Spinal cord atrophy in triple A syndrome associated with a novel compound heterozygous mutation

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Abstract

A 38-year-old male patient was admitted with slowly progressive spastic gait disturbance. Imaging revealed general spinal cord atrophy. Because of adrenal insufficiency, alacrima and achalasia, triple A syndrome was suspected. This is a case report of a triple A syndrome patient with a predominance of neurological features and a new heterozygous compound mutation in triple A syndrome gene.

CASE REPORT

BACKGROUND

The triple A syndrome (Allgrove syndrome, OMIM 231550) is a rare autosomal recessive disease that generally manifests during childhood by alacrima, achalasia of the cardia and adrenocorticotrophic hormone (ACTH)-resistant adrenal insufficiency. A highly variable phenotype and variable sequence of presenting symptoms make diagnosis difficult (Ismail *et al.* 2006; Allgrove *et al.* 1978). Various neurological abnormalities are common, but general spinal cord atrophy, as we present in this 38-year old male patient, is not described.

CASE

Our patient was admitted with a slowly progressive spastic gait disturbance and hypernasal speech since the age of 18 years. At the age of 32, barium swallow revealed achalasia. For the past years, the patient suffered from persistent fatigue and irregular episodes with fever of unknown origin.

Clinical examination revealed increased skin pigmentation, hypernasal speech and brisk reflexes. The patient displayed a paresis with preferential distal muscular atrophy in all extremities and paraspastic gait. There was no sensory impairment besides mildly reduced bimalleolar pallesthesia.

Cortisol levels were below the detection limit (1.1 µg/dl, normal 220–552 µg/dl) and ACTH (249 pg/ml, normal < 46 pg/ml) was elevated in morning endocrine laboratory investigations. Morning aldosterone (34 pg/ml) and renin (11.7 ng/l) were within the reference range. Electromyography disclosed signs of axonal-demyelinating sensorimotor polyneuropathy and slightly spontaneous activity. Motor evoked potentials

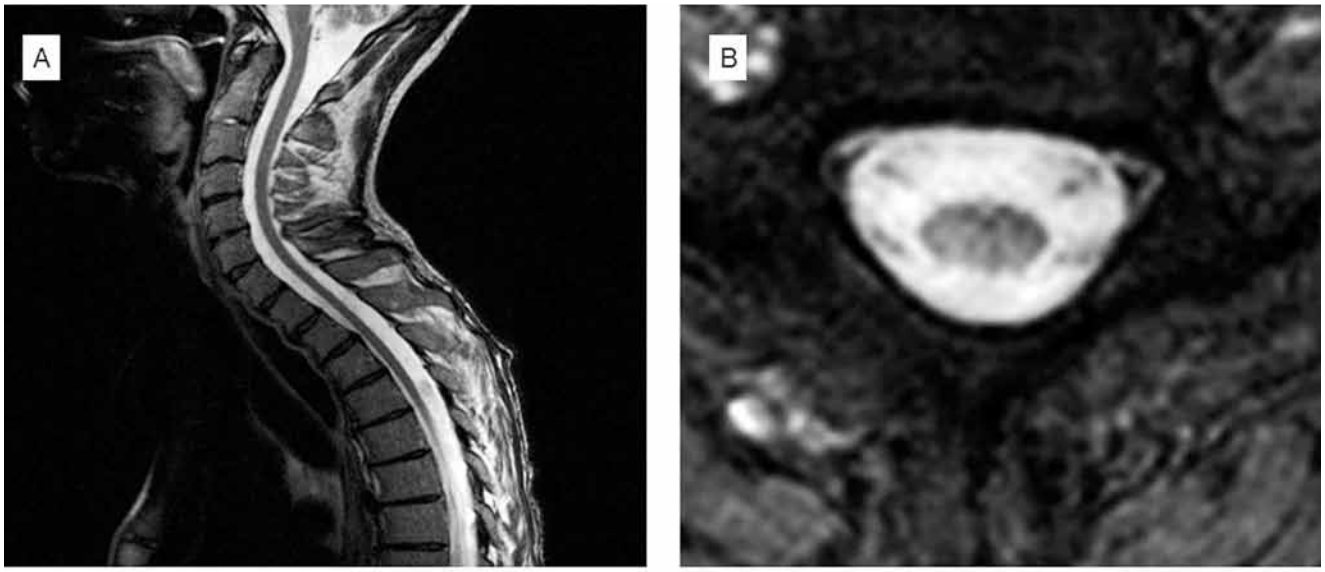

Fig. 1. Spinal cord atrophy in a patient with triple A syndrome.
(**A**) T2-weighted MRI of the cervicothoracic spinal cord demonstrating general atrophy over the entire range without signs of contrast enhancement.
(**B**) T2-weighted MRI of spinal cord at level C7 (spinal cord cross sectional area: 44.7 mm^2).

revealed delayed peripheral and central motor latency to all extremities. Ophthalmologic investigations identified a reduced tear production. Magnetic resonance imaging (MRI) of the spinal cord showed general atrophy without signs of contrast enhancement (Figure 1A–B) while MRI of the brain was normal. The spinal cord cross sectional area at level C2/C3 was 51.8 mm^2, which is clearly reduced. Mean spinal cord cross sectional area of a healthy control group at this age is stated at 78.1 mm^2 (range 70.1–86.1 mm^2) (Brex *et al.* 2001).

X-linked adrenomyeloneuropathy was excluded due to absence of mutations in the *ABCD1* gene. Because of adrenal insufficiency, alacrima and achalasia, triple A syndrome was suspected. Indeed, analysis of all 16 exons of the *triple A syndrome* gene revealed the heterozygous compound mutations c.787T>C (p.Ser263Pro) and c.922delT (p.Ser308fs). Whereas the first mutation is known, the second sequence change has not been described so far.

DISCUSSION

A large portion of mutations found in *AAAS* induce frameshifts and no clear genotype-phenotype correlation could be established (Brooks *et al.* 2005). It therefore seems likely that the phenotypic features found in our patient with the novel c.922delT (p.Ser308fs) mutation in combination with the known mutation c.787T>C (p.Ser263Pro) has to be interpreted as an example for the very broad variability of the clinical presentation. Mutations lead to a severe truncation of the gene product ALADIN (for alacrima, achalasia, adrenal insufficiency, neurologic disorder), which is likely to entail protein degradation. The ALADIN protein is widely expressed, especially in neuroendocrine, intestinal, cerebral and cerebellar cells (Brooks *et al.* 2005; Tullio-Pelet *et al.* 2000). A possible function of the protein is the nuclear import of the ferritin heavy chain protein (FTH1). FTH1 has been shown to protect from apoptosis due to oxidative stress (Storr *et al.* 2009).

Our patient received 15+5+5 mg hydrocortisone daily. During the following year there was a rapid improvement of abnormal fatigue. The fever attacks stopped directly, body weight normalized and there was a continuing significant improvement of gait disturbance. Whether such a therapy positively influences the mostly progressive neurological syndromes remains to be seen. In most cases, the adrenocortical function was preserved in spite of progressive multisystem neurological disorders (Kimber *et al.* 2003). However, monitored replacement therapy and increases in corticosteroid treatment during stress episodes improve quality of life and decrease risk of life-threatening events. Probably, the irregular episodes of fever in our patient could be due to acute episodes of adrenal insufficiency (Nieman *et al.* 2006).

Taken together, this is the first description of general spinal cord atrophy in a patient with Allgrove triple A syndrome. Our case suggests that the rare autosomal recessive triple A syndrome should be considered as differential diagnosis in patients with adrenal insufficiency and various neurological symptoms.

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