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# Striking anticipation in spinocerebellar ataxia type 7: the infantile phenotype

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Sirs: Autosomal dominant cerebellar ataxia type II (ADCA II) is characterised clinically by progressive cerebellar ataxia and pigmentary macular degeneration [9]. Age-at-onset may be highly variable, ranging from 1 month to 76 years, with a mean age of 32 years [2, 7, 11]. ADCA type II is genetically homogeneous and caused by a pathological CAG repeat expansion in the spinocerebellar ataxia type 7 (SCA7) gene on chromosome 3 [1]. The gene encodes for the ataxin–7 protein, the function of which remains unknown [4, 6]. Pathological repeat sizes range from 37 to 306 repeats, while normal alleles contain 4 to 35 CAG units [2, 14]. The expanded CAG repeat results in an elongated polyglutamine stretch in the ataxin–7 protein. SCA7 is therefore added to the growing list of polyglutamine tract diseases, that also includes Huntington's disease (HD) and other SCAs. In all polyglutamine expansion diseases, an inverse relationship exists between repeat length and age-at-onset, i. e. the longer the repeat, the earlier the disease begins. These disorders also feature the phenomenon of anticipation: successive generations experience an earlier age-at-onset. This is largely due to expansion of the unstable repeat during meiosis. In SCA7, the expanded repeat is more unstable in paternal than in maternal transmission [3, 8].

The rarely documented infantile SCA7 phenotype, characterised by additional extraneurological manifestations and a rapidly progressive course, is associated with enormous repeat expansions on paternal disease transmission [2, 11–13].

Here we report a family in which the onset of ataxia and subsequent detection of the SCA7 mutation in the father retrospectively explained a fatal multisystem illness in two children who died young.

Family report (figure 1): *Proband III–3* presented with visual complaints at age 35 years, being specified as blurred vision for distant objects with clearer vision in dimmed light. An ophthalmologist diagnosed bilateral cone dystrophy. Because of consanguinity of the proband's parents, an autosomal recessive pattern of inheritance was considered.

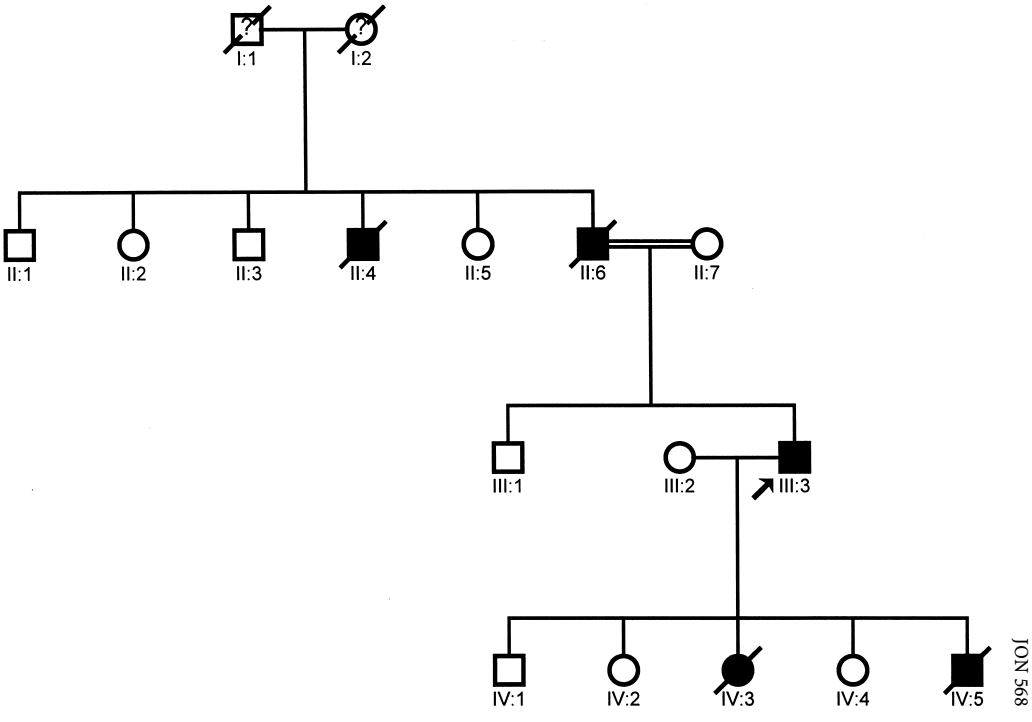


**Fig. 1** Family pedigree (□ = man, ○ = woman, ■ and ● = affected, / = deceased, double line = consanguinity)

Two years earlier, *patient IV–3* (a girl) was born. Acute respiratory distress resulted in immediate admission to the neonatal Intensive Care Unit (ICU). Cardiological examination revealed an atrial septum defect and a patent ductus arteriosus, which were surgically closed at 7 months of age. Physical examination showed hepatomegaly, and multiple hemangiomas of the trunk, abdomen and right upper leg, without dysmorphic features. Her motor development was delayed from birth onwards due to generalised hypotonia. Eye contact was poor; an ophthalmologic examination at the age of 7 months revealed retinitis pigmentosa. A metabolic disorder was suspected, particularly as repeated episodes of low serum lactate levels (< 0.1 mmol/L) were reported. Extensive metabolic studies were performed in blood, cultured skin fibroblasts, liver, and muscle, which excluded peroxysmal disorders and defective glycogenolysis. Chromosomal analysis was normal. After cardiac surgery, the patient developed severe capillary leak syndrome. At age 8 months she suffered arterial hemorrhage complicating a liver biopsy, which led to fatal multi-organ failure. An autopsy was not permitted. In the follow-up genetic counselling, it was mentioned that the girl most probably had suffered from a recessive metabolic disorder and a twenty-five percent recurrence risk for future offspring was likely.

Three years later (several months after the onset of visual disturbances in the father), *patient IV–5*, the three-month-old son, was admitted, because of persisting vomiting and failure to thrive. Physical examination showed tachypnea, a continuous cardiac murmur grade II-III, hepatomegaly, roving eye movements, and generalised hypotonia. No typical dysmorphic characteristics were present. Echocardiography indicated a patent ductus arteriosus and an atrial septum defect. An ophthalmologist, consulted because of decreased visual contact, again diagnosed retinitis pigmentosa. Evaluation of brainstem-evoked auditory potentials showed central conduction disturbances. Electroretinography showed no detectable retinal activity. Additional electrophysiological investigations gave normal findings. Neuroimaging indicated cerebellar atrophy. Reconsidering the clinical features of the deceased sister, autosomal recessive metabolic disorders, including mitochondrial disease, peroxysmal disorders, and carbohydrate deficient glycoprotein syndrome, were suspected. However, biochemical analyses of blood, cerebrospinal fluid, bone marrow, and muscle, as well as endocrinological screening, chromosomal analysis, and muscle and renal biopsy were all normal, as was a sweat test. The patent ductus arteriosus and the atrial septum defect were operatively corrected. Postoperatively, the patient deteriorated owing to severe capillary leak syndrome and was admitted to the ICU, where, at 5 months of age, he died with multi-organ failure resulting from *Klebsiella oxytoca* sepsis. Autopsy examination revealed multi-organ involvement compatible with septic shock and bronchopneumonia. Microscopic examination of the eye showed alternating hyper- and hypopigmentation of the retinal pigment epithelium with focal photoreceptor degeneration, compatible with early-stage retinitis pigmentosa. Neuropathological studies revealed oedematous changes of cerebral cortex and a small focus of ischemia in the cerebellar cortex; gross structural abnormalities and migratory disturbances were absent. In the subsequent genetic counselling session the autosomal recessive pattern of inheritance of an unclassified systemic disorder was re-emphasised.

At the age of 38 years, one year after the death of his son (patient IV–5), the *proband III–3* noticed gait difficulties and clumsiness of the hands. He recalled that his father (II–6) and an uncle (II–4) had walking difficulties as well. Neurological examination showed severe slowing of horizontal and vertical saccades, central scotoma, cerebellar dysarthria, limb and gait ataxia, and symmetrical hyperreflexia with indifferent plantar responses. Neuroimaging revealed marked cerebellar atrophy.

A clinical diagnosis of ADCA type II was made. Genetic analysis revealed an expansion of the CAG repeat (49 repeats) in the SCA7 gene. Southern blot analysis of DNA extracted from stored peripheral leukocytes of patient IV–5 (figure 2) and from stored fibroblasts of patient IV–3 using a SCA7 probe indicated enormous repeat expansions of 325 and 460 repeats, respectively, the latter constituting the largest ever reported.

The infantile SCA7 phenotype

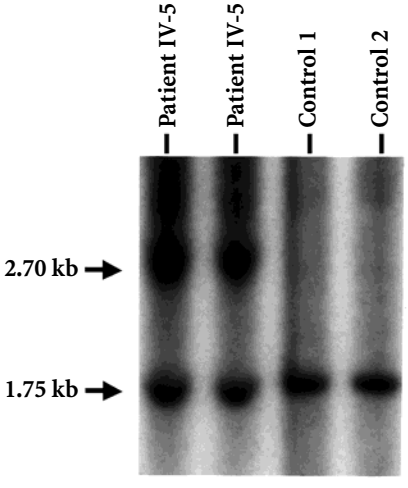


**Fig. 2** Identification of the *SCA7* mutation in patient IV-5 by Southern blot analysis. 8 SymbolmArialg DNA of patient IV-5 (in duplo, lanes 1+2) and two normal controls (lanes 3+4) was digested using EcoRI, separated on a 0.8 % agarose gel, and transferred to a Hybond-N Plus membrane (Amersham Pharmacia Biotech). Hybridization was carried out with a 32P-labeled probe of a *SCA7* PCR product, made using the 4 U1024 and 4 U716 primers as described by David et al. [4]. Arrows indicate the signals of the 1.75 kb wild-type alleles (10 CAG repeats) and the 2.70 kp mutated alleles (~325 repeats).

has been reported previously. Benton et al. described an infant with the onset of congestive heart failure due to patent ductus arteriosus at the age of 2 months [2]. Additional irritability, mild hypotonia, acquired microcephaly, swallowing difficulties, inability to visually track objects, and cerebellar atrophy on neuroimaging were found. The infant died at the age of 6 months. His father had only mild tandem walking difficulty at the age of 45 years. The father's SCA7 allele contained 43 repeats, while in the infant 306 repeat units were detected. The infant reported by Hsieh et al. was found to have nystagmus at 1 month of age and developed severe hypotonia, signs of visual impairment, and developmental delay [11]. Aspiration pneumonia was the cause of death at age 17 months. SCA7 mutation-analysis was not carried out. The father, 44 years old, was still asymptomatic with 41 CAG repeats in the SCA7 gene. Johansson et al. briefly described an infant with > 200 repeat units, whose father noticed ataxia at the age of 35 years and was found to have 49 CAG repeats [12]. Clinical features in the child included poor weight gain, patent ductus arteriosus, breathing problems, and metabolic acidosis. The infant died at 7 months of age. Finally, Neetens et al. described an ADCA type II pedigree that included an infant with a cardiac anomaly, which caused death at the age of 6 weeks. The father was the transmitting parent [13].

Generalised hypotonia and retinal pigment abnormalities in the two siblings reported here, led to an extensive differential diagnosis that mainly included metabolic disorders. At that time, no one recognised the possible relationship with the retinopathy in the father.

In the infantile form of SCA7, the neurological involvement is more severe and the clinical spectrum extends beyond neurological and ocular signs. Cardiac abnormalities, mainly patent ductus arteriosus, are reported in all but one infant. In addition, the infants reported here also showed hepatomegaly, multiple hemangiomas, and severe capillary leak syndrome after surgery. Apparently, large CAG repeat expansions that result in dysfunction of the ataxin–7 protein may lead to congenital abnormalities such as patent ductus arteriosus. The function of ataxin–7 and the way the polyglutamine sequence in the ataxin–7 protein exerts its cellular toxicity remain unknown. It is possible that mutant ataxin–7 accumulates into aggregates and resists ubiquitin-mediated proteolytic processes, with subsequent disruption of nuclear structure, nuclear stability and/or nuclear machinery. Ataxin–7 is also thought perhaps to function as a transcription factor and, accordingly, the mutant ataxin–7 protein could interfere with transcriptional processes [4]. Because SCA7 usually presents in adulthood with neurological and ophthalmological signs only, we postulate the existence of a dose-effect relationship and a decreased vulnerability to polyglutamine-mediated cytotoxicity in peripheral tissues.

All infantile cases reported here and in the literature, occurred on paternal disease transmission with extreme anticipation (disease onsets of 35 to 45 years earlier) accompanied by enormous (4 to 9 fold) increases in repeat expansions. In SCA7, mean anticipation was found to be 17±14 years, but anticipation is significantly greater on paternal transmission [1]. This is currently explained by the high repeat instability during spermatogenesis in SCA7, as is the case in other SCAs and HD [10]. On paternal transmission, the mean increase in repeat size is 15±20 repeats, compared with 5±5 repeats on maternal transmission [5]. To our knowledge, the CAG repeat expansions of 325 and 460 units in this report are the largest ever detected. The differential diagnosis of neonatal hypotonia includes neuromuscular disorders (e. g. spinal muscular atrophy type I, congenital myopathies, congenital muscular dystrophies, and metabolic myopathies) and central nervous system diseases (e. g. Prader-Willi syndrome, Zellweger syndrome, and cervical myelopathy). Hypotonia is reported in most of the infantile SCA7 cases and in patient IV–3 the hypotonia was documented in the neonatal period. Therefore, the infantile form of SCA7 should be included in the differential diagnosis of neonatal hypotonia.

We emphasise the importance of recognising this phenotype, because of associated consequences regarding diagnostic efficiency, prognostic issues, and genetic counselling. In unexplained neurological diseases, autosomal dominant disorders with extreme anticipation should always be considered.

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