronal involvement manifesting as an associated (demyelinating, sensory) neuropathy is however a consistent feature in clinically closely related conditions, for example CCFDN (C ongenital C ataracts, F acial D ysmorphism and N europathy) [OMIM 604168] due to an Eastern European founder mutation in *CTDP1* [8], and in patients with genetically unresolved early-onset cerebellar ataxia (EOCA) [9], Friedreich's ataxia and distinct subgroups of the spinocerebellar ataxias (SCAs). In addition, histopathological evidence of segmental demyelination and axonal degeneration has been reported in one genetically unresolved patient with typical clinical features of MSS [10]. Moreover, Filézac de L'Etang and colleagues demonstrated recently that loss of a functional *SIL1* allele results in exacerbation of motor neuron dysfunction and denervation in a mouse model of amyotrophic lateral sclerosis (ALS) [11], providing further supportive evidence for a neuronal phenotype associated with *sil1* deficiency.

Abnormalities of the lysosomal–autophagic pathway, one of the pathological mechanisms also identified in *SIL1*-related MSS [4], have recently emerged as a common denominator of a group of neurodevelopmental, neurodegenerative and neuromuscular disorders with substantial overlap. Other neurodevelopmental disorders within this group include Vici syndrome (VS) [OMIM 242840] due to recessive mutations in *EPG5*, encoding a key autophagy regulator involved in autophagolysosome formation [12], and Chediak–Higashi syndrome (CHS) [OMIM 214500] due to recessive mutations in *LYST* [13], encoding a lysosomal trafficking regulator with a proposed role in autophagosome–lysosome biology. As in our patient with MSS, neuronal involvement has also been found in a subset of patients with CHS [14] and VS (unpublished personal observation). MSS, VS [15] and CHS [16] also share

a skeletal muscle myopathy with prominent vacuoles, the hallmark of myopathies due to primary autophagy defects [17,18], further indicating a communality of muscle and nerve involvement in disorders with abnormalities of the lysosomal–autophagic pathway.

Marked bradykinesia, hypomimia and difficulties initiating movements were the predominant features in our patient before the ataxia typically associated with *SIL1*-related MSS became more prominent. Interestingly, an early-onset bradykinetic movement disorder with prominent Parkinsonian features has also been reported in a subset of patients with CHS [19–22], and features of neurodegeneration evolving over time have been observed in humans with *EPG5*-related Vici syndrome [12] and animal models of *epg5* deficiency [23]. Taken together, these findings suggest an intriguing link between early-onset neurodevelopmental disorders such as VS, CHS and MSS associated with defective autophagy, and the increasing number of adult-onset neurodegenerative disorders including dementia, ALS and Parkinson's disease (PD) due to defects in the molecular machinery involved in autophagic and lysosomal degradation [24]. Such a link is further supported by the recent observation of *sil1* downregulation as a contributory factor to the neuronopathy in *SOD1*/ALS mice, very specifically indicating this protein as a key player in neurodevelopmental and neurodegenerative disorders with peripheral nerve involvement [11].

In conclusion, this case indicates that an associated motor neuronopathy may be part of the spectrum of *SIL1*-related MSS and should be actively investigated in genetically confirmed cases. The additional observation of a bradykinetic movement disorder suggests an intriguing continuum between neurodevelopmental and neurodegenerative multisystem disorders intricately linked in the same cellular pathways. MSS may be considered part of an increasing spectrum of conditions combining neuropathic and Parkinsonian features [25].

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Appendix: Supplementary material

Supplementary data to this article can be found online at [doi:10.1016/j.nmd.2015.04.003](https://doi.org/10.1016/j.nmd.2015.04.003).

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