Electrophysiology in spinocerebellar ataxia

Diagnostic value and progression marker

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Spinocerebellar ataxia (SCA) is the collective term introduced by the genetic classification to autosomal dominantly inherited cerebellar ataxias. SCA comprises a clinically and genetically heterogeneous group of neurodegenerative disorders with ataxia as key symptom (for review see Schöls et al. 2004). SCA does not necessarily mean that degeneration involves the spinal cord or is restricted to spinocerebellar systems. Some SCA subtypes are restricted to pure cerebellar degeneration (e.g. SCA6) while others spread to pontine nuclei, basal ganglia, retina, cerebral cortex, spinal tracts or peripheral nerves (Figure 1).

Earlier pathoanatomical classifications tried to categorize variability of neurodegeneration in SCAs by introducing terms describing spread of pathoanatomic changes like cerebellar cortical atrophy (CCA), olivopontocerebellar atrophy (OPCA), spinocerebellar atrophy (here meant as a pathological description not as a collective term for the whole group), dentatorubral atrophy or spinal ataxia (Greenfield 1954). This neuropathological classification fell through because of its restricted applicability post mortem and, even more important, because of the variability of the diseases leading to different classification (e.g. as CCA, SCA or OPCA) of the same disorder (e.g. SCA3) sometimes even within the same family.

Molecular genetics facilitates a precise, cheap and early (even prenatal) diagnosis and a classification linked to the molecular cause of the disease and thus to pathophysiology and – hopefully in the not too far future – causal therapy. However, genetic classification is not interested in phenotypic and clinical aspects of the diseases.

Thorough clinical characterization of the phenotype is mandatory i) to direct genetic analyses (Figure 1) and enable a cost-saving genetic diagnosis and ii) to analyze complex clinical pictures and introduce symptomatic treatment alleviating Parkinsonian features, dystonia, spasticity, bladder dysfuntion, sleep disturbance or peripheral neuropathy and iii) to monitor the course of the disease. In this sense, neurophysiological investigations are used in SCA to search for spreading of the disease to non-cerebellar systems, to guide direct genetic testing and as potential progression markers for therapeutical trials in the future.

Nerve conduction studies

Most SCA subtypes show an involvement of the peripheral nervous system. Sensory or sensory-motor neuropathy is found in about half of patients with SCA1, in 80% of SCA2

patients and in 75% of patients with SCA3. In SCA6 up to 60% show mild sensory-motor neuropathy whereas nerve conduction studies are normal or at most mildly abnormal in patients with SCA7 *(Schöls et al. 1997; Kubis et al. 1999; van de Warrenburg2004)*.

Neuropathy is almost always of axonal type but nerve conduction velocities are slower in SCA1 than in other subtypes (Schöls et al. 1997; *Kubis et al. 1999*). Clinical presentation of neuropathy may be predominantly motor or sensory but at least in the most frequent subtypes in Europe (SCA1, SCA2, SCA3 and SCA6) electrophysiology discloses involvement of both sensory and motor fibers as a rule. Pure sensory neuropathy has been reported for SCA2 and SCA4 and may affect arms more severely than legs in SCA2 (*Flanigan et al. 1996;* van de Warrenburg et al. 2004).

Severity of peripheral neuropathy is highly variable. E.g. in late-onset forms of SCA3, neuropathy may dominate the clinical picture and complaints of patients whereas e.g. in SCA6 it may be subclinical and is detected by nerve conduction studies and electromyography only (Figure 2). SCA4, SCA18, and SCA25 are reported to develop prominent neuropathy. However, these data rely on few families and e.g. for SCA4 a family with "pure" cerebellar ataxia has been described, recently (*Flanigan et al. 1996;* Brkanac et al. 2002; Stevanin et al. 2004; Nagaoka et al. 2000).

In SCA3 the factors determining neuropathy have been analyzed. A cross sectional study using multivariate regression analysis demonstrated that the degree of peripheral damage does not depend on CAG repeat length, age at onset or disease duration but develops in an age-dependent manner with a faster annual decline of compound muscle action potentials (CMAP) and sensory nerve action potentials (SNAP) in patients than in controls (Klockgether et al. 1999). Anyway, longitudinal studies are still missing.

Little is known whether peripheral nerve involvement in SCA is typical length-dependent neuropathy rather than primary neuronopathy due to degeneration of motor neurons in the anterior horns and dorsal root ganglia.. The only study addressing this issue found evidence of both neuropathy and neuronopathy without clear differences between genetic subtypes (van de Warrenberg 2004).

Motor evoked potentials

Motor evoked potentials (MEP) help to analyze central motor pathways. SCA1 can be differentiated from other subtypes in that central and/or peripheral motor conduction time (CMCT / PMCT) is substantially prolonged. E.g. PMCT > 18ms and CMCT > 10ms to the first dorsal interosseus muscle are highly suggestive of SCA1, whereas SCA2, SCA3 and

SCA6 show at most mildly prolonged conduction times (Figure 2). Using these criteria, MEP can be used to predict the underlying genotype in undiagnosed SCA families and to save costs in genetic analyses for SCA1 (Schöls et al. 1997).

Furthermore, TMS revealed changes in motor cortex excitability with an elevated motor threshold in SCA1 and reduced intracortical fascilitation in SCA2 and SCA3 (Schwenkreis et al. 2002).

Visual, auditory and somatosensory evoked potentials

Abnormalities in visual evoked potentials (VEP) were observed in 78% of SCA1 but in only 36% of SCA2 and 25% of SCA3 patients (Abele et al. 1997). In SCA7 VEP showed poorly formed or absent potentials with normal or only mildly increased latencies (Enevoldson et al. 1994).

Brainstem auditory evoked potentials (BAEP) were abnormal in 50% of SCA1, 42% of SCA2 and 63% of SCA3 patients and affected to similar frequencies wave I, III, V and interpeak latencies indicating affection of all parts of the auditroy pathway in all genetic SCA subtypes.

Somatosensory evoked potentials (SEP) after tibial nerve stimulation are frequently abnormal in SCA1 (75%), SCA2 (69%) and SCA3 (87%). However, only results of cortical recordings have been reported and do not allow differentiation of peripheral or central damage of somatosensory pathways (Abele et al. 1997).

In general, abnormalities in evoked potentials in SCA comprise loss of amplitude as well as prolonged latency. The increase in latency is thaught to be attributed to the loss of fast conducting nerve fibres in central pathways with associated slowing of conduction, however detailes neuropathological studies of visual, auditory or somatosnesory pathways are missing.

Electrooculography

Oculo-motor abnormalities in SCAs have been studied by electro-oculography. Positioning downbeat nystagmus, coarse horizontal gaze-evoked nystagmus, poor visual suppression of the vestibulo-ocular reflex and vertical saccade dysmetria are characteristic features of SCA6 (Yabe et al. 2003; Gomez et al. 1997). In contrast, severely reduced saccadic velocity (80-260°/s) and the absence of gaze-evoked nystagmus are typical findings in SCA2 (Figure 3). Mildly slowed saccades (120-320°/s) are also found in SCA1, SCA3 and SCA7 (Bürk et al. 1999; Rivaud-Pechoux et al. 1998; Buttner et al. 1998). Saccade velocity in SCA2 is mainly determined by CAG repeat length and to a lesser extent by disease duration in a cross-sectional analysis. Longitudinal data are missing (Velazquez-Perez 2004).

Electroencephalography

Systematic analysis of electroencephalography (EEG) have not been performed in SCA since genetics allow precise diagnosis and differentiation of subtypes. In our experience apart from mild general slowing no systematic or major abnormalities are seen in EEG in SCA. SCA10 may be an exception where epilepsy has been described in more than 70% of patients and *EEG abnormalities (mainly slow, fused and disorganized activity) in all* patients of Mexican origin (Rasmussen et al. 2001). However, 28 SCA10 patients from Brazil did not present with epilepsy (Teive et al. 2004).

Polysomnographic recording

Sleep disturbances in SCA have been overlooked for a long time. They are most pronounced in SCA3 but also occur in SCA1 and SCA2 *(Schöls et al. 1998; Abele et al. 2001)* . Restless legs syndrome (RLS) and periodic leg movements in sleep (PLMS) are the most frequent cause of impaired sleep in SCA (Figure 4). Restless legs are not restricted to patients with peripheral neuropathy and do respond to dopaminergic therapy in most cases. PLMS may occur even with a history negative for RLS and can be demonstrated by polysomnographic analysis that, in addition, may diclose further causes of sleep disturbances like **REM behavior disorder,** central apnoe or chronic obstructive apnoe syndrome *(Friedman et al. 2003)*

Electrophysiological parameters as progression markers

Determinants of abnormal electrophysiological parameters have rarely been analyzed in SCA. Little is known about the influence of genetic or age dependent factors on the development of peripheral neuropathy, sensory and motor pathways assessed by evoked potentials or oculomotor functions. General considerations suggest that the genetically determined disease mechanisms cause early and permanent damage to the nervous system. Since longitudinal studies are missing, it remains unclear, when abnormalities detected by electrophysiological methods start. This may begin at birth or even before birth or later on when the pathogenic process overwhelms potential compensating mechanisms. Similarly nothing is known about progression of electrophysiological abnormalities that may be a linear, exponential or logarythmic process. Anyway, functional relevance, non-invasive recording techniques and high reproducibility make electrophysiological parameters interesting candidates as progression markers in SCA.

Cross-sectional analyses demonstrate age effects on compound muscle action potentials (CMAP) and sensory nerve action potentials (SNAP) in nerve conductions studies in corresponadance with progressive axonal neuropathy. Similarly, decline in VEP amplitudes correlate with age and duration of the disease. However, there is substantial scattering questioning the usefulness of these parameters as progression markers for therapeutical trials. Longitudinal studies in SCA patients as well as in healthy controls are mandatory to clarify this issue and are under way in the European SCA network, EuroSCA, started in 2004.

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Figures

Figure 1: Genotype – phenotype correlations in SCA subtypes. Pure cerebellar ataxias are represented in the red inner circle. For additional signs the most likely genetic diagnosis is shown in the corresponding segment, e.g. for the combination of ataxia and dementia SCA17 should be tested first.

Figure 2: Motor (A) and sensory (B) nerve conduction studies in SCAs demonstrating mild predominantly motor neuropathy in SCA1, predominantly sensory neuropathy in SCA2, motor and sensory axonal neuropathy in SCA3 and no significant neuropathy in SCA6. Huge inter-individual variability in all SCA subtypes as demonstrated by large standard deviations.

Figure 3: Motor evoked potentials in SCA. Central and peripheral motor conduction time is significantly prolonged in SCA1 but not in SCA2, SCA3 and SCA6.

Figure 4: Visual evoked potentials demonstrate reduced amplitudes in SCA1, SCA2 and SCA3 but not in SCA6. Prolonged latencies occur with reduction of amplitudes and are thought to be caused by loss of fast conducting fibres.

Figure 5: Electro-oculography. Massive slowing of horizonal saccades in a typical SCA2 patient compared to a healthy control.

Figure 6: Polysomnographic recording in a patient with SCA3. Periodic leg movements in sleep cause frequent arousals and impair sleep structure.

Spinocerebellar ataxias
Clinical characteristics of genetic subtypes

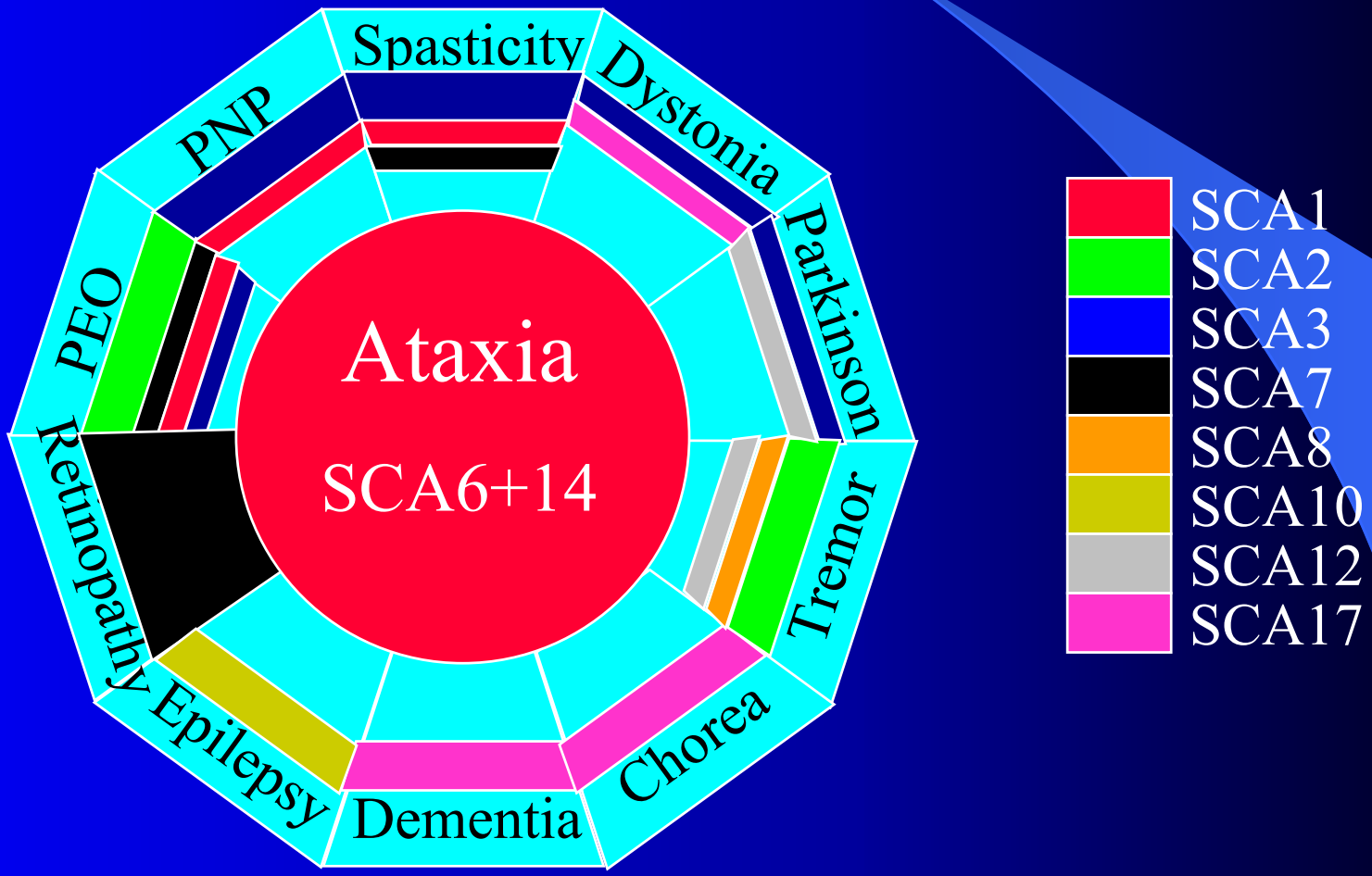
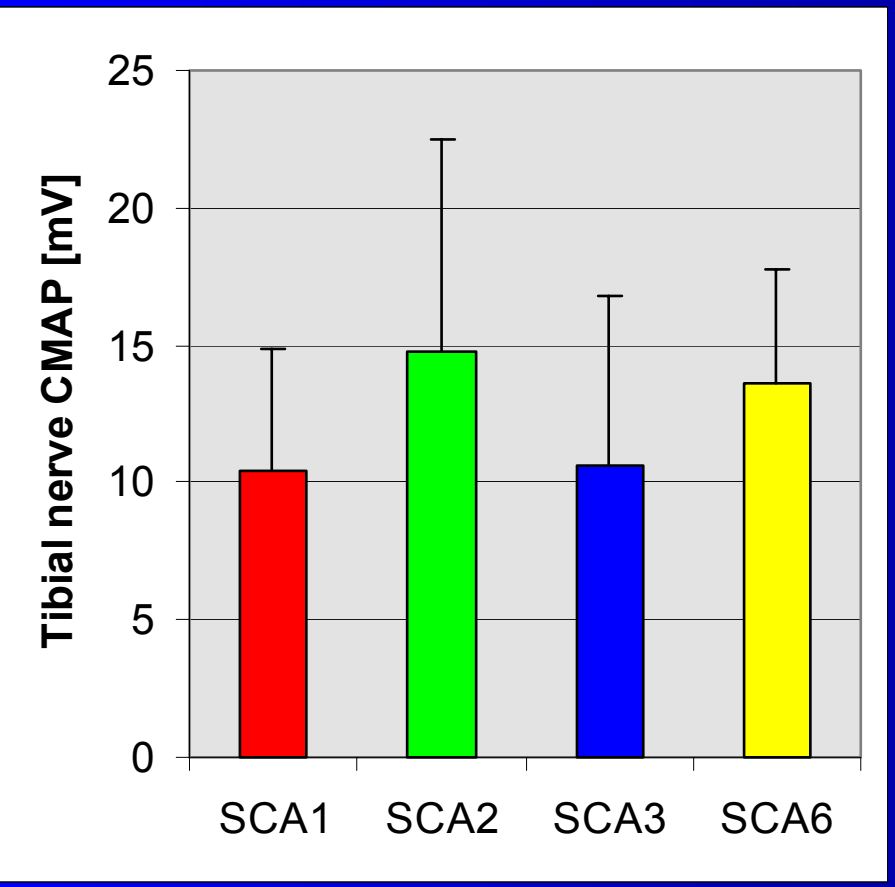


Figure 1

Motor nerve conduction studies in SCA

Axonal neuropathy in SCA1 and SCA3



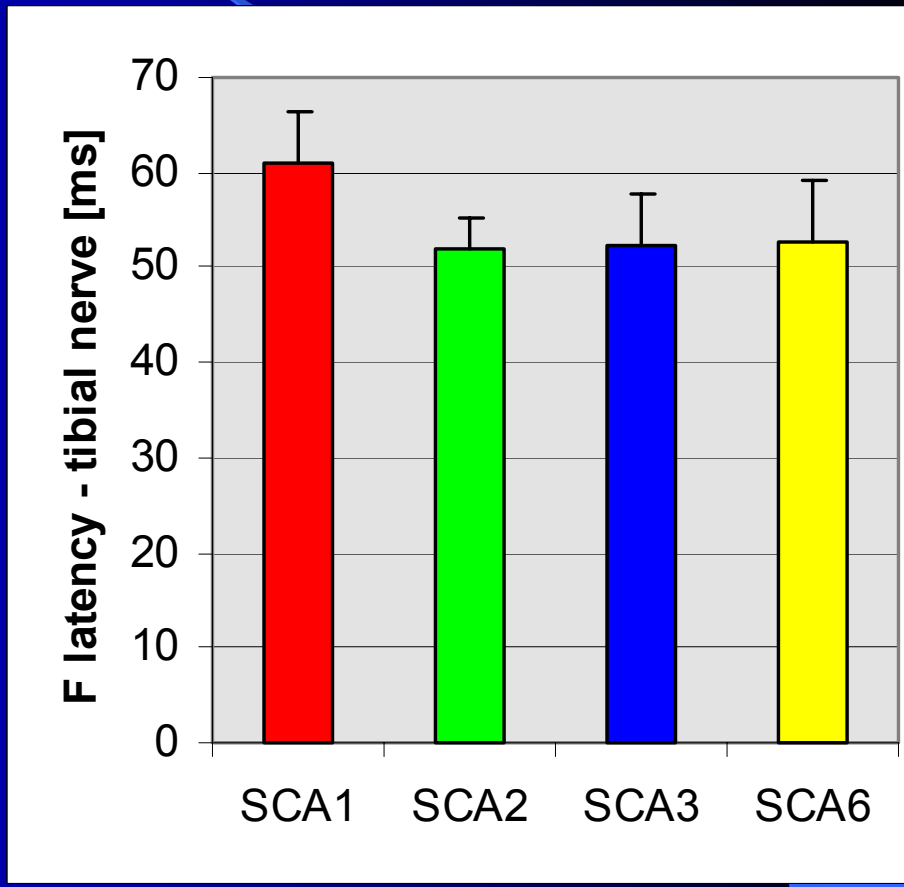
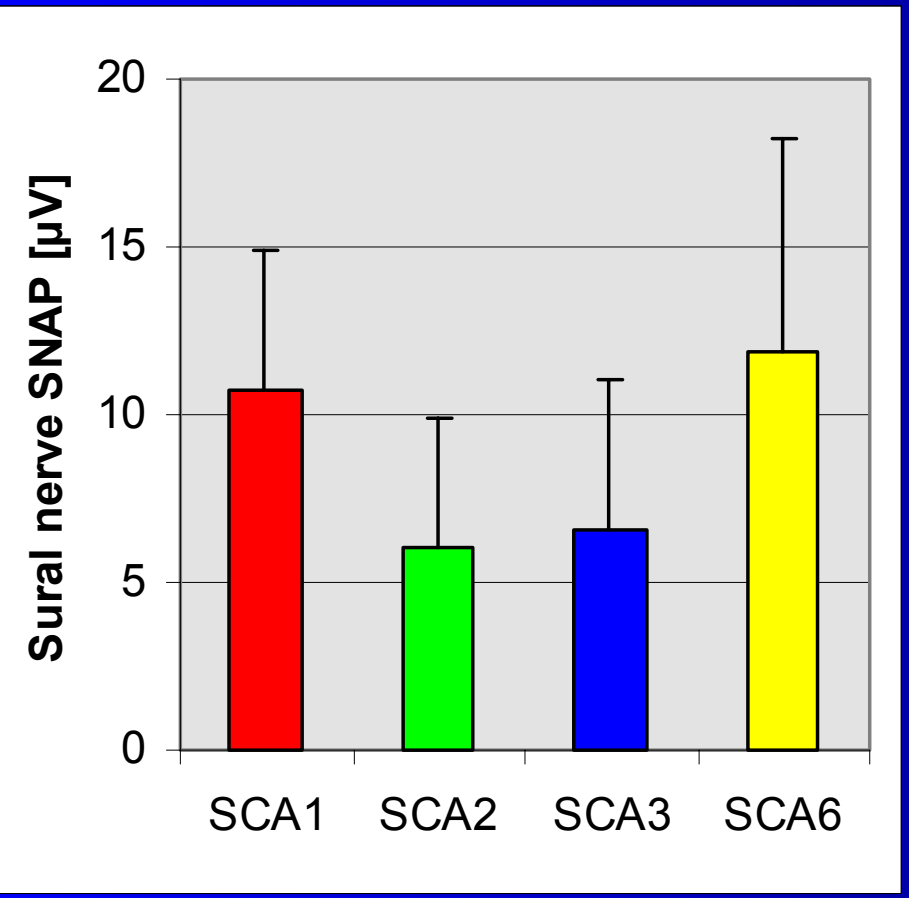


Figure 2a

Sensory nerve conduction studies in SCA
Axonal neuropathy in SCA2 and SCA3



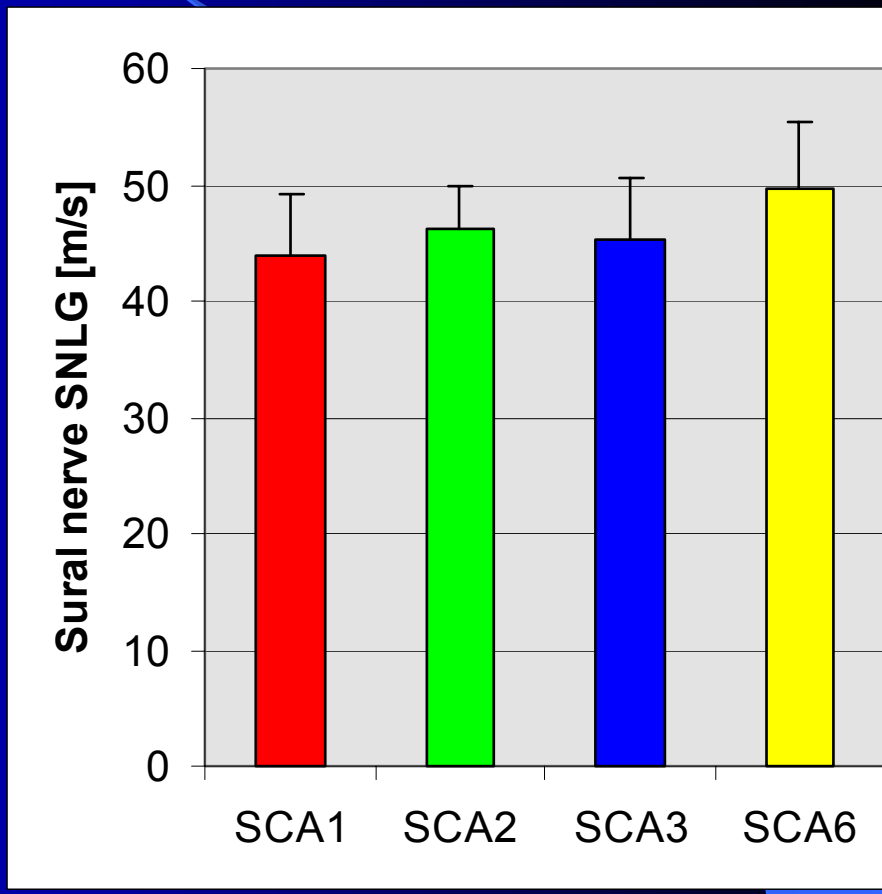


Figure 2b

Motor evoked potentials in SCA

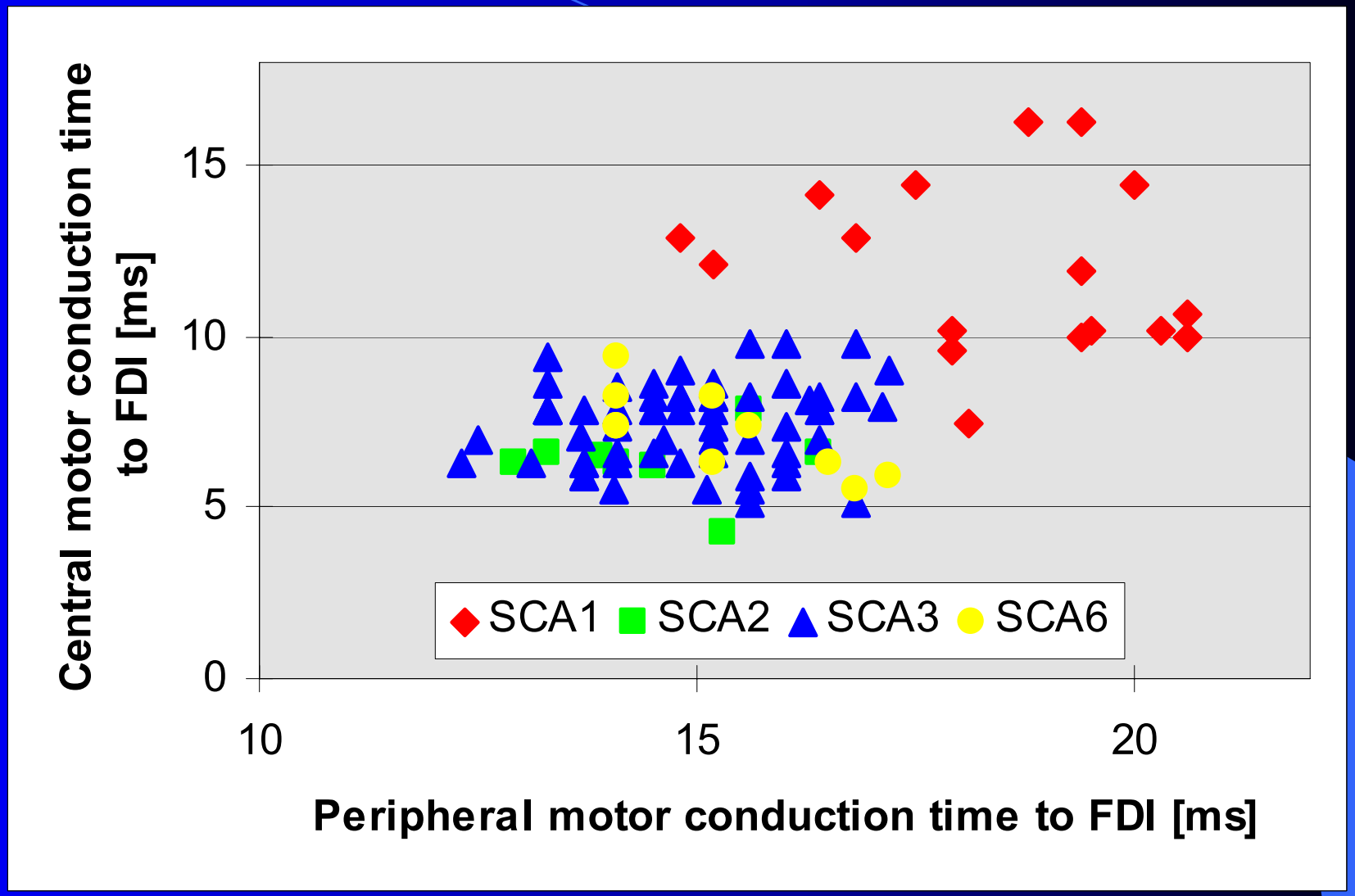
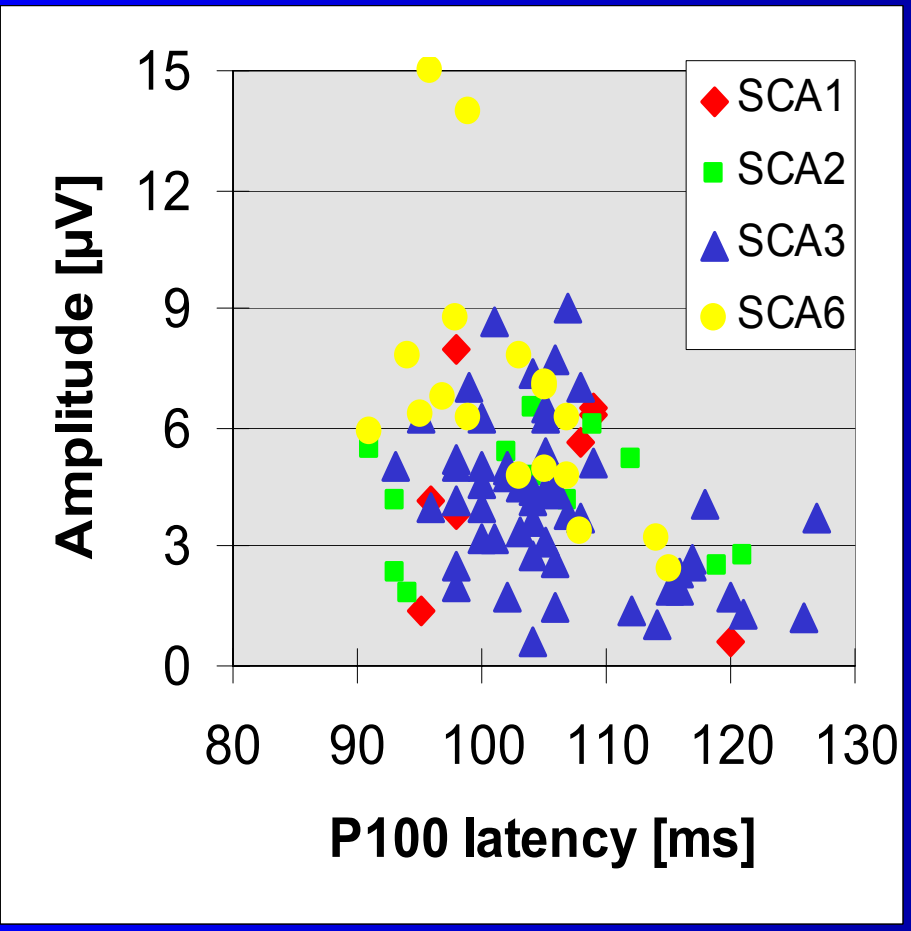


Figure 3

Visual evoked potentials in SCA



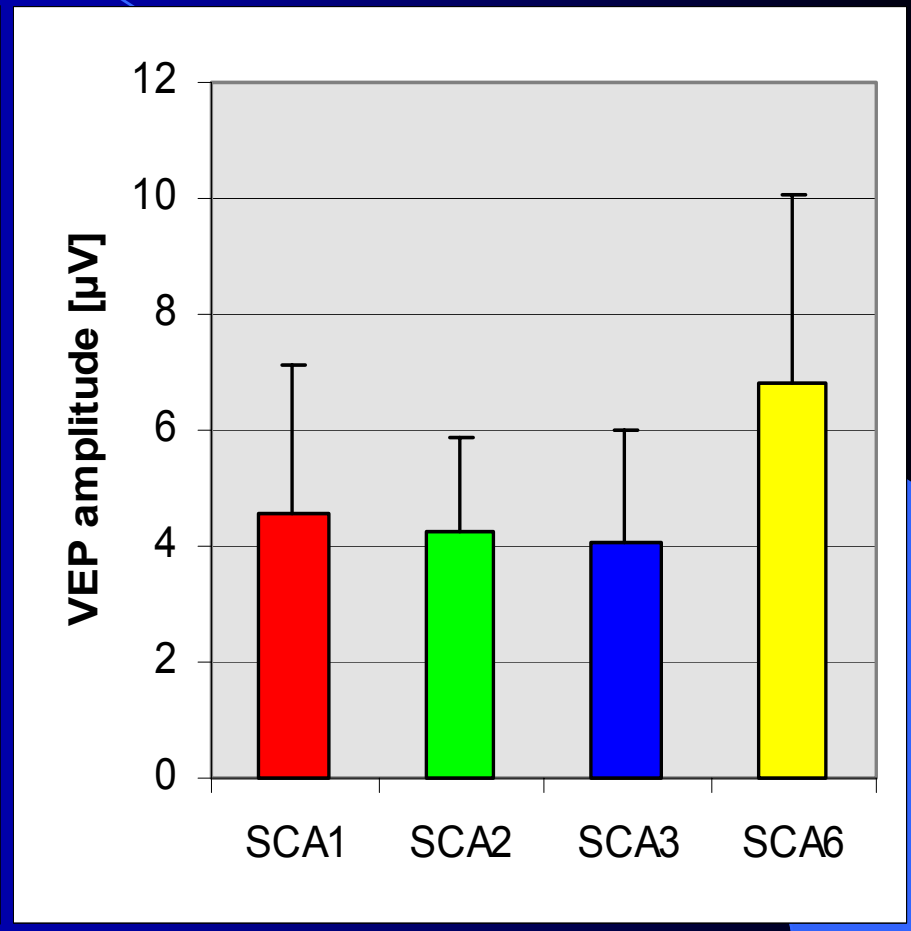
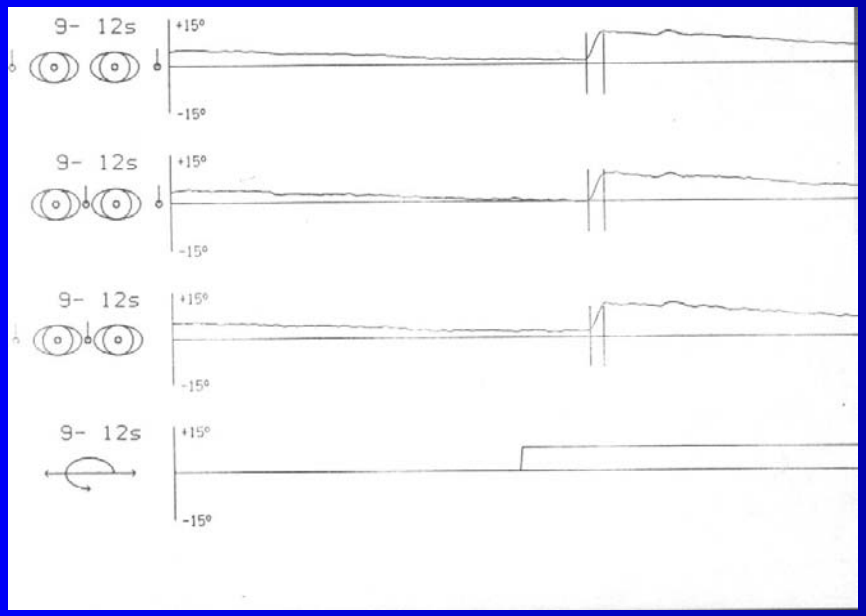
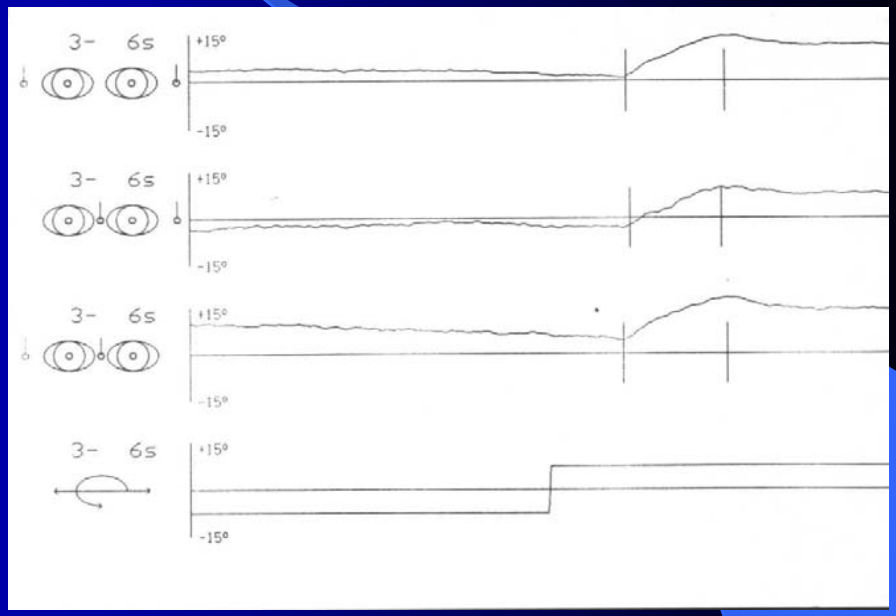


Figure 4

Electro-oculography
Reduced saccadic velocity in SCA2





Healthy control **SCA2 patient**

Figure 5

Polysomnographic recording in SCA3

Periodic leg movements (arrow) cause arousal and impair sleep structure

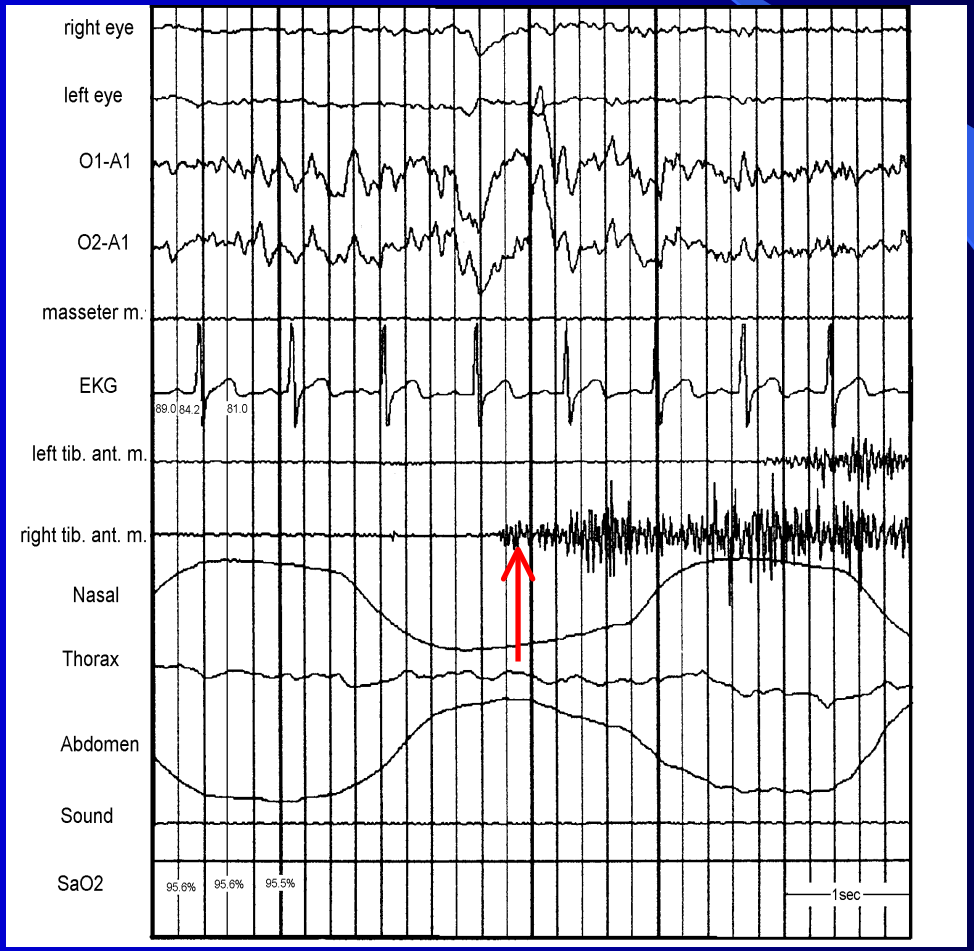


Figure 6