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Short communication

Mitochondrial recessive ataxia syndrome mimicking dominant spinocerebellar ataxia

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ABSTRACT

We studied the genetic background of a family with SCA, showing dominant inheritance and anticipation. Muscle histology, *POLG1* gene sequence, neuropathology and mitochondrial DNA analyses in a mother and a son showed typical findings for a mitochondrial disorder, and both were shown to be homozygous for a recessive *POLG1* mutation, underlying mitochondrial recessive ataxia syndrome, MIRAS. The healthy father was a heterozygous carrier for the same mutation. Recessively inherited MIRAS mutations should be tested in dominantly inherited SCAs cases of unknown cause, as the high carrier frequency of MIRAS may result in two independent introductions of the mutant allele in the family and thereby mimic dominant inheritance.

1. Introduction

Autosomal dominant cerebellar ataxias [ADCA or spinocerebellar ataxias (SCAs)] — are the most common subgroup of dominant hereditary ataxias [1], which are most often caused by polyglutamine expansions. However, diagnosis is typically based on clinical characteristics, family history and brain imaging; genetic diagnosis is found in a minority of cases [2]. SCAs show wide clinical variability, but unsteady ataxic gait, clumsiness and dysarthria, beginning typically at 20's or 30's, are their common hallmarks. Anticipation in age of disease onset is typical for disorders with polyglutamine expansion.

Mitochondrial dysfunction has shown to be an important cause of SCAs, often combined with sensory neuropathy and epilepsy. Friedreich's ataxia is caused by recessive frataxin mutations, associated with defective mitochondrial iron metabolism [3], whereas mitochondrial recessive ataxia syndrome (MIRAS; or MSCA-E; mitochondrial SCA with epilepsy) and infantile-onset SCA are caused by recessive nuclear gene mutations in mitochondrial DNA (mtDNA) maintenance proteins [4–7]. Here we present a mitochondrial SCA family, with MIRAS-like symptoms, but autosomal dominant-like inheritance pattern and age of onset suggestive of anticipation.

2. Materials and methods

2.1. Patients

The study was approved by Helsinki University Central Hospital Ethical Review Board, and the subjects gave their written informed consent.

P1 (mother) developed gait disturbance by the age of 35, progressing to increasing clumsiness in lower extremities, dysarthria, diplopia, and occasional amnesia at the age of 44. She developed ataxia, slight polyneuropathy, and external ophthalmoplegia. At the age of 46 she had slightly increased plasma creatine kinase levels (178–261 U/l, reference 0–150 U/l) and symmetrical cerebellar peduncular white matter signal intensity increase in brain MRI. The first epileptic seizure, requiring treatment by general anesthesia, occurred at the age of 55, after which she was hospitalized permanently. From her 30's, she received psychiatric care due to anxiety and depression. A neuropsychological examination revealed decrease in visual reasoning and memory functions. She deceased at the age of 56 due to pneumonia and pulmonary embolism.

P2 (Father) is a 63-year-old male, with no history of neurological symptoms, but who has type-2 diabetes and hypertension.

P3 (Son) is a 41 year old male, who had gait disturbance since childhood. Early onset suggested anticipation. In his 20's he developed photophobia and general clumsiness and benign paroxysmal positional vertigo. From the age of 37 he has had unspecific sensory

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polyneuropathy, confirmed by electromyography. He had several simple partial seizures at the age of 39, and has mild anxiety and depression. Occasionally he has had increased levels of plasma creatine kinase (336–571 U/l, reference 50–400 U/l) and plasma gamma-glutamyl transpeptidase (131 U/l, reference 10–80 U/l). Brain MRI revealed symmetrical increased white-matter signal intensities in cerebellar peduncles.

P3 has a healthy brother.

No SCA mutation screening was done on either patient, as this was not in routine clinical use at the time of diagnosis. No consanguinity was reported by the family members.

2.2. DNA analysis

DNA extraction from muscle samples, *POLG1* mutation analysis, long-range PCR analysis of mtDNA, real-time quantitative PCR of mtDNA and mtDNA point mutation load analysis were done as previously [8, 9], with cytochrome B and APP genes used as controls in qPCR. Mutation frequency was determined scoring every mutation once, to evaluate *de novo* mutagenesis instead of clonal expansion of single mutations *in vivo*.

3. Morphologic studies and neuropathological examination

Muscle biopsy samples (P1, P3), electron microscopy and sural nerve biopsy (P3) preparations were analyzed according to routine diagnostic protocols.

The neuropathological examination of P1 included dissection of the formalin-fixed brain and spinal cord specimens, stained with hematoxylin-eosin and luxol fast blue-cresyl violet. Immunohistochemistry was performed on selected samples with monoclonal antibodies against glial fibrillary acidic protein (GFAP; MO761, 6F2; Dako Carpinteria, CA; dilution 1:300), non-phosphorylated neurofilament proteins (SMI-311; Sterberger Monoclonals, Inc., Baltimore, MD; dilution 1:2500), and microtubule-associated protein 2 (AP-2; M-4403; Sigma, St. Louis, MO; dilution 1:5000). Pre-treatment was performed with citrate buffer for GFAP, and MAP-2, and with Tris–EDTA for SMI-311. The detection kit was Envision Advanced (DAKO) for GFAP and MAP-2, and Envision for SMI-311.

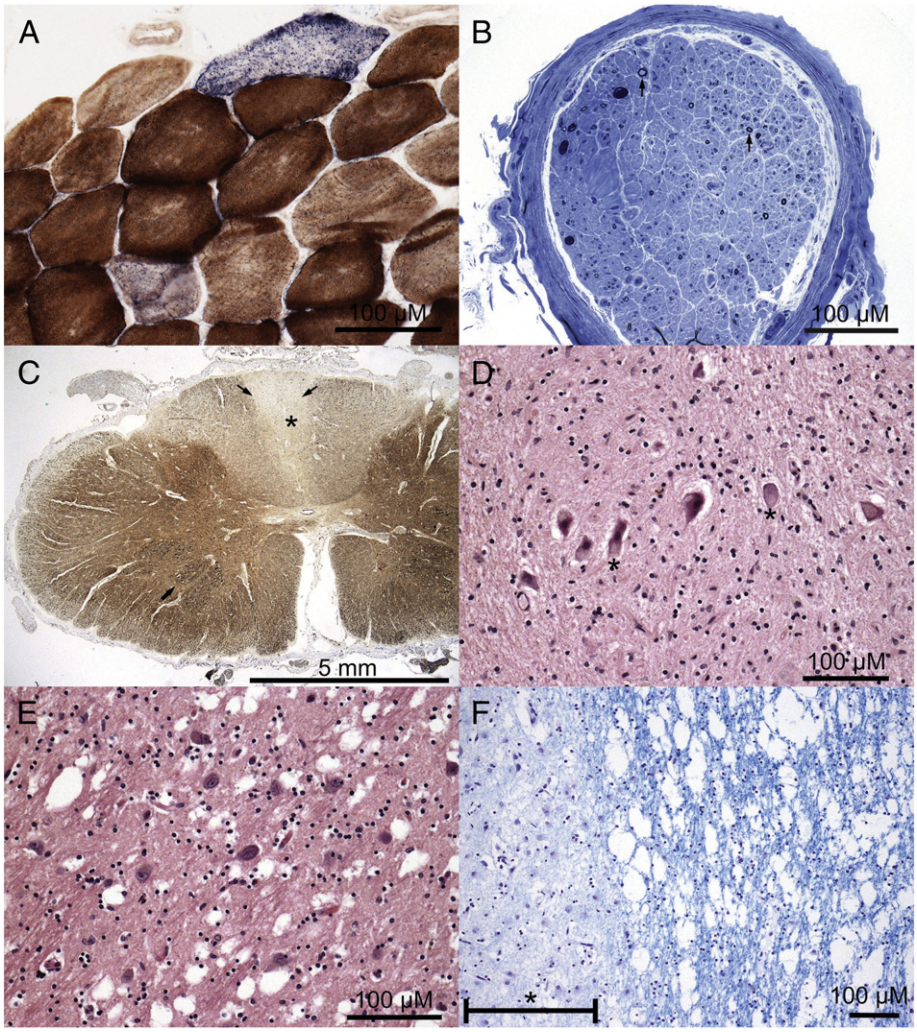

Fig. 1. Morphological studies of muscle, n. suralis, spinal cord and brain. A: The histological analysis of skeletal muscle biopsy sample from patient 3 shows some fiber size variation and two bluish COX-negative fibers. Frozen section, COX–SDH double histochemical staining, original magnification ×200 B: P3 sural nerve shows a subtotal loss of large myelinated fibers (arrows indicate few examples). Plastic section, toluidine blue ×200 C: P1 autopsy sample of spinal cord at level C7; neurofilament immunohistochemistry shows a clear pallor of the posterior columns (asterisk), and also the posterior spinocerebellar tracts are slightly fiber-depleted (thin arrow). The motor neurons in the anterior horn are preserved (thick arrow) Paraffin sections, SMI-311 IHC ×10. D: Loss of neurons and gliosis can be observed in this sample from the dentate nucleus, and remaining neurons are shrunken and partly chromatolytic (asterisks). Hematoxylin and eosin staining, ×200. E: Neuronal loss and vacuolization in the mediodorsal nucleus from thalamus. Hematoxylin and eosin staining, ×200 F: The lower laminae of the parieto-occipital cortex are severely depleted of neurons with gliosis (asterisk), while in the right two-thirds of the picture the white matter is markedly spongiotic in appearance. Luxol fast blue staining, ×100.