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First families with spinocerebellar ataxia type 7 in Poland

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ABSTRACT

Introduction. We present the first two Polish families diagnosed with spinocerebellar ataxia type 7 (SCA7) and draw attention to cardiac involvement as a new potential manifestation of this disease.

Material and methods. Two well-documented kindreds are presented.

Results. The proband from Family 1 presented aged 54 years with vision worsening followed by progressive imbalance. Brain MRI demonstrated cerebellar atrophy. Genetic testing confirmed CAG repeat expansion (42/10) in *ATXN7* gene. The proband from Family 2 developed imbalance at age 20, followed by progressive deterioration of vision. Brain MRI revealed cerebellar atrophy. Additionally, she developed chronic congestive heart failure and, at age 38, had cardiomyopathy with an ejection fraction of 20% and significant mitral and tricuspid regurgitation. Genetic analysis found abnormal CAG expansion in the *ATXN7* (46/10).

Conclusions and clinical implications. Vision loss due to pigmentary retinal degeneration is the distinguishing feature of SCA7 and often the initial manifestation. Although SCA7 is one of the most common SCAs in Sweden, it has never been reported in neighbouring Poland. Until now, cardiac abnormalities have only been described in infantile-onset SCA7 with large CAG repeats. The observed cardiac involvement in Family 2 may be coincidental, albeit a new possible manifestation of SCA7 cannot be excluded.

Key words: SCA7, hereditary, retinal degeneration, neurodegenerative

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Introduction

Spinocerebellar ataxia type 7 (SCA7) is a rare autosomal-dominant neurodegenerative disorder caused by abnormal CAG expansion (typically above 36 repeats) in the *ATXN7* gene encoding Ataxin-7 protein [1, 2]. SCA7 is very rare, with an estimated prevalence of less than 1:100,000 and accounting for 2% of all SCA cases worldwide [1, 2]. However, its prevalence is higher in Scandinavians, indigenous South Africans, and Mexicans, constituting approximately 50%, 22%, and 7% of all SCAs in those countries and regions, respectively [2]. Interestingly, until now, only one isolated case from Eastern Europe (Czechia) has ever been reported [3].

In this work, we present the first two Polish families diagnosed with SCA7 and draw attention to cardiac involvement as a new potential manifestation of the disease.

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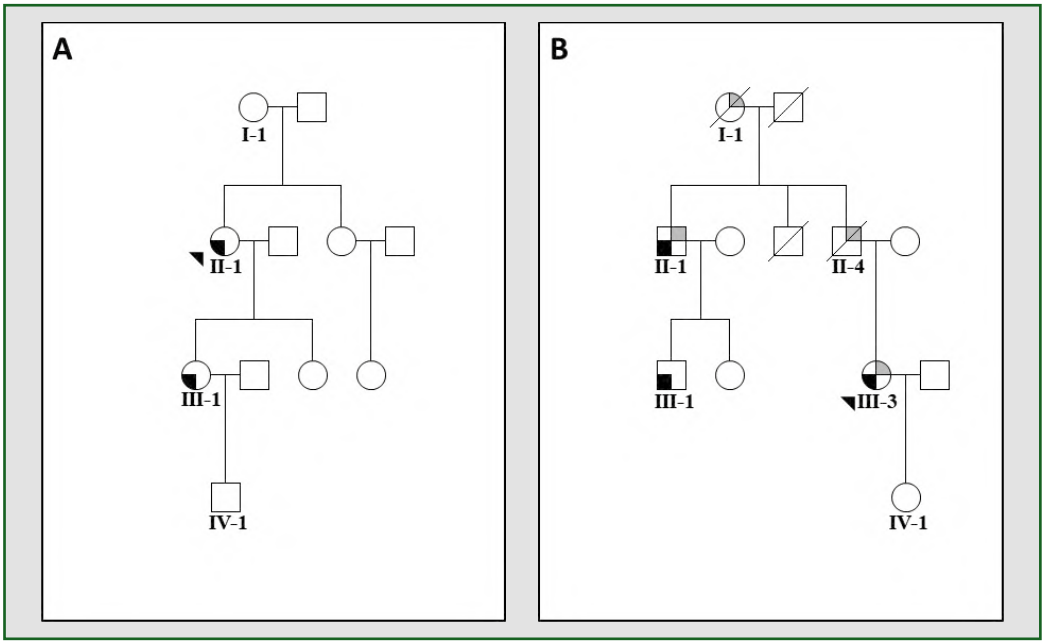

Figure 1. Pedigrees of Family 1 (**A**) and Family 2 (**B**). For family pedigrees, standard pedigree symbols are used: arrowhead indicates proband; circle indicates female; square indicates male; slash through symbol indicates diseased individual; left lower quadrant black symbol indicates affected individual with ataxia; right upper quadrant grey symbol indicates affected individual with cardiac disease

Material and methods

Family 1 (Fig. 1A)

A 54-year-old female (II-1) noticed a blurring of vision, and optical coherence tomography revealed degeneration of the optic nerve. Brain magnetic resonance imaging (MRI) demonstrated cerebellar atrophy. Subsequently, her vision deteriorated, and she developed imbalance. Neurological examination at age 57 showed dysarthria, vision loss, four-limb ataxia, and wide-based gait. Genetic testing confirmed CAG repeat expansion (42/10) in *ATXN7*. Her symptoms slowly worsened over time. During a follow-up evaluation at age 67, she had dysarthria, severe vision deficiency, impaired vertical gaze, four-limb ataxia, increased muscle tension of the mixed rigid-spastic type, brisk tendon reflexes, bilateral ankle clonus, and Babinski sign on the left side. She could stand only with intermittent support and walk with the strong support of an accompanying person. Her follow-up brain MRI showed progression of the cerebellar atrophy.

Her daughter (III-1) presented aged 32 with slurring of speech and difficulties with word retrieval. She was diagnosed with oligoastrocytoma WHO grade III in the left temporal lobe and underwent surgical excision, chemo- and radiotherapy. Despite recovering from the brain tumour, she experienced worsening of speech and imbalance. Genetic testing found abnormal CAG repeat expansion in *ATXN7* (43/10). On neurological examination aged 43, she had dysarthria, horizontal nystagmus during lateral gaze, four-limb ataxia, spasticity, exaggerated tendon reflexes, and Babinski sign on the left side. She could walk unsupported but occasionally staggered, was unable to walk in tandem, and had reduced right arm swing.

A second daughter, a 41-year-old (III-2), is asymptomatic, with genetic testing revealing abnormal CAG repeat expansion in *ATXN7* (42/10). The family history for similar symptoms in other family members was negative. Based on the genealogical information going three generations back, the family originated from the Greater Poland region.

Family 2 (Fig. 1B)

A 20-year-old female (III-3) developed imbalance and gait difficulty, followed by progressive vision loss. On neurological examination aged 28, she had dysarthria, vision deficiency, impaired vertical and horizontal gaze, spasticity in the lower limbs, exaggerated tendon reflexes, and four-limb ataxia. She needed an accompanying person or a walker to ambulate. Brain MRI revealed cerebellar atrophy. Genetic analysis found abnormal CAG expansion in the *ATXN7* (46/10). In subsequent years, her symptoms progressed, and she developed chronic congestive heart failure and was diagnosed with cardiomyopathy. Transthoracic echocardiography at 38 showed global hypokinesia with an ejection fraction of 20% and significant mitral and tricuspid regurgitation. Neurological examination at 39 revealed severe dysarthria, ophthalmoplegia with complete vision loss, four-limb ataxia, spasticity in the lower limbs, and bilateral Babinski sign. She could only walk a short distance with a walker or the strong assistance of an accompanying person. She depended on a caregiver for all her daily activities, and remained recumbent for most of the day.

The family history was positive for similar symptoms. Her father (II-4) did not suffer from a visual deficiency or gait difficulty, but developed cardiomyopathy at 50 and died suddenly while asleep at 60. However, the patient's uncle (II-1) noticed imbalance and gait difficulty at 54, and slowly progressed over the years. He also suffered from a cardiac disorder (atrial fibrillation). His son (III-1) presented gait and balance problems at 40. They both had genetic testing, which confirmed abnormal repeat expansion in the *ATXN7*. Of note, the proband's paternal grandmother (I-1) died suddenly at 57, of suspected cardiac arrest. The paternal side of the proband's family descended from central Poland, which they had inhabited for at least three generations.

Discussion

Normal *ATXN7* encodes a protein involved in the regulation of transcription and stabilisation of microtubules; however, the mutation results in an aberrant polyglutamine protein with a propensity to accumulate in the cerebellum, spinal cord, brainstem, and retina [1, 2]. Therefore, the disease usually manifests with progressive cerebellar ataxia, dysarthria, oculomotor disturbances, motor neuron symptoms, and vision deficiency due to pigmentary retinal degeneration [1, 2]. The latter feature distinguishes SCA7 from other hereditary ataxias and often is the first manifestation.

SCA7 has been reported in North and South America, Africa, Asia, Oceania, Europe, and the Caribbean [1, 2, 4]. It is one of the most common SCAs in Sweden, but interestingly, it has never been reported in neighbouring Poland [4, 5]. Although the two countries are separated by the Baltic Sea, they have a rich history of bilateral relations and migration in both directions. Previous studies on haplotyping suggested a common founder in a few populations with SCA7, including the Swedish one [4]. On the other hand, many cases, including the one from Czechia, were sporadic [3]. This may be due to the high intergenerational instability of CAG repeat length in the *ATXN7* gene, which may increase from low to pathogenic range even over one generation [6]. In particular, paternal transmission poses a risk of expanding CAG repeat length [3]. As the age of onset and severity of the phenotype is inversely proportional to the extent of CAG expansion, the next generation can present decades earlier [3]. In everyday clinical settings, most cases of ataxia are due to causes other than genetic ones [7, 8]; however, as many of the reported SCA7 cases were isolated, the disease should be included in the differential diagnosis of sporadic ataxia.

Interestingly, cardiac involvement has only been reported in infantile-onset SCA7 [9, 10]. It has been postulated that large (above 180 CAG repeats) *ATXN7* expansions may damage cardiac tissue and lead to congestive heart failure [9, 10]. In light of this, the relatively small size of the CAG expansion may suggest another aetiology of heart failure, including a genetic one, which cannot be precluded based on the available data regarding Family 2. However, the number of reported SCA7s is limited, and new data on its and other SCAs' possible symptomatology, including urinary dysfunction, is emerging [11]. Therefore cardiac involvement as a new manifestation of adult-onset SCA7 cannot be excluded.

At present, there is no approved specific therapy for SCA7, and the management remains symptomatic and supportive [2]. Physiotherapy has been shown to improve motor coordination and mobility in patients with other types of SCA, and these effects persisted beyond one year of follow-up [2, 12]. Although there is no consensus as to the optimal regimen of physiotherapy, its beneficial effects were shown by many previous studies with variable protocols used [2, 13–16]. Therefore, we suggest tailoring the form and intensity of physiotherapy to the needs of the individual patient. Occupational and speech therapy should also be considered [1, 2]. Diplopia may be alleviated with prism correction. Patients with spasticity may benefit from botulinum toxin injections [17–19]. Neuropathic pain and paresthesia may be mitigated with pregabalin and gabapentin; however, caution should be used as these medications can aggravate dizziness and imbalance. Therefore, acupuncture may also be considered in patients' neuropathic symptoms [2]. Neuropsychiatric symptoms (depression, behavioural abnormalities) should be managed in the first place with selective serotonin reuptake inhibitors [2].

Clinical implications/future directions

In this short communication, we present the first two Polish families with SCA7 and highlight the need to include this disease in the differential diagnosis. We draw attention to cardiac abnormalities in SCA7, which may be other possible disease manifestations. Further research is needed to investigate the genotype-phenotype correlations in SCA7 and to better our understanding of the disease's pathomechanism.

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