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Electrophysiology in spinocerebellar ataxias: Spread of disease and characteristic findings

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Abstract
Spinocerebellar ataxias (SCAs) comprise a clinically and genetically heterogeneous group of autosomal dominantly inherited neurodegenerative disorders affecting the cerebellum and to variable degrees further parts of the nervous system. Electrophysiology is a potent tool to prove impairment of multiple neuronal systems and fibre tracts and even to decipher subclinical affection. Electrooculography, evoked potentials, nerve conduction studies and polysomnography are especially helpful in the setting of SCAs. Severely slowed saccades are a hallmark of SCA2. Vertical nystagmus occurs most frequently in SCA3 and SCA6. Visual potentials recede especially in SCA7. Substantially prolonged central motor conduction times in motor-evoked potentials occur frequently in SCA1 even in patients without clinical signs of pyramidal affection. Thus, electrophysiological analyses may help to predict the SCA genotype and direct molecular genetic diagnostics. Polymsomnography is a helpful tool in the analysis of sleep disorders and frequently helps to decipher treatable causes like periodic leg movement in sleep and REM sleep behaviour disorder in SCAs. Nerve conduction studies reveal sensory neuropathy in all common SCA subtypes, but to variable degrees. Age rather than CAG repeat length appears to be the most important determinant for neuropathy and makes sensory nerve action potentials a potential progression marker in SCA.

Key words:

Introduction

Autosomal dominant cerebellar ataxias (ADCA) comprise a clinically and genetically heterogeneous group of neurodegenerative disorders affecting the cerebellum. ADCAs are genetically recognized as spinocerebellar ataxias (SCAs) and are divided according to clinical features into three groups. ADCA type III comprises 'pure' cerebellar ataxia. ADCA type II is characterized by retinal degeneration in association with cerebellar disease. ADCA type I subsumes cerebellar degenerations with variable affection of additional parts of the nervous system like optic atrophy, external ophthalmoplegia, extrapyramidal features like dystonia, tremor, myoclonus, chorea or akinetic-rigid syndrome, pyramidal affection, peripheral neuropathy, incontinence, dementia or epilepsy (1,2). Assignment to ADCA subgroups is helpful since prognosis is more favourable in ADCA III than in the other subtypes (3). Additionally, this clinical classification helps to direct genetic diagnosis due to some phenotype/genotype relationships summarized in Table I (4).

Electrophysiology is a potent tool to prove impairment of multiple neuronal systems and fibre tracts and even to decipher subclinical affection (Figure 1). Especially ADCAs I and II frequently present as complex movement disorders that are not easy to analyse for the affected systems by clinical tools only. For example, SCA3 frequently presents with pronounced stiffness and cramps that are very disabling and painful for the patient and hinder sleep. Multisystem involvement in SCA gives rise to many causes for these complaints that respond to distinct treatment like neuropathy, dystonia, parkinsonism, spasticity, and restless legs. Due to the complexity of muscle tone alterations, movement abnormalities, and sensory deficits in SCAs it is not easy to decipher the major players only by clinical examination. Here electrophysiology helps to identify potential targets for symptomatic therapy.

Additionally, electrophysiology is helpful in differential diagnosis as pronounced demyelinization is uncommon in SCAs and points to immunological diseases like multiple sclerosis or neurometabolic disorders like adrenomyeloneuropathy (AMN) mimicking SCA.

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Table I. Genotype phenotype correlations in SCA.

Phenotype	Genotype
ADCA type I:	**SCA1**
Ataxia+dementia, epilepsy, optic atrophy,	**SCA2**
external ophthalmoplegia, extrapyramidal	**SCA3**
features, pyramidal affection, peripheral	SCA4
neuropathy or incontinence	SCA8
	SCA10
	SCA12
	SCA13
	SCA14
	SCA17
	SCA18
	SCA19
	SCA20
	SCA21
	SCA23
	SCA24
	SCA25
	SCA27
	SCA28
ADCA type II:	SCA7
Ataxia+retinal degeneration	
ADCA type III:	SCA5
'Pure' cerebellar ataxia	**SCA6**
	SCA11
	SCA15
	SCA16
	SCA22?
	SCA26

Since SCA can affect almost all parts of the nervous system several standard electrophysiological techniques are likely to detect deviations. Table II lists electrophysiological investigations that are especially helpful in the differentiation of SCA subtypes or in the differential diagnosis of SCAs. Further techniques especially analyses of autonomic dysfunction like sympathetic skin response, heart rate variability and tilt table testing have not been systematically applied in SCA. Electrophysiological findings in the more prevalent subtypes of SCA are summarized in Table II.

Electroencephalography (EEG)

With the exception of SCA10, epilepsy is rare in SCA and in general appears to be not more frequent than in the general population although neuropathological studies described cortical affection in several SCA subtypes. SCA10 patients present with seizures (partial motor seizures, partial complex seizures or generalized tonic-clonic seizures) in about 70% of patients. EEG reveals abnormalities in all patients, most commonly slow, disorganized basal activity with generalized bursts of slow, sharp polymorphic waves (5).

Electrooculography

Electrooculography reveals abnormal eye movements in almost all SCA patients including abnormal smooth pursuit, gaze-evoked nystagmus, dysmetric saccades and impaired optokinetic nystagmus. Whereas these findings indicate cerebellar disease, an decreased gain of the vestibulo-ocular reflex points to an affection of bilateral vestibular neurons or brainstem vestibular pathways. Reduced saccadic

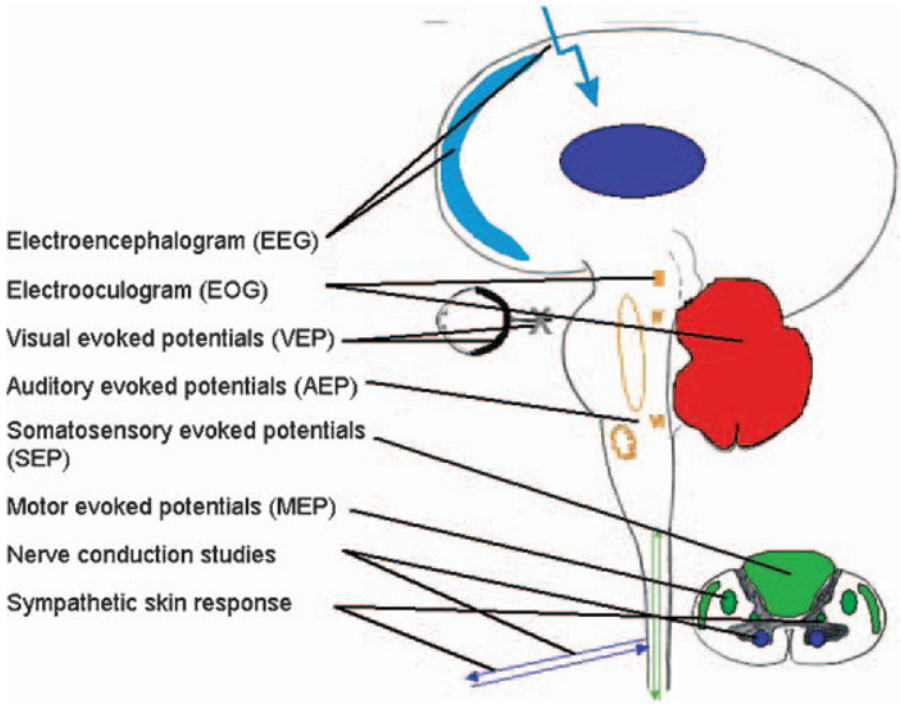

Figure 1. Multisystem degeneration in SCAs and electrophysiological assessment of cortical, retinal, cerebellar, brainstem, spinal, and peripheral affection.

Table II. Electrophysiological findings in more prevalent SCA subtypes. References (6,7,10–15,25,27–31).

	SCA1	SCA2	SCA3	SCA6	SCA7
Nerve conduction studies	Moderate slowing of motor and sensory nerves	Axonal, sensory neuropathy	Axonal, sensory and motor neuropathy+ neuronopathy	At most mild axonal sensory-motor neuropathy	Normal
VEP: Loss of P100	0%	9%	6%	0%	100%
Delayed P100	78%	36%	25%	0%	
AEP abnormal	50%	42%	63%	36% (peripheral damage)	100%
SEP: Loss of P40	100%	46%	27%	0%	
Delayed P40		23%	60%	33%	
MEP: Loss of MEP	24%	9%	0%	0%	
Prolonged CMT	76%	9%	28%	0%	
Electrooculography					
Saccadic slowing:	Moderate	Severe	Mild	Normal	
Gaze-evoked N:	Mild	Missing	Prominent	Severe	
Others:				Downbeat N	
Polysomnography		REM sleep without atonia; Absence of REM sleep	Periodic leg movements in sleep; REM sleep behaviour disorder	Periodic leg movements in sleep	

AEP, Acoustic-evoked potentials; CMT, Central motor conductions time; MEP, Motor-evoked potentials; N, Nystagmus; SEP, Somatosensory-evoked potentials of the tibial nerve; VEP, Visual-evoked potentials.

velocity is indicative of pontine pathology especially in the paramedian pontine reticular formation.

Investigation of saccadic velocity and vertical nystagmus helps in the differentiation of SCA subtypes. Slowing of saccades is most severe in SCA2, moderate in SCA1, mild in SCA3, and absent in SCA6, however, with substantial overlap between groups (6,7). Slow saccades also occur in 55% of patients with SCA7 and may even comprise the earliest clinical finding in otherwise asymptomatic patients (8,9). In SCA2, saccadic velocity is reduced in almost all patients and is determined primarily by the CAG repeat length (10). As in SCA7 slow saccades may be the only presymptomatic finding in subjectively unaffected mutation carriers of SCA2. A longitudinal study investigating saccadic velocity as a potential biomarker of disease progression in SCA2 is on the way.

Gaze-evoked nystagmus is rare in SCA2 probably due to impaired generation of fast components, but is recorded in almost all SCA1, SCA3, and SCA6 patients. SCA6 patients regularly show striking horizontal and vertical gaze-evoked nystagmus, dysmetric saccades, and frequently present with spontaneous downbeat nystagmus (6,11). How saccadic slowing influences saccadic dysmetria is not systematically studied.

Visual-evoked potentials (VEP)

P100 in VEP is frequently reduced in amplitude especially in SCA1 and SCA2 whereas P100 latency is almost normal (Figure 2). Preliminary data of a European consortium studying SCA (EUROSCA) found P100 amplitude to be <3 mV in 18% of SCA1, 12% of SCA2, 3% of SCA3, and 0% of SCA6 patients. Since nystagmus and diplopia is most pronounced in SCA3 and SCA6, the decrease in P100 amplitude is most likely due to affection of the visual system and not because of poor fixation secondary to oculomotor disturbances. In SCA7, abnormal VEP are a hallmark of the disease due to retinal degeneration which goes along with ataxia in this SCA subtype (12). In the differential diagnosis of SCAs, restoration of P100 amplitudes after optic neurit may help to prove demyelination and remyelination in inflammatory disease like multiple sclerosis (MS). In contrast, in neurodegenerative processes like SCA reduction of VEP amplitude is relentlessly progressive. Although prolonged P100 is thought to indicate dysmyelination, P100 latency is a less reliable parameter in the differentiation of SCA and MS; especially in SCA1 but also in SCA2 and SCA3 P100 may exceed 125 ms (EUROSCA study).

Acoustic-evoked potentials (AEPs)

AEPs are frequently abnormal in SCAs. Whereas peripheral damage with loss or delay of peak I also occurs in ADCA III (e.g., SCA6), alterations of peaks III–V (with normal peak I signal) indicate central conduction failure and brainstem affection that questions a pure cerebellar nature of the disease (13,14). In limitation of this statement, ADCAs I, II, and III are not defined by electrophysiological analyses, but by clinical findings.

Somatosensory-evoked potentials (SEP)

SEPs do not strictly correlate with clinical findings but may be abnormal even without sensory deficits in clinical examination. SEP is especially helpful to show impairment of central sensory tracts as it frequently occurs in ADCAs I and II. As such SEP

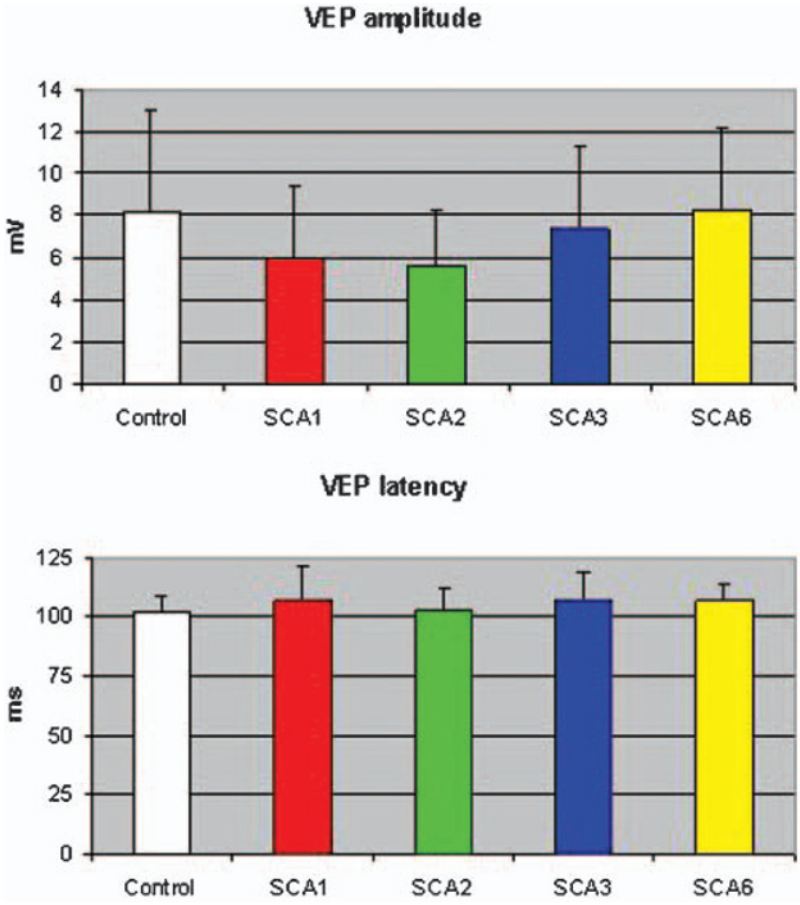

Figure 2. Visual-evoked potentials in more frequent subtypes of SCA.

can indicate afferent deficits that potentially aggravate cerebellar ataxia. Above this no specific changes have been described in SCA subtypes (13).

Motor-evoked potentials (MEPs)

MEPs help to prove subclinical affection of the corticospinal tracts. This occurs especially frequent in SCA1. Almost all SCA1 patients present with prolonged central motor conduction times (CMCT) and peripheral motor conduction times (PMCT) not only to the legs, but also to upper extremities (15). Since MEPs from leg muscles are lost in several cases and do no longer allow determination of CMCT, recordings from hand muscles are predestined to indicate characteristic changes of SCA1. Using magnetic stimulation of the motor cortex and cervical radices, complete differentiation of SCA1 from other genotypes was demonstrated in a large cohort of SCA patients with CMCT to the first dorsal interosseus >10 ms and PMCT >18 ms only in the SCA1 group (14).

Interestingly, whereas slowed motor conduction is the rule in SCA1 patients independently of clinical signs of pyramidal damage, MEPs are frequently normal in SCA3 despite severe spasticity in the clinical examination indicating primarily axonal damage in SCA3. So far morphological equivalents of this different pyramidal affection in SCA1 and SCA3 are missing and await systematic neuropathological studies.

Motor cortex excitability is distinctly altered in SCA subtypes. Recordings after paired pulse stimulation revealed reduced intracortical facilitation in SCA2 and SCA3, whereas SCA1 patients showed increased motor threshold. Silent period and intracortical inhibition were not altered in SCAs (16). Inhibitory effects were only impaired in patients with a lesion at cerebellar efferent or dentatothalamocortical pathways (17).

Nerve conduction studies

Neuropathy in SCA is thought to be of axonal type. In accordance with this view SCA2, SCA3, and SCA6 mostly have normal conduction velocities. In contrast, most patients with SCA1 show mildly reduced nerve conduction velocities in sensory as well as in motor nerves. Whether this reflects a demyelinating component of the disease process in SCA1 or conduction velocity is reduced due to the loss of the fastest conducting fibres is unclear since representative neuropathological studies are lacking.

Amplitude reduction is more frequent in sensory rather than motor nerves and is most pronounced in SCA2 and SCA3 (Table II) whereas SCA6 shows a

milder form of axonal sensory-motor neuropathy (13,14,18). Apart from these more frequent SCA subtypes, pronounced peripheral neuropathy occurs in SCA4 (19), SCA18 (20), and SCA25 (21).

Determinants of peripheral neuropathy have been investigated only in SCA3. According to a cross-sectional analysis of 58 SCA3 patients, age at examination but neither age at onset of symptoms nor duration of symptoms nor CAG repeat length determinate the decline of sensory nerve action potential (22). Presently, nerve conduction is investigated by a European consortium (EUROSCA) in a longitudinal study to decipher determinants of peripheral neuropathy in more SCA subtypes and to analyse nerve conduction parameters as potential biomarkers of disease progression in SCA.

Electromyography (EMG)

In addition to nerve conduction studies, EMG can help to determine floridity of peripheral nerve damage by pathological spontaneous activity. EMG may reveal fasciculation indicating anterior horn cell affection even in patients without clinical signs of lower motor neuron affection. This is more frequently observed in SCA3, but has not been studied systematically and may occur in several SCA subtypes since anterior horn cell loss is also described in post-mortem studies in SCA1 and SCA2 (23,24).

EMG was proposed for the differentiation of proximal and distal affection of motor nerves. In a combined approach of nerve conduction studies and EMG the simultaneous presence of neuropathy and neuronopathy has been demonstrated in SCA3, but to a lesser degree as well in SCA1 and SCA2 (18).

Polysomnography

Many SCA patients suffer from sleep disturbances (25–29). History taking including spouses may help to presume restless legs syndrome (RLS) or REM sleep behaviour disorder (RBD) or sleep apnoe syndrome (SAS). Characteristic history should result in tentative dopaminergic treatment for RLS or determination of oxygen saturation for SAS in an outpatient setting. If sleep disturbances persist, polysomnography is indicated to decipher events preceding awakenings (Figure 3). Periodic leg movement in sleep and restless legs syndrome normally respond well to dopaminergic therapy in SCA, but sometimes need additional treatment like tilidine (25). Clonazepam is efficient in RBD, but should be handled with caution in SCA since it may aggravate ataxia.

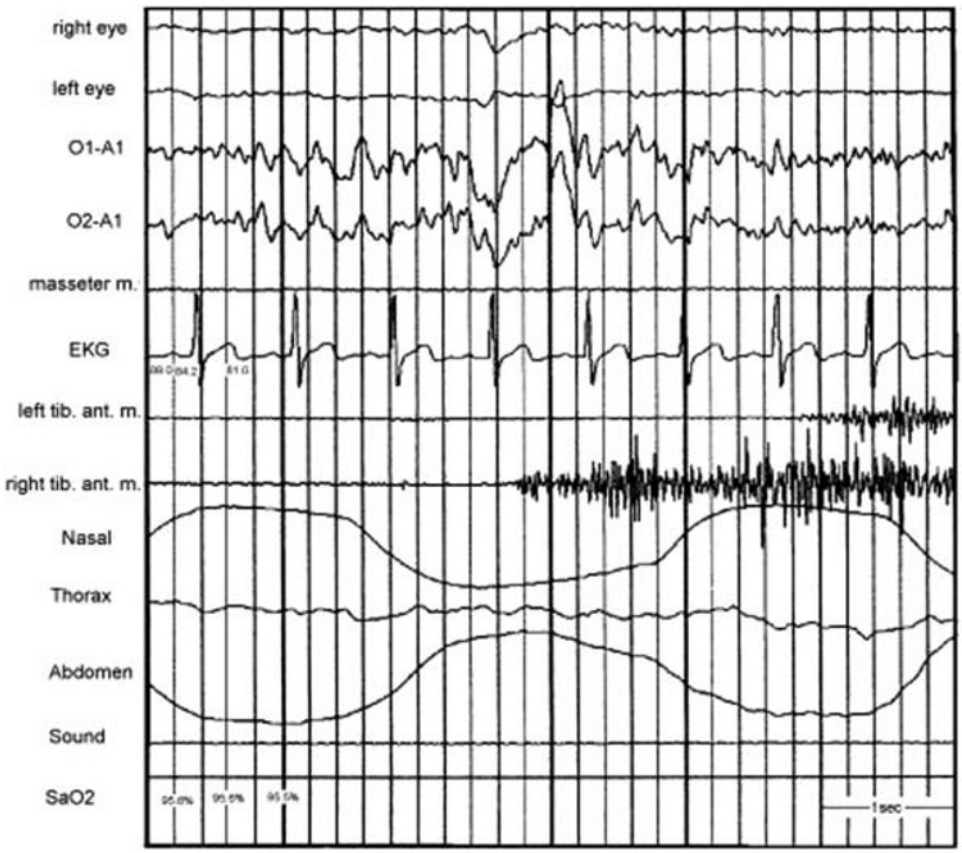

Figure 3. Polysomnographic recording of periodic leg movements in sleep (PLMS) starting in the right tibialis anterior muscle (channel 8) followed by an arousal with K-complex and consecutive alpha activity in EEG (channels 3 and 4).

Table III. Goals for electrophysiology in SCA.

Analysis of clinical pictures
• To disclose subclinical affection
• To discriminate pure cerebellar from multisystemic disease
• To introduce symptomatic treatment, e.g., for PLMS
Characteristic findings suggesting SCA subtype
• To direct genetic analyses
• To save costs in genetic diagnosis
Progression markers essential for therapeutic trials
• To be developed in EUROSCA

Conclusion

In summary, electrophysiology is valuable in SCAs in the analysis of clinical pictures, directing of genetic analyses, and as a potential progression marker (Table III). Additionally, electrophysiology helps to identify potential targets for symptomatic treatment.

Acknowledgements

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