Clinical assessment of a patient with spinocerebellar ataxia - the challenge of clinical research

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What is the subject of clinical research in SCA ?

In the case of spinocerebellar ataxia (SCA) we are dealing with a disease entity that today is based on recent and ongoing genetic findings. We now distinguish more than 20 SCA subtypes with distinct gene loci. These genetic SCA subtypes allow classification based on genetic findings in approximately 60% to 80% of ADCA families. In single families with other neurological disorders as a leading symptom and autosomal inheritance, e.g. familial parkinsonism, a genetic diagnosis of SCA could be established (Giunti, 1995). Vice versa, with genetic testing becoming more and more available, approximately 12% of cases with sporadic ataxia of adult onset (i.e. without family history suggestive of autosomal-dominant trait) have been defined as carriers of SCA mutations (Abele, 2002, Schöls, 2000). Nevertheless, there remain several families suggestive of ADCA with as yet unidentified genetic cause.

The disease itself has been recognized and described well before genetic work-up was available with first reports dating back to 1892 (Brown) and 1983 (Marie). These early reports already give the main features of the clinical presentation of a patient with SCA:

- family history suggestive of autosomal-dominant trait
- adult onset, mostly between 30-40 years
- cerebellar ataxia with signs and symptoms of extra-cerebellar involvement in the majority of cases
- slow progression resulting in progressive impairment
- variable phenotype within one family

Early pathological findings failed to reliably distinguish different disease entities in correlation with clinical findings (Holmes, 1907; Waggoner, 1938). Variable pathological findings have been reported within the same family. Again, it was noted that involvement of other neurological systems like spinal cord (including posterior roots, dorsal column, spinocerebellar tracts, anterior horn cells), pontine nuclei, inferior olives, basal ganglia and even cerebral cortex, is a frequent finding and that pathology confined to the cerebellum was comparatively rare in these conditions.

From careful clinical assessment of several families with autosomal-dominant cerebellar ataxia, Harding (1981) suggested a classification based on clinical findings:

- ADCA I: cerebellar ataxia with randomly distributed additional features (ophthalmoplegia/ optic atroophy / dementia / extrapyramidal features / amyotrophy)
- ADCA II: cerebellar ataxia with pigmental retinal degeneration (and ophthalmoplegia / dementia / extrapyramidal features)
- ADCA III: „pure“ cerebellar syndrome (without ocular or extrapyramidal features or dementia) with alter onset (60 or over)

She concluded that among the families described clinically as having an autosomal-dominant cerebellar ataxia there is genetic heterogeneity – an assumption that has been proven by later genetic findings. Secondly, within the same family – i.e. the same suspected genotype – the clinical findings are heterogeneous. Later phenotype descriptions in different SCA genotypes support this notion (Giunti 1995, Schöls, 1997). It is now assumed that so-called „modifying factors“ are responsible for variance of phenotype expression and disease progression within the same SCA subtype. One yet identified factor which partially explains the variance of age at onset within a family is the number of trinucleotid repeats („reapeat length“) in the respective SCA locus.

For details of genetic findings and current pathogenetic concepts I would like to refer to recent reviews (Everett and Wood, 2004; Schöls et al., 2004). The majority of SCA mutations defined so far consist of trinucleotid repeats (CAG or CTG) in the coding region of different genes, leading to an extended polyglutamine stretch in the coded protein („PolyQ-disease“). However, in some cases (SCA8 and SCA12) this repeat is located in the untranslated region of the respective gene. In addition, a pentanucleotide expansion has been reported in SCA 10 and also a missense point mutation for SCA 14. Inhowfar the molecular pathways of different genetic SCA subtypes share common pathogenetic mechanisms is the focus of current molecular research.

What are the objectives of clinical reserach in SCA?

One main effort in clinical research on degenerative neurological diseases is the establishment of diagnostic criteria. This is essential to define populations for the evaluation of diagnostic or therapeutic interventions. Examples are the UK Brain Bank criteria for probable/ possible Idiopathic Parkinson’s Disease or the criteria for probable/ possible Multiple Systems Atrophy (Gilman, 1999). Both deal with disease entities based on histopatholgical findings which cannot be reliably assessed during lifetime.

With SCA however, even the earlier descriptions of ADCA families (see above) as well as later phenotype-genotype correlations (Bürk 1996) failed to establish clinical diagnostic criteria for different genotypes. First, the symptoms of cerebellar involvement are essentially the same irrespective of genetic or other cause. Second, the distribution of additional symptoms varies only statistically for example between SCA 1, 2 and 3 (fig.). Thus, even educated clinical assessment of an individual patient with ADCA I will often fail to establish the genetic subtype of SCA (Giunti, 1995).

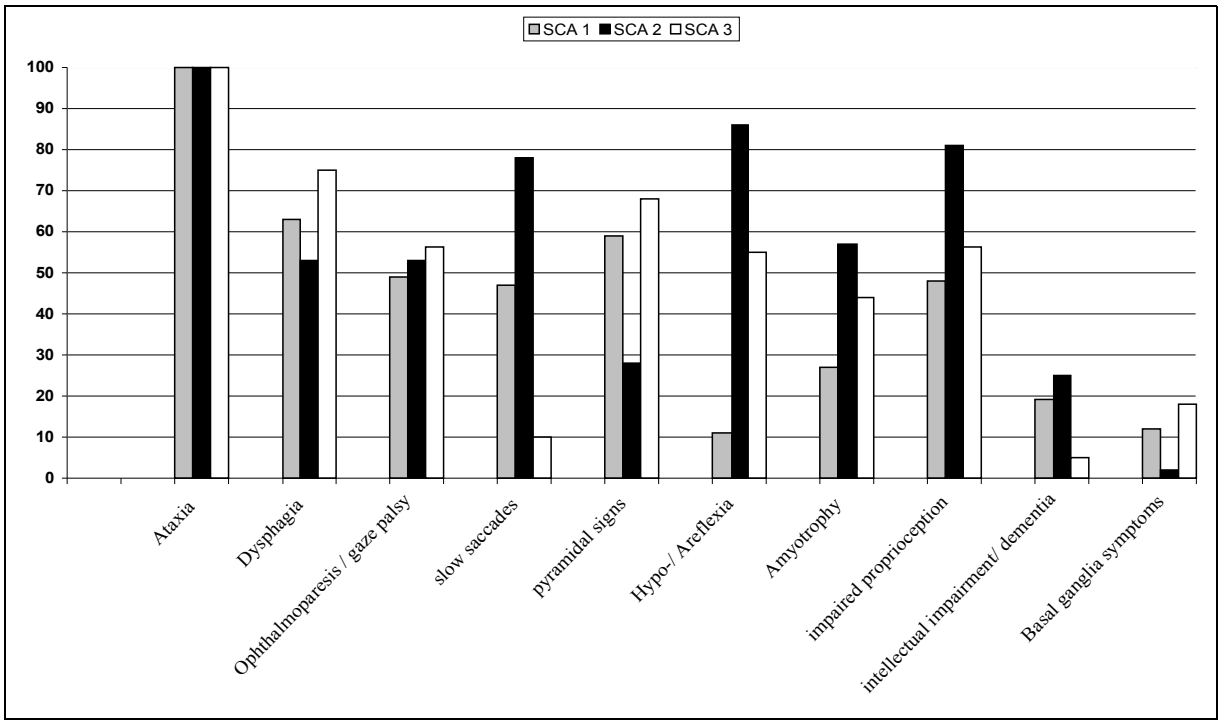

Figure 1: *Reported frequency (in percent of patients examined) of additional findings in spinocerebellar ataxia type 1-3 (adapted from: Klockgether (ed.): Handbook of Ataxia Disorders, 2000)*

Exceptions are SCA subtypes with „pure“ cerebellar ataxia (ADCA III: SCA 6 most frequent, but also 5, 14, 16) or more pathognomonic combinations of symptoms like ataxia with retinal degeneration (SCA 7) or ataxia with myoclonus and epilepsy (SCA 10). For the more recently mapped SCA subtypes that have been described with distinct phenotype in single families only, it must be kept in mind that further genetic testing might reveal different phenotypes linked with the same mutation.

In conclusion, given the growing number of different SCAs, the establishment of clinical criteria for genetic subtypes seems not feasable. At the same time, it might be considered somewhat superfluous in a condition that can well be defined on a genetical basis. The type of classification used for clinical studies will probably differ from the kind of study: possible markers of disease progression will most probably be evaluated in genetically defined subgroups whereas therapeutic studies might be confined to a more clinically defined

subgroup e.g. ADCA I – depending on the construct of the intervention. In this sense, A.Harding's classification still has some relevance.

However, detailed clinical description of individuals and more so of families with SCA is essential for genetic research in order to detect modifying factors or establish new gene loci associated with disease. In addition, markers of disease progression as well as further epidemiological data are needed for the planning and conduct of clinical trials once molecular research yields putative therapies for SCA. The low prevalence of this disease certainly requires a multi-centric approach for clinical studies.

Thus, standardized clinical assessment of SCA patients, standardized reporting of findings as well as estimates of progression rates and progression predictors are the current focus of the clinical project within EUROSCA:

- A graded standardized clinical assessment („rating scale") has been developed for use in SCA patients. A large two-step validation trial in 316 patients has been performed in cooperation of 11 European centers. The eight-item Scale for the Assessment and Rating of Ataxia (SARA) has good metric properties and inter-rater reliability, is easy to use and seems a promising outcome measure for future clinical trials (Schmitz-Hübsch et al., in press).
- A large multi-center longitudinal study has started in August 2005 in 13 European centers. To date, nearly 400 symptomatic patients with genetically diagnosed SCA1, SCA2, SCA3 or SCA6 (i.e. the most common forms in Europe) will be followed for 3 years with assessment of SARA, functional measures, treatment and co-morbidity. The main aim is to prove sensitivity to change of our ataxia scale (SARA). In addition, data will allow to study the variance and predictors of progression rate and thus, power calculations for future clinical trials. Furthermore, relevant epidemiological data will be obtained in this largest cohort of SCA patients.
- A common database has been developed in which affected patients/family members are registered in connection with basic clinical and genetic data. This database no contains over 2000 entries and is used for correlation analyses to reveal further disease-associated genes in ADCA of yet unknown genetic cause and promote studies of modifying factors in known SCA subtypes. It will also be useful for feasability check and recruitment of patients in future clinical trials.
- Other clinical subprojects deal with different progression markers (MRI, electrophysiology), the reliability in reported age at onset of symptoms and incidence and impact of falls in SCA patients.

How to assess a patient with SCA?

In the majority of cases, the history reveals cues suggestive of ADCA:

- Positive family history
- Adult onset with complaints suggestive of cerebellar disease like unsteadiness of gait, poor balance standing, falls, blurred vision or double vision, slurred speech, difficulty in limb coordination but also unspecific complaints like cramps, numbness, restless legs, clumsiness, tremor, dysphagia.
- Slow progression of symptoms

Exceptions are „sporadic“ cases due to early death of then pre-symptomatic parent, especially in late-onset disease like SCA 6, false fatherhood or family history not informative.
Assessing the age at onset in a patient is a challenge and can be considered a destillation from different sources: patient, relatives/ carers, previous medical reports. For research purposes, the time-point of first subjective impairment might not always be the most appropriate.

The clinical assessment of a SCA patient should try to yield a full description of signs and symptoms and weigh their contributions to functional impairment. Thus, assessment always includes a full neurological exam. Within the clinical project of EUROSCA, we therefor constructed a Scale for the Assessment and Rating of Ataxia (SARA) that ist supplemented by an Inventory of Non-Ataxia Symptoms (INAS).

The assessment of ataxia:

Cerebellar dysfunction results in a specific incoordination of movement called ataxia (*ancient Greek: absence of order*).
Ataxia can affect different parts of the body to different extents. This can be assessed in different functional tasks as listed below along with the typical findings in cerebellar ataxia.

	Clinical test	**Findings**
Postural control	1)**Stance**, narrow base	**Sway**, enhanced on narrow basis (tandem stance or standing on one foot)
	2) **gait,** tandem gait	**Broad based** stance and gait, more difficult on tandem walk Staggering and difficulties turning
	3) truncal control in sitting	**Falling,** decreased postural control during arm movements

Control of limb movement arms /legs	1) **alternating movements** 2) fast pointing movements (**finger chase**) 3) sustaind movements (**finger-nose test, line drawing**) 4) handwriting	**Dysdiadochokinesia:** Reduced fluency/ rhythmicity of alternating movements **Dysmetria:** Inaccuracy of pointing with over-shoot/ under-shoot **Decomposition:** (jerky) deviations from the movement trajectory **Action tremor:** Oscillating/ rhythmic lateral deviations from the movement trajectory, often enhanced towards the end of the moevement
Control of eye movement	1) Fixation 2) Smooth pursuit 3) Reflexive saccades 4) Vestibulo-ocular reflex 5) Fixation-suppression of vestibulo-ocular reflex (VOR)	**Spontaneous** (down-beat) **nystagmus** **Square wave jerks on fixation** **Gaze-evoked nystagmus** **Saccadic broken-up pursuit** **Hypermetric/ hypometric saccades** **Reduced fixation-suppresssion of VOR**
Control of speech	conversation, test syllables (assessing coordination of diaphragm vocal cord tongue)	Slurring, reduced clarity Reduced fluency **Cerebellar dysarthria**: Incoordination of volume/breath interruptions Dysdiadochokinesia of the tongue

Ataxia is variable with

- complexity of the task
  Standing with arms outstretched/ feet in tandem or on one leg will be more sensitive to detect mild ataxia than spontaneous stance. The same is true for gait (tandem walk) or postural control in sitting (knees together and arms outstretched).
- performance speed
  This is most relevant when testing limb ataxia. It has to be kept in mind that ataxia patients will often and unconsciously compensate for dysmetria/ dysdiadochokinesia by slow task performance. Then, only attempts of faster performance will reveal these signs (or otherwise slowing itself can be taken as a sign of incoordination). The opposite can be true for decomposition/ action tremor that can be less pronounced in fast performance. Accordingly, only attempts of slower performance will reveal these signs.
  A „dysmetria turning point“ has also been shown in healthy persons, which means that the accuracy of movement gets worse when performance speed exceeds an individual limit (Giovannoni, 1999). This has also been called the speed-accuracy trade-off.

- attention/ exercise
  Attention contributes to variability and might lead to worse ratings in patients with intellectual impairment or a tired patient. In the contrary, some patients will perform better with repeated performance. Thus, assessment of ataxia should be based on several repetitions of each test item.
- visual control
  Excluding visual control can lead to deterioration of cerebellar ataxia, but this effect is non-specific and has been shown to occur to the same extent in healthy persons (Baloh, 1998). That is, e.g. positive Rombergism does not exclude cerebellar ataxia and as such does not add to diagnostic specificity. However, standardized follow-up should consider these effects and specifiy conditions for testing.
- severity of extra-cerebellar symptoms
  Spasticity, dystonia or sensory disturbance can all affect test performance even in the above-mentioned clinical tests for cerebellar ataxia. The assessment of cerebellar/ extra-cerebellar contributions to the impairment in test performance can be difficult to distinguish. The same applies to eye movement coordination: if during the course of disease a patient develops brain stem/supranuclear disturbance of eye movement (slow saccades, gaze palsy, ophthalmoparesis) it might become impossible to identify the genuine cerebellar disturbance of gaze evoked nystagmus, saccadic overshoot or deficits in smooth pursuit.

Clinical assessment can be complemented by technical tests looking for the same phenomena. Posturography or kinematic analysis of gait, timed tapping, pegboard test, computerized assessments of upper limb ataxia as well as electronystagmography have been helpful to delineate the nature of cerebellar disturbance. However, their use as progression markers in this disease has never been established.

The assessment of non-ataxia symtpoms:

It is important to look for signs and symptoms that indicate extra-cerebellar involvement. Some of these respond to symptomatic treatment:

spasticity
paresis
extensor plantar response
hyperreflexia
decreased or absent tendon reflexes
sensory loss, might be confined to single qualities (vibration sense, thermaesthesia)
myatrophy
fasciculations

cramps
restless legs syndrome
dystonia
bradykinesia
rigidity
„non-cerebellar“ resting tremor
chorea
myoclonus
epilepsy
cognitive impairment
behavioural abnormalities
„bulbar speech“
dysphagia
„extra-cerebellar“ oculomotor signs (saccadic slowing, gaze palsy, reduced optokinetic nystagmus, external ophthalmoparesis)
autonomic dysfunction (urinary dysfunction, sphincter disturbance, orthostatic dysregulation, sleep disturbance)

Again, quantified testing can be helpful prove and follow-up some of these symptoms, for example electrophysiology for the assessment of the sensorimotor system, electro-oculography, MRI or radioligand methods to establish distribution of brain regions involved, neuropsychological testing for the assessment of cognitive disturbance or screening tests for psychiatric co-morbidity. Both MRI volumetry and ENG are part of our protocol of the ongoing study on the natural progression of SCA to evaluate their use as progression markers for clinical studies.

However, if used as outcome measures, technical findings have to be correlated with clinical findings. Thus, a comprehensive, practicable, valid and reliable graded clinical assessment of the patient with SCA is a prerequisite for all further clinical reasearch in that patient group.