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Early diagnosis of spinocerebellar ataxia

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Abstract: It is hard to define the initiation of genetically determined neurodegenerative diseases because of their gradual and slowly progressive nature. This is particularly true for spinocerebellar ataxia (SCA) due to differing affection of many parts of the nervous system and tremendous symptom variability. In 287 patients with SCA1, SCA2, SCA3 or SCA6, we investigated early symptoms and calculated the influence of CAG repeat length on age of onset depending on (1) the definition of onset of disease, (2) the definition of onset, and (3) the duration of the symptoms. The primary symptom in two-thirds of patients was discomfort with gait. In 4% of patients, respectively, ataxia accompanied double vision, dysarthria, poor hand writing and episodic vertigo. Data on on onset of disease ranged for 1 year or more in 44 percent of cases between patients and family. Repeat period effect on age of onset was highest when the onset was identified as the beginning of permanent gait disturbance and cases with symptoms were excluded for more than 10 years. Under these conditions, the repeat duration of CAG determined 64 percent of the onset variability in SCA1, 67 percent in SCA2, 46 percent in SCA3, and 41 percent in SCA6 indicating substantial influence of nonrepeat variables on the onset of disease in all SCA subtypes. Identifying such factors as potential targets for disease-modifying compounds is of interest. In this context, it is important to consider the early symptoms that develop before ataxia occurs to assess the change from presymptomatic to affected status for SCA.

Introduction:

Spinocerebellar ataxia (SCA) consists of a community of multisystem neurodegenerative disorders, whose key feature is progressive ataxia. It is caused by mutations in more than 25 genes of which 14.[2–4] In seven subtypes, including the most prevalent genotypes (SCA1, SCA2, SCA3, and SCA6), the expansion of a CAG trinucleotide repeat in the coding region of the respective gene triggers the disease. SCA is a phenotypically heterogeneous latent condition characterized by slowly progressive gait ataxia and additional variable symptoms including visual problems, dysarthria, dysphagia, limb ataxia, spasticity, parkinsonism, dystonia, peripheral neuropathy, restless leg syndrome and urge incontinence. Because of its genetic existence, it is likely that the pathogenic process begins early in life or even before birth. Nevertheless, the precise origin of the disease still remains unclear.

Determination of the initiation of the disease may vary whether patients are being asked to initiate gait ataxia or, instead, to initiate any other form of behavioral or neurological problem. Despite the lack of standardization in the onset age assessment, important associations were observed between the onset age and the number of CAG motifs in the extended allele in all the more specific SCA subtypes (SCA1, SCA2, SCA3, and SCA6) and repeat lengths that account for 50 to 80 percent of the onset age variability. To what degree variations in the determination of the initiation of disease lead to the unexplained portions of variation is unclear. Besides recurrent expansions of CAG, alternative genetic or environmental factors influencing age of onset in SCA have rarely been identified[5–7]—although they are of great interest due to their likely role as disease progression modifiers.

The aim of this study was to determine the early symptoms that may occur before gait ataxia began to form compounds with the intention of delaying the disease

Key words: spinocerebellar ataxia; early symptoms; determinants of age at onset; CAG repeat expansion

Material and methods: patients were recruited. In specialized ataxia clinics, two hundred and eighty-seven patients were recruited, including 78 patients with SCA1, 97 patients with SCA2, 62 patients with SCA3 and 50 patients with SCA6. Age data, severity of the disease as determined by the ataxia assessment and rating scale (SARA[14]) and repeat length of the CAG. Additionally, 122 age- and sex-matched control subjects were interviewed for symptoms that may occur early in SCA without a history of neurological disease. Structured interviews with patients and their close relatives on the year of onset of symptomes of SCA. Disease duration is given as years with gait disturbance as fixed by the patients after discussion with their relatives. Higher SARA sum scores indicate more severe disease. In addition, they asked for other early symptoms from the patient's point of view that may be linked to SCA. They asked patients to address these discrepancies with their relatives in the case of incongruent details. Ultimately, patients set the year of onset of symptoms. The repeat length of CAG was analyzed in DNA from blood samples from EDTA. There were 259 patients with DNA available (SCA1:73, SCA2:87, SCA3:53, SCA6:46). Both analyzes were carried out in the same laboratory (Human Genetics, Tu¨bingen) to maximize the comparability of repeat lengths. For effective amplification of all SCA

mutations in one PCR assay, a multiplex PCR assay (described in Ref.7) was further optimized: Genomic DNA of 250 to 500 ng was used per PCR reaction. Upon request, first sequences, PCR conditions and fragment analysis information will be given. Because CAG repeats do not result in a 3-bp spacing perfectly, predicted fragment lengths have been compared with established (sequenced) genotype standards and the naming of the allele has been adjusted accordingly. -1

Results: Data about onset of permanent gait disturbance varied frequently (44%) between SCA patients and their relatives for 1 year or more. In 8.5% of patient-relative pairs these differences exceeded 5 years. In two-thirds (66%) of all SCA patients, gait difficulty was reported as the initial symptom. Symptoms preceding gait ataxia were in the order of frequency cramps (9%), dysarthria (5%), sleep disturbance (5%), double vision (4%), problems with hand writing (4%), episodic vertigo (4%), neuropathic symptoms like weakness or sensory complaints (3%), restless legs syndrome (3%), urinary urgency (3%), reduced visual acuity (2%), frequent throat clearing suggesting beginning dysphagia (1%), and other symptoms preceding gait disturbance (1%). Only double vision, dysarthria, hand writing problems, and episodic vertigo occurred more often in SCA patients compared to the control group (Table 2). -1

TABLE 2. Symptoms preceding gait abnormalities in SCA

	Co	All SCA	SCA1	SCA2	SCA3	SCA6
Double vision	–	4.3	1.3	3.2	10.0**[a]	4.2
Reduced visual acuity	4.1	2.1	5.1	1	–	2
Dysarthria	–	4.7	2.6	5.6*	3.3	8.2*
Frequent throat clearing	–	1.4	2.6	1.1	1.6	–
Problems with hand writing	–	4	5.3	5.6*	1.7	2.1
Episodic vertigo	1.6	3.9	2.6	2.1	1.6	12.2*
Neuropathic symptoms	4.1	2.9	4	–	4.8	4.1
Cramps	8.2	8.9	11.5	9.9	4.9	8
Restless legs syndrome	6.3	2.8	5.3	2.1	1.6	2
Sleep disturbances	9.0	4.7	2.6	2.2*	5	12.5
Urinary urgency	1.6	2.8	3.9	3.2	1.6	2
Other preceding symptoms		0.7	1.3	–	1.7	–

Proportion of patients (%) who reported onset of the respective symptom prior to gait ataxia.
*$P < 0.05$; **$P < 0.01$ (comparison of SCA vs. control group; Fisher's Exact Test after adjustment for age and sex).
[a]$P < 0.05$ (comparison to SCA1, 2, and 3).

CAG repeat length in the expanded allele was responsible for about 60% of variability in age at onset of gait ataxia in SCA1 and SCA2, for about 25% in SCA3, and about 20% in SCA6. No significant differences in connection with repeat length were

found when patients or their families provided information about the onset age or when both were examined

Discussion: This systematic disease onset study in SCA showed that in only two-thirds of patients, gait ataxia is the initial complaint. Only 16% of SCA patients report other issues than gait as the earliest symptom when somewhat unspecific symptoms such as cramps, restless legs, and sleep disturbance were removed. In particular, prior to the onset of gait ataxia, diplopia and episodic vertigo, but also dysrthria and clumsiness occurred. There was no specificity for a certain SCA subtype of early clinical signs, but episodic vertigo was more common in SCA6. This reflects the close relationship between SCA6 and type 2 (EA2) episodic ataxia, both caused by mutations in the voltage-gated neuronal calcium channel's a1A-subunit. –8. Although EA2 patients frequently develop MRI cerebellar atrophy and long-term gait ataxia, episodic ataxia has rarely been reported in SCA6 patients. -9.

If disease modulating compounds become available, when introduced to patients at the early stages of the disease, they may be most efficient. On the other hand, treatment with potential side effects before the onset of disease may not be advisable in drugs. Onset has been defined as beginning of progressive gait ataxia. Their results suggest that first symptoms may occur a decade or more before the onset of gait instability. In this regard, it is important to note that not only patients at the late stages of the disease reported early symptoms several years before gait problems began, However, patients with a short duration of disease and low SARA scores indicating less advanced disease also reported problems such as preceding gait ataxia for up to 15 years. Assessment of disease onset was poorly standardized in former studies.4.

In this study, in 17% of cases with a span of 5 to 20 years with mean differences between 1,2 and 4,5 years depending on the genotype, close relatives ' views of the onset of gait ataxia differed from those of the patient. When the duration of the disease exceeded 10 years, the largest differences between patients and relatives were observed. Such findings underline the importance of systematic assessment in order to produce the most reliable results and stress the need for prospective disease onset studies in SCA. Why SCA3 patients have recognized the onset of gait ataxia about 1 year earlier than their relatives, while SCA2 patients have not been clear about the onset of gait difficulty 1 year later than their relatives. It would be reasonable to

expect patients to experience changes in gait stability before it becomes apparent from outside. lead to the improvement in perception or memory in SCA2. Their data shows that repeat duration of CAG can only partially explain variation in SCA's starting age. Their data revealed the closest correlation with CAG repeat length. Under all circumstances, in SCA3 and SCA6, CAG repeat length accounted for less than 50 percent of variability in starting age. In SCA6, the influence of repeat length may be masked by the expanded allele's rather uniform size (22 CAG in 74 percent of patients with SCA6).

However, their data show that variability of onset in all SCA subtypes is driven by other remaining identifiable genetic or environmental factors. Given the enormous variability in onset data depending on the evaluation strategy, prospective studies with standardized disease onset evaluation procedures are required to identify disease modifiers with minor effects in expanded alleles than repeat lengths. Recent progress in understanding disease pathways in polyglutamine disorders and promising findings in animal models [10–11]. Give possible disease-modifying compounds prospects in the near future for clinical trials. If such compounds are intended to delay disease, a precise start-up age prediction is justified. For individual patients, this may not be possible, but it is feasible for larger cohorts. To this end, it is mandatory and will require prospective studies to recognize early symptoms that may develop before gait ataxia begins.

Conclusion: onset study in SCA showed that in only two-thirds of patients, gait ataxia is the initial complaint. Only 16% of SCA patients report other issues than gait as the earliest symptom such as cramps, restless legs, and sleep disturbance. prior to the onset of gait ataxia, diplopia and episodic vertigo, but episodic vertigo was more common in SCA6. Their results suggest that first symptoms may occur a decade or more before the onset of gait instability. Their data shows that repeat duration of CAG can only partially explain variation in SCA's starting age. Their data revealed the closest correlation with CAG repeat length when beginning of permanent gait disturbance is defined and long-standing disease patients were excluded. However, their data show that variability of onset in all SCA subtypes is driven by other remaining identifiable genetic or environmental factors.

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