JNNP Online First, published on November 3, 2012 as 10.1136/jnnp-2012-303634

LETTER

The ARSACS phenotype can include supranuclear gaze palsy and skin lipofuscin deposits

INTRODUCTION

The autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) phenotype was first characterised in patients from Quebec, all of whom had young onset spasticity and gait ataxia. Other features included distal amyotrophy, extensor plantar responses, cerebellar speech, saccadic intrusion in smooth pursuit and hypermyelinated retinal nerve fibres.[1] Seven percent had seizures. Spasticity and ataxia were progressive. Electromyography showed denervation. Nerve conduction studies showed reduced conduction velocities with absent sensory action potentials. Nerve biopsy showed a lack of large myelinated axons.[2] Subsequent analysis of this cohort has shown two founder mutations in the *SACS* gene—c.6594delT and c.5254C>T.[3]

Identification of mutations in *SACS* as the cause of ARSACS facilitated the detection of further cases worldwide, revealing greater phenotypic variation. Vermeer *et al* screened 43 patients presenting with ataxia prior to age 25 (suggesting an autosomal recessive cause[4]), finding 16 patients with *SACS* mutations.[5] One patient had onset aged 12, two showed dystonia. Baets *et al*[6] screened 85 patients with at least two of cerebellar ataxia, spasticity and peripheral neuropathy, finding 18 different mutations. In five of these patients, disease onset was at over 20 years, one patient had no signs of peripheral neuropathy, several patients presented primarily with peripheral neuropathy and only one had hypermyelinated retinal nerve fibres using standard fundoscopy. Two patients had mild cognitive impairment and one epilepsy. Breckpot *et al*[7] detected a deletion of *SACS* combined with a hemizygous *SACS* mutation causing early-onset ARSACS with hearing impairment.

CASE REPORT

We describe a 37-year-old patient who first walked at 23 months. Aged seven, he had cerebellar ataxia and brisk reflexes in all limbs. Cognitive function has been normal but ataxia and spasticity have progressed. He also developed epilepsy, myoclonus and hypothyroidism. Examination reveals cerebellar dysarthria, limb ataxia and horizontal nystagmus and, since his early 20s, vertical (not horizontal) supranuclear gaze palsy. He has spasticity with extensor plantar responses, absent ankle jerks and distal weakness. Vibration and joint position sense are reduced to the ankles. Although careful ophthalmological examination did not reveal clinical evidence of a thickened retinal nerve fibre layer, optical coherence tomography (OCT)[8] demonstrated retinal nerve fibre layer thickness above the 95th percentile. Nerve conduction studies showed slowed motor conduction velocities (ulnar 39 m/s). Compound motor action potentials (CMAPs) were reduced and sensory action potentials absent. EEG showed slowing but no unequivocal signs of myoclonus.

Sural nerve biopsy showed normal density of myelinated fibres for age, although morphometric analysis revealed a much smaller proportion of large myelinated fibres (>7 μm diameter). There were no bands of Bungner, degeneration, regeneration or demyelination.

MRI brain and skin biopsy (considering Lafora body disease) are illustrated (figure 1). Muscle biopsy showed an increase in lipid content was otherwise unremarkable.

Sequencing the coding region and intron/exon boundaries of the *SACS* gene identified three variants; c.5151dupA (p.Ser1718fsX1736), c.6392delT (p.Phe2131fsX2144) and c.5948C>T (p.Ser1983Phe). His unaffected father was heterozygous for the c.5151dupA mutation and his unaffected mother heterozygous for the c.6392delT mutation and c.5948C>T variant, confirming that the patient was compound heterozygous for the two frameshift mutations. These mutations were not detected in over 200

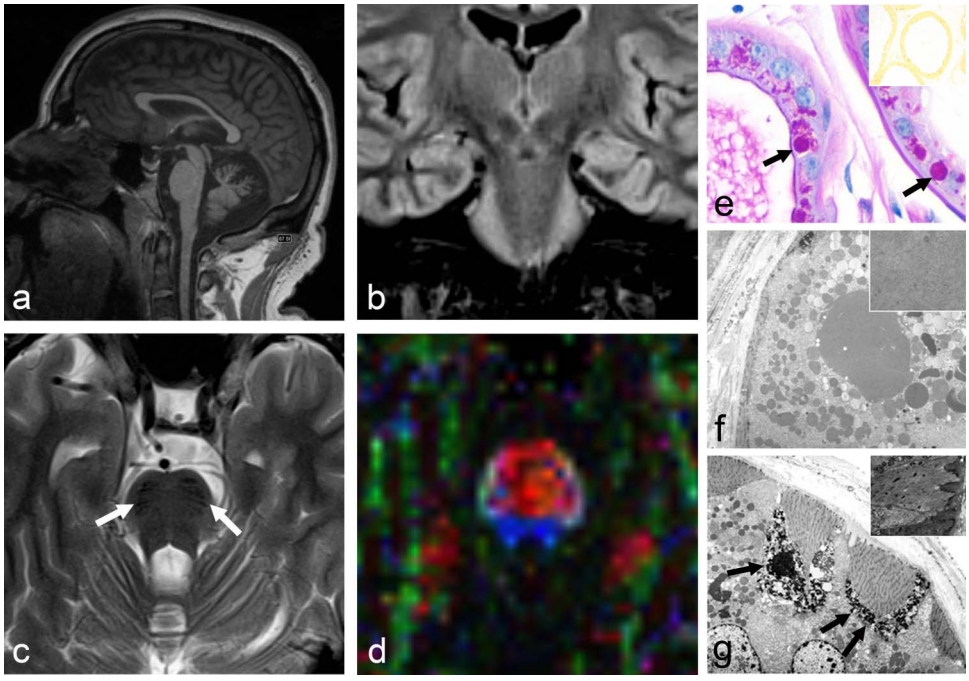

Figure 1 MRI of the brain on (A) sagittal T1-weighting demonstrating corpus callosal, superior cerebellar vermis and spinal cord volume loss, (B) coronal fluid attenuated inversion recovery (FLAIR) showing the sharp delineation between the normal central and hyperintense peripheral pons, (C) axial T2-weighting illustrating the characteristic medial paired hypointense regions correlating with the corticospinal tracts[11] (white arrows) and (D) correlating coloured fractional anisotropy map demonstrating loss of anisotropy of the corticospinal tracts (absence of the pair medial blue tracts) and preservation of the transverse pontocerebellar fibres (red), similar to that recently reported.[11 12] Skin biopsy findings showing (E) globular, discrete periodic acid-Schiff (PAS)-positive inclusions resembling Lafora bodies (arrows) are seen within apocrine glands. However, the Lugol's iodine reaction is negative (inset). (F) Ultrastructurally, they contain filamentous aggregates, features not typical of Lafora bodies (inset). (G) Prominent lipofuscin is present in some basal myoepithelial cells (arrows), but absent in similar cells from an age matched control (inset). This figure is only reproduced in colour in the online version.

control alleles. Other causes of a progressive neurodegenerative syndrome were excluded including detailed metabolic screen and genetic testing for Friedreich's ataxia, spinocerebellar ataxias 1,2,3,6,7,17, Dentato-Pallido-Luysian atrophy, BSCL2, POLG and mitochondrial disease.

The mutations found in the patient are predicted to lead to a truncated sacsin protein, missing the C-terminal DnaJ and HEPN domains (implicated in chaperone activity) but the ubiquitin-like domain (implicated in proteasomal interaction) is still present.[9]

DISCUSSION

We report a patient with cerebellar ataxia, spasticity and neuropathy, characteristic of ARSACS. Neurophysiological and MRI findings were consistent with previous reports. Genetic sequencing of *SACS* confirmed compound heterozygosity for two novel frameshift mutations. This patient had additional features of supranuclear gaze palsy, myoclonus and epilepsy. Although epilepsy has been reported in a small proportion of patients with genetically confirmed ARSACS, myoclonus and supranuclear gaze palsy have not. Although lipofuscin aggregates have been reported in cerebellar cortical neurons in ARSACS,[2] they have not been seen in skin; however, skin biopsy has only been documented in one patient with ARSACS.[6]

Lipofuscin is a lysosome derived membrane-bound, non-degradable cellular waste that accumulates at varying rates with increasing age in postmitotic cells including those of the nervous system. This 'ageing pigment' is fine, granular yellow-brown by conventional microscopy, autofluorescent, containing oxidised lipid and protein residues, carbohydrates and metals. Increased lipofuscin has been observed in early degenerating neurons and senile plaques in protein misfolding disorders such as Alzheimer's disease. Storage of lipofuscin and related 'ceroid' material in neurons with widespread neurodegeneration is the pathological hallmark in neuronal ceroid lipofuscinosis, a heterogeneous group of lysosomal storage disorders. Autopsy studies on two patients with ARSACS have revealed both Purkinje cell loss and swollen cerebellar cortical and thalamic neurons with dense lipofuscin-like granules. Sacsin contains several regions with extensive homology to heat shock proteins, molecular chaperones which facilitate correct folding of proteins. Sacsin has been shown to play a role in chaperoning aggregation-prone proteins in vitro.[9] Loss of the C-terminal DnaJ and higher eukaryotes and prokaryotes nucleotide binding (HEPN) domains, predicted in this case, may impair this chaperone activity, resulting in a phenotype associated with abnormal protein aggregation. Inhibition of proteasome activity has been shown to alter neural mitochondrial homeostasis and mitochondrial turnover resulting in increased oxidative stress and increased levels of lipofuscin in cells. Furthermore, mitochondrial dysfunction/mislocalisation has been demonstrated in ARSACS.[10] The loss of sacsin function may contribute to increased lipofuscin accumulation in cells by adversely impacting proteasome and mitochondrial functions.

This report further broadens the ARSACS phenotype, demonstrating supranuclear gaze palsy, myoclonus and skin lipofuscin aggregation.

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Acknowledgements MMR is grateful to the Medical Research Council (MRC) and the Muscular Dystrophy Campaign and SMM and MMR are grateful to the NINDS/ORD (1U54NS065712-01) for their support. SN and PG are grateful to Ataxia UK for their support. This work was undertaken at University College London Hospitals/University College London, which received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme.

Contributors JCS wrote the initial manuscript and contributed to the analysis and interpretation of data. SMM, ID, RP, GA, SN, FB, PG and MMR contributed to drafting and rewriting the initial manuscript as well as to the analysis and interpretation of data. All authors give approval for publication. PG and MMR contributed equally to this manuscript.

Funding This work was supported by the National Institutes of Neurological Diseases and Stroke and office of Rare Diseases, Grant number U54NS065712 (to SMM, MMR), Ataxia UK (SN, PG) the Medical Research Council and the Muscular Dystrophy Campaign (MMR).

Competing interests SMM has received support for her research from the National Institutes of Neurological Diseases and Stroke and office of Rare Diseases (U54NS065712). SN has received research grant funding from Ataxia UK. PG has received research grant funding from Ataxia UK. MMR serves on the editorial boards of the Journal of Neurology, Neurosurgery and Psychiatry, Neuromuscular Disorders and the Journal of the Peripheral Nervous System and on the editorial advisory board of Brain. MMR is grateful to the Medical Research Council (MRC) and the National Institutes of Neurological Diseases and Stroke and office of Rare Diseases (U54NS065712) for their support. This work was undertaken at University College London Hospitals/University College London, which received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme.

Provenance and peer review Not commissioned; externally peer reviewed.

Received 13 July 2012
Revised 24 September 2012
Accepted 26 September 2012

J Neurol Neurosurg Psychiatry 2012;**0**:1–2.
doi:10.1136/jnnp-2012-303634

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J Neurol Neurosurg Psychiatry published online November 3, 2012