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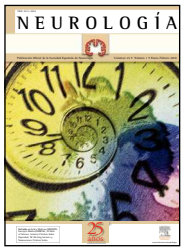

ORIGINAL ARTICLE

Multimodal neurophysiological study of SCA2 and SCA3 autosomal dominant hereditary spinocerebellar ataxias☆

S. Álvarez-Paradelo,[a,*] A. García,[a] J. Infante,[b] J. Berciano[b]

[a] *Servicio de Neurofisiología Clínica, Hospital Universitario Marqués de Valdecilla (IFIMAV), Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Santander, Spain*
[b] *Servicio de Neurología, Hospital Universitario Marqués de Valdecilla (IFIMAV), Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Universidad de Cantabria, Santander, Spain*

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Abstract
Background: The spinocerebellar ataxias (SCA) are a group of genetic neurodegenerative diseases, clinically and pathologically heterogeneous, characterized by slowly progressive cerebellar ataxia.
Objective: To identify the neural pathways affected neurophysiologically, correlate the findings with the size of CAG expansion and determine the contribution of neurophysiological studies in the differential diagnosis of the two most prevalent genotypes in Spain, SCA2 and SCA3.
Method: We examined 10 SCA2 and 12 SCA3 patients by electromyography, electroneurography motor and sensory, multimodal evoked potentials, transcranial magnetic stimulation, blink reflex and masseter reflex. In the statistical analysis linear regression studies were performed, and the Spearman correlation coefficient and nonparametric test U of Mann-Whitney calculated.
Results: We detected the presence of a predominantly sensory neuropathy in most SCA2 patients and in a minority of SCA3 patients; the central somatosensory pathway showed significant defects in both populations. We recorded a high incidence of brain-stem electrophysiological abnormalities in SCA2 patients; in particular, the masseter reflex was abnormal in all SCA2 patients, remaining intact in all SCA3 patients. The study of cortico-spinal pathway showed a greater percentage of abnormalities in both populations than in previous studies.
Conclusion: SCA2 is a model of sensory neuronopathy with central and peripheral axonopathy. Studies of brain-stem pathways show a higher incidence of abnormalities in SCA2 patients. SCA3 patients show major changes in the central somatosensory pathway

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*Corresponding author.
E-mail: doctoraparadelo@hotmail.com (S. Álvarez-Paradelo).

with relative normality of the electroneurography. The masseter reflex was the most useful test in the differential diagnosis between both genotypes.

PALABRAS CLAVE
Ataxia espinocerebelosa;
Electroneurografía;
Potenciales evocados multimodales;
Reflejo mandibular;
Reflejo de parpadeo;
SCA2 y SCA3

Estudio neurofisiológico multimodal en las ataxias espinocerebelosas con herencia autosómica dominante de tipo SCA2 y SCA3

Resumen
Introducción: Las ataxias espinocerebelosas (SCA) son un grupo de enfermedades neurodegenerativas genética, clínica y patológicamente heterogéneo, caracterizado por presentar una ataxia cerebelosa lentamente progresiva.
Objetivo: Identificar las vías nerviosas neurofisiológicamente afectadas, correlacionar los hallazgos con el tamaño de la expansión CAG y determinar la contribución del estudio neurofisiológico al diagnóstico diferencial de los dos genotipos más prevalentes en España, SCA2 y SCA3.
Método: Hemos examinado 10 pacientes SCA2 y 12 SCA3 mediante electromiografía, electroneurografía motora y sensitiva, potenciales evocados multimodales, estimulación magnética transcraneal, reflejo de parpadeo y mandibular. En el análisis estadístico empleamos estudios de regresión lineal, coeficiente de correlación de Spearman y el test no paramétrico "U de Mann-Whitney".
Resultados: Detectamos anomalías compatibles con una neuronopatía sensitiva con axonopatía periférica en la mayoría de pacientes SCA2 y en una minoría de SCA3; la vía somatosensorial central presentó abundantes anomalías en ambas poblaciones. Registramos importantes alteraciones tronco-encefálicas en SCA2; particularmente, el reflejo maseterino estuvo alterado en todos los pacientes SCA2, manteniéndose intacto en los SCA3. El estudio de la vía córtico-espinal demostró un mayor porcentaje de anomalías en ambas poblaciones que estudios previos.
Conclusiones: SCA2 es un modelo electrofisiológico sugestivo de una neuronopatía sensitiva con axonopatía periférica y central. Los estudios de las vías tronco-encefálicas demuestran una mayor incidencia de alteraciones en los pacientes SCA2. En los pacientes SCA3 se observaron importantes alteraciones de la vía somatosensorial central con relativa normalidad del estudio electroneurográfico. El reflejo mandibular fue el test de mayor utilidad en el diagnóstico diferencial de ambos genotipos.

Introduction

Cerebellar ataxias with autosomal dominant transmission are a group of neurodegenerative diseases characterized by slowly progressive cerebellar ataxia as the main symptom, caused by the degeneration of the cerebellum and its afferent and efferent connections. In most families, clinical and pathological evidence has been detected of involvement of other structures in the nervous system such as the extrapyramidal system, the oculomotor nerves, the peripheral nervous system and spinal cord.[1] Recent molecular genetics studies have detected that the most frequent molecular defect is a dynamic expansion of the CAG triplet encoding for polyglutamine tracts,[2,3] locating 30 different *loci*[4] designated with the term "spinocerebellar ataxia" (SCA1 to SCA30).

The prevalence of SCA varies from one country to another, with a predominance in Spain of genotypes SCA2 and SCA3.[2,5] The main goal of our study has been to identify neurophysiologically the altered nerve pathways, to establish the correlations of the neurophysiological alterations observed with the underlying expansion size (CAG) and to determine the possible contribution of the neurophysiological study to the differential diagnosis of genotypes SCA2 and SCA3.

Patients and method

Patients with clinical signs of late-onset cerebellar ataxia were studied if their genetic study had shown the existence of the underlying mutation for SCA2 and SCA3. In addition, the members of the propositus's family were studied if they presented the mutation, either as asymptomatic or symptomatic carriers. For details of the molecular study, we would refer the reader to the reference by Infante et al.[5] The study was approved by the Cantabrian Ethics Committee.

In short, 10 patients (7 females and 3 males) from 6 unrelated SCA2 families were studied. They had a mean age at the time of the study of 48.3±12.7 years and a mean duration of the illness of 9.8±4.3 years. Another 12 members (3 females and 9 males) from three unrelated SCA3 families were also studied. They had a mean age of 43.6±11.7 years and a mean duration of the illness of 7.3±5.8 years at the time of the study.

No statistically significant differences were found between both populations for either the mean age or mean duration of their illness ($p>0.05$).

Electromyography

This was carried out using concentric needle electrodes inserted into the muscle belly of the *tibialis anterior* (TA) to record motor unit potentials, of which we analyzed duration and morphology. In addition, spontaneous muscle activity and the maximum stress pattern were also recorded. Electromyographic recordings of the facial muscle was only done in two of the SCA2 patients with clinical myokymias.

Electroneurography

The medial and peroneal nerves were studied by stimulation at different points along their route using bipolar surface electrodes to record the motor potentials with surface electrodes with the active electrode on the muscle belly and the reference electrode on the tendon insertion. We analyzed the amplitude of the motor potential, distal motor latency (DML), the motor conduction velocity (MCV) and the minimal latency of the F waves. We took the values presented by Preston and Shapiro[6] as normal.

The orthodromic recording method was used to study the sensory component of the medial nerve, whereby the sensory potential was recorded proximally to the electrical stimulus. The stimulator used comprised to flexible ring electrodes that adapt to the perimeter of the fingers (one and three), locating the anode on the distal knuckle and the cathode 2 cm more proximal. We only used the antidromic recording method to explore the sural nerve, with the sensory potential being recorded behind the external malleolus in response to an electrical stimulus (distal cathode) applied 14 cm proximally to the recording electrode. The sensory potential in both nerves was recorded with surface electrodes and the parameters studied were the peak to peak amplitude of the sensory potential and the sensory conduction velocity (SCV).

For the sensory potentials in the medial nerve, we took the normal values obtained at our laboratory, whereas for the sural nerve we used those presented by Preston and Shapiro.[6]

Somatosensory evoked potencials

These were obtained by stimulating the medial nerve in the wrist by placing the recording electrodes in the contralateral postrolandic area (positions C3'/C4') and in the cervical region (Cv7) with the reference in the frontal region (Fpz). Somatosensorial evoked potentials (SSEP) on the posterior tibial nerve were obtained by stimulating this nerve behind the internal malleolus, recording the response 2 cm posterior to the cerebral vertex (position Cz'), and also with a cephalic reference (Fpz). We analyzed the latency and amplitude of the different components, as well as the central somatosensorial conduction time (CSCT).

We used those presented by Chiappa[7] as normal values.

Magnetic stimulation

Motor evoked potentials (MEP) were obtained by transcranial magnetic stimulation (TMS), using Magstim equipment (Model 200 with a 90 mm high power coil), on the motor cortex, the cervical and lumbar region with recording using surface electrodes located on the *abductor pollicis brevis* muscles (APB) on the upper limbs and the *extensor digitorum brevis* (EDB) or TA on the lower limbs, at rest. We analyzed the absolute latency of the MEP and the central motor conduction time (CMCT) by the F wave method described by Rossini et al.[8]

We used the technique and the normal values obtained at our laboratory and presented by Calleja et al.[9]

Visual evoked potentials

These were recorded in the occipital areas (O1, Oz and O2) with the reference at Fz stimulating both eyes independently with a checkerboard screen (pattern VEP). We analyzed latency and amplitude of the P100 wave.

We have taken the normal values presented by Chiappa[7] as our reference.

Auditory evoked potentials

These were obtained by applying an acoustic stimulus at 80 dBnHL of intensity with the response recorded on the earlobe lead of the ipsilateral ear (A1/A2)-vertex (Cz). We analyzed the absolute and peak-to-peak latencies of the different components in the response.

We have taken the normal values presented by Chiappa[7] as our reference.

Blink reflex

This was obtained by stimulating the supraorbital nerve where it emerges through the lateral frontal orifice. The recording was made simultaneously using surface electrodes located on both *orbicularis oculi* muscles, analyzing the latencies in the R1 and R2 responses ipsilateral to the stimulus and the R2 response contralateral to it.

We have taken the normal values presented by Kimura et al[10] as our reference.

Mandibular reflex

To obtain the mandibular reflex, we used a reflex hammer connected to the amplifier, through which we applied a mechanical stimulus on the chin through an interposed finger of the examiner. The recording was taken using surface electrodes located on the masseter muscle (active: muscle belly; reference: 2 cm below the angle of the jaw) on both sides. We thus bilaterally and simultaneously

Table 1 Sural nerve

SCA	Case	CAG Rep.	Age at debut (years)	Age in study (years)	SCV (m/s)	AMPL (μV)
SCA2	1	37	52	60	45.8	3.84
SCA2	2	35	50	64	43.5	2.98
SCA2	3	41	22	35	43.8	5.98
SCA2	4	41	34	43	42	9.24
SCA2	5	43	28	40	40.9	1.2
SCA2	6	44	23	24	42.7	1.73
SCA2	7	37	28	44	50	2.73
SCA2	9	36	53	59	44.2	1.75
SCA2	10	38	42	51	47.2	4.58
SCA3	11	74	40	48	48.2	7.23
SCA3	12	74	41	46	43.6	7.38
SCA3	13	79	27	38	39.9	6.47
SCA3	14	67	55	68	48.1	7.07
SCA3	15	67	49	65	42.4	9.06
SCA3	16	70	–	39	44.7	8.3
SCA3	17	68	–	35	52.9	19.5
SCA3	18	72	–	33	50	13.6
SCA3	19	71	31	41	42.9	3.96
SCA3	20	71	35	38	48.3	5.98
SCA3	21	71	25	32	53.8	6.39
SCA3	22	71	31	41	48.8	9.7

SCV: velocity of sensory conduction; AMPL: amplitude; –: asymptomatic.

obtained at least 10 consecutive responses. Subsequently, the existence or absence of a reflex response was evaluated along with its latency.

We have taken the normal values presented by Cruccu et al[11] as our reference.

Statistical analysis

We used the SPSS 8.0 statistics package to calculate means, standard deviation and range for all the electrophysiological parameters obtained. Linear regression study and Spearman's correlation coefficient allowed us to determine whether there was any kind of relationship (degree and direction) between the different electrophysiological parameters obtained and the number of CAG repetitions in the underlying mutation, whereas for the comparison of mean values between the two populations (SCA2 versus SCA3), we used Mann-Whitney's non-parametric U test for small samples. In the comparison of proportions, we used the Chi squared test applying Fisher's exact test. Statistical significance was established at a p value of $p<0.05$.

Results

Electromyographic recording of the TA muscle in SCA2 patients revealed normal parameters except for 2 cases (20%) in which a chronic neurogenic pattern was recorded. Furthermore, only 2 SCA3 patients (16%) showed the same pattern in the electromyographic recording of the TA muscle.

Clinically facial myokymias were observed in 6 SCA2 patients (67%) and in one SCA3 patient (8%). The EMG recording of the facial muscles showed spontaneous repetitive discharges of isolated and grouped motor unit potentials with a discharge frequency of 22 Hz, compatible with myokymias in two SCA2 patients.

Electroneurography presented the most relevant anomalies in the study of the sural nerve, the most outstanding being a reduction in the amplitude of the sensory potential in 8 (88%) of the 9 SCA2 patients studied against only 2 (16%) of the 12 SCA3 patients, with normal SCV values (table 1). The statistical analysis only revealed that the amplitude of the sensory potentials in both the medial and sural nerves was significantly lower in SCA2 patients ($p<0.01$). No relationship was found between the parameters obtained and the number of CAG repetitions in the mutation.

The SSEP of the medial nerve presented anomalies in 7 SCA2 patients (77%) and in 5 SCA3 patients (42%), including the absence of some of the components in the response (N20 and/or N13), delayed latencies and an increase in the CSCT (N13-N20). Anomalies in the SSEP on the posterior tibial nerve were detected in 8 SCA2 patients (88%) and 8 SCA3 patients (66%), with the absence or delays in P40 cortical response and/or a reduction in its amplitude being the most noteworthy. All patients with anomalies in the SSEP from the upper limbs also presented anomalies in the response from the lower limbs. The comparative analysis showed that only CSCT was significantly more prolonged in SCA2 patients ($p<0.05$), with no significant differences being found for the rest of the parameters. No relationship was found between the parameters obtained and the size of the expansion.

Table 2 Auditory evoked potentials

SCA	Case	CAG Rep.	Age at debut (years)	Age in study (years)	Auditory evoked potentials					
					Left ear Latency (ms)			Right ear Latency (ms)		
					I	III	V	I	III	V
SCA2	1	37	52	60	2.02	3.89	6.14	1.83	3.92	5.67
SCA2	2	35	50	64	2.3	4.15	6.27	2.15	4.03	7.29
SCA2	3	41	22	27	1.58	3.98	5.48	1.46	3.8	5.4
SCA2	4	41	34	43	1.85	A	5.86	1.69	4.23	5.56
SCA2	5	43	28	31	1.64	3.79	5.41	1.68	3.9	5.31
SCA2	6	44	23	24	1.89	3.72	5.74	2.02	4.15	5.63
SCA2	7	37	28	44	1.47	3.42	5.75	1.95	4.18	6.65
SCA2	8	35	60	60	A	A	A	A	A	6.68
SCA2	9	36	53	59	1.8	4.02	5.61	1.69	3.88	5.87
SCA2	10	38	42	51	1.8	4.2	7	1.65	3.79	6.34
SCA3	11	74	40	48	2.28	4.18	6.26	1.42	3.55	6.3
SCA3	12	74	41	46	1.86	4.41	6.2	2.0	3.61	6.36
SCA3	13	79	27	38	1.74	4.13	6.03	1.87	4.16	5.93
SCA3	14	67	55	68	A	4.29	6	2	4.35	6.27
SCA3	15	67	49	65	1.87	3.83	5.79	1.89	4	5.71
SCA3	16	70	-	39	2.04	4.67	5.98	2.07	4.23	5.81
SCA3	17	68	-	35	1.91	4.36	5.96	1.89	4.09	5.83
SCA3	18	72	-	33	1.99	4.2	5.93	1.75	4.11	5.77
SCA3	19	71	31	41	1.74	3.74	5.71	1.84	3.95	5.74
SCA3	20	71	35	38	2.09	4.28	6.01	1.96	3.99	5.76
SCA3	21	71	25	32	1.88	4.05	6.2	1.9	4.27	6.08
SCA3	22	71	31	41	1.98	4.38	5.88	1.74	4.3	5.86

A: response was absent; –: asymptomatic.

The study of the corticospinal pathway highlighted anomalies in 5 SCA2 patients (55%) and in 3 SCA3 patients (25%), consisting in the absence of MEP in the lower limbs and increases in the CMCT in both upper and lower limbs. No significant differences were found for CMCT between the two populations, nor was there any relationship between these parameters and the size of the expansion.

In the SCA2 patients studied, 5 (71%) presented anomalies in the study of the visual pathway; in three of them, the amplitude of the P100 response was diminished, in one the latency was prolonged and in the other case both anomalies were detected. In SCA3 patients only 2 (16%) presented a diminished amplitude for the P100 wave. Despite this, the comparative analysis did not show any significant differences for the two variables (amplitude and latency) studied. The statistical analysis also failed to show any significant relationship between these variables and the size of the underlying expansion.

The brainstem auditory evoked potentials (BSEAP) presented alterations in 4 SCA2 patients (40%) and in 2 SCA3 patients (17%), including a notable delay in the absolute and/or peak-to-peak latencies in some of the components in the response together with poor repeatability (table 2). However, no significant differences were found between the two populations, nor was there a significant correlation between these variables and mutation size.

In the blink reflex study, anomalies were detected in 6 (67%) of the 9 patients studied with the SCA2 mutation; in 4 of them, the anomalies corresponded to a delay in the latency of the polysynaptic components of the response and in the other two the delay was detected in the direct R1 response. In SCA3 patients, a delay in the contralateral R2 polysynaptic response was only appreciated in 2 patients (17%) (table 3). No significant differences were found, however, between the two populations for the latencies of the different components in the reflex arch.

Finally, the mandibular reflex was pathological in all 9 SCA2 patients (100%) studied; no reflex was obtained in 8 of them and the other one gave a diminished amplitude response (< 0.1 mV) and bilaterally prolonged latency (11.1 and 11.2 ms). On the other hand, all 12 SCA3 patients examined (100%) presented a normal mandibular reflex (latency<10 ms) (table 4). The comparative analysis of the proportions between both the SCA2 and SCA3 populations showed a significant difference ($p<0.001$).

Discussion

In most of the SCA2 patients, we observed electrophysiological signs compatible with a sensory neuronopathy with peripheral axonopathy. These results coincide to a large

Table 3 Facial nerve and blink reflex

SCA	Case	CAG Rep.	Age (years)		Facial nerve				Blink reflex					
					DML (ms)		Amplitude (mV)		Left supraorbital			Right supraorbital		
									Latency (ms)			Latency (ms)		
			Debut	Study	Left	Right	Left	Right	R1	R2i	R2c	R1	R2i	R2c
SCA2	1	37	52	60	3.2	3.1	1.06	1.55	11	40.1	44.8	10.2	37.3	42.4
SCA2	2	35	50	64	3.8	2.8	0.68	0.52	11.7	38.6	47.2	8.8	39.3	34.8
SCA2	3	41	22	35	4.7	4.6	0.53	0.68	9.7	47.7	49.3	8.2	43.2	46.3
SCA2	4	41	34	43	2.5	3.6	1.33	0.66	13.7	32.7	34.9	10.2	33.3	35.7
SCA2	5	43	28	40	3.4	3	0.31	0.19	8.3	34	36.8	13.3	37.4	38.6
SCA2	6	44	23	26	3.4	3.4	0.58	0.55	11.5	31.2	34.1	12.8	34.6	37.2
SCA2	7	37	28	44	3	2.4	0.63	0.63	9.6	32.8	35.2	9.8	34	30
SCA2	9	36	53	59					11.3	32.8	34.4	10.8	32.6	35.3
SCA2	10	38	42	51					11.1	50.3	47.8	10.6	42.3	42.6
SCA3	11	74	40	48	3.1	2.1	1	0.7	10.7	33.4	36.6	12.1	34.6	34.9
SCA3	12	74	41	46	3.3	3.2	1.25	0.91	12	29.2	31.1	11.2	36	34.7
SCA3	13	79	27	38	3.4	4.1	1.34	1.21	9.4	33.7	32.4	12.6	34.5	35.1
SCA3	14	67	55	68	3.1	3.1	2	2.04	10.6	38.1	38.9	10.3	33	34.1
SCA3	15	67	49	65	3.1	3.4	0.64	0.39	9.7	36.9	38.1	9.2	36.7	41.4
SCA3	16	70	–	39	2.82	3.2	2.48	2.5	11.8	38.9	44.7	9.3	34.2	35.4
SCA3	17	68	–	35	2.35	2.45	1.91	2.09	9.3	34.7	35.6	10.7	37.6	37.7
SCA3	18	72	–	33	2.16	3.03	1.66	1.41	8.2	33.1	33.2	9.5	30.2	30.6
SCA3	19	71	31	41	2.28	2.82	1.08	1.22	10.5	32.2	35.1	9.9	37.8	44.7
SCA3	20	71	35	38	3.35	3.15	0.47	0.29	10.9	30.4	31.3	8.8	31.5	32.6
SCA3	21	71	25	32	2.2	1.85	0.99	1.71	9.8	34.2	37.2	10.3	36.5	41.3
SCA3	22	71	31	46	3.6	2.7	1.28	0.91	10.4	36.7	35.1	8.8	34.8	35

R2i: R2 ipsilateral; R2c: R2 contralateral; –: asymptomatic.

Table 4 Mandibular reflex

SCA	Case	Rep. CAG	Age at onset (years)	Age in study (years)	Latency	
					Right	Left
CA2	1	37	52	60	A	A
SCA2	2	35	50	64	11,1	11,2
SCA2	3	41	22	32	A	A
SCA2	4	41	34	43	A	A
SCA2	5	43	28	40	A	A
SCA2	6	44	23	26	A	A
SCA2	7	37	28	44	A	A
SCA2	9	36	53	59	A	A
SCA2	10	38	42	51	A	A
SCA3	12	74	41	46	8,4	8,7
SCA3	13	79	27	38	8,6	8,5
SCA3	14	67	55	68	9,3	9,8
SCA3	15	67	49	65	7,8	7,3
SCA3	16	70	–	39	9,3	8,8
SCA3	17	68	–	35	8,6	9,5
SCA3	18	72	–	33	9,3	7,6
SCA3	19	71	31	41	8,2	9,2
SCA3	20	71	35	38	9,8	9,05
SCA3	21	71	25	32	7,8	9,6
SCA3	22	71	31	46	8,9	8,1

A: response was absent; –: asymptomatic.

extent with the anomalies in the peripheral nervous system described in patients with olivopontocerebellar atrophy[12-16] and in patients genetically classified as SCA2.[17-20] They are also in line with the histological findings detected in the autopsies of patients with these neurodegenerations, such as the loss of neurons in the dorsal root ganglia, with the subsequent degeneration in the large and medium calibre myelinic fibres of the dorsal roots and the posterior columns of the spinal cord.[14,16,17,21,22] In our SCA3 patients, we have found hardly any signs of peripheral neuropathy, unlike the findings described by other authors.[18-21,23-26] we believe that these discrepancies may be due to the great phenotypical variability of this disease, as only 2 of the 12 SCA3 patients could be classified within sub-type III, characterized by presenting prominent signs of distal polyneuropathy.

In both the SCA2 and SCA3 genotypes, we encountered similar anomalies in the somatosensorial pathways as those described previously by other authors in SCA2[18,19,27-29] and SCA3[23,29] patients. These alterations have been linked to the loss of fibres in the dorsal columns of the spinal cord detected in the autopsy of SCA2[30,31] and SCA3[32,33] patients.

Our results suggest that the involvement of the corticospinal pathway in both SCA2 and SCA3 patients is more frequent that has been described to date.[28,29,34,35] We feel that this discordance may be due to the evaluation of the pathway in the upper and lower limbs, since the severity of the pathological process seems to depend on the length of the motor tracts.[28] Another factor to be borne in mind is the duration of the illness as we know that the involvement of the corticospinal pathway depends on the timing of the degenerative process.[36,37] In fact, we have seen in our study that those patients with anomalies in the corticospinal pathway were those presenting the longest recorded clinical condition (up to 16 years).

A large number of SCA2 patients showed anomalies in the VEP, coinciding with the findings reported by such authors as Perreti et al[28] but disagreeing with other authors such as Abele et al[29] and Velázquez et al,[18] whose studies showed a trend towards the conservation of the visual pathway in these patients. This variability may be influenced by the methodological differences in the technique used to obtain the VEP. Although there are no neuropathological studies of the visual pathways in these patients, Abele et al[29] suggest that the alterations in VEP may be related to a loss of large or medium calibre myelinic fibres in the optical nerve. In SCA3 patients, our results suggest the conservation of the visual pathway coinciding with the results presented previously.[23,29]

Almost half our SCA2 patients, compared to a minority of SCA3 patients, showed alterations in the BSEAP, suggesting the presence of a diffuse involvement of the auditory pathway for both the peripheral component and the brainstem-encephalic part. These findings are similar to those described by Perreti et al[28] and by Abele et al.[29] The high incidence of anomalies in SCA2 patients has been associated with the presence of major brainstem-encephalic alterations in the pathology and neuroimaging studies.

All our SCA2 patients presented alterations in the mandibular reflex[38] and although most of them presented signs suggesting neuronopathy, this cannot be responsible for these alterations as the fibres constituting the afferent pathway in the reflex arch are located in the mesencephalic

nucleus of the trigeminus (brainstem) and not in the cranial-spinal ganglia.[39] Thus, the pathological alteration responsible might be found in the brainstem itself, a fact that might be supported by the pathology findings described in SCA2 patients, in whom a marked loss of motor neurons has been detected in all the nuclei of the trigeminus;[21,31] on the other hand, no such anomalies have been described in the pathology studies carried out on SCA3 patients,[32,33,40,41] correlating with the presence of an intact mandibular reflex in all SCA3 patients in our study.

The anomalies found in the blink reflex in most of our SCA2 patients can also not be related to a neuronopathy, as the fibres making up the afferent pathway, although found in the Gasser ganglion, are medium and small calibre fibres that are not affected in this process. This leads us to think that the cause responsible for these anomalies is located in the brainstem, specifically in the main and spinal nuclei of the trigeminus, which, as we have seen, are severely damaged in SCA2 patients.[31]

Finally, electromyographic recordings corroborated the clinical presence of facial myokymias in SCA2 patients. According to the studies by Valls-Solé et al,[42] we can suggest that the high incidence of facial myokymias is due to a brainstem-encephalic neuronal hyperexcitability, whereas the low incidence of the same together with the scant involvement of the brainstem-encephalic reflexes in SCA3 patients would agree with the scant alterations in the brainstem-encephalic structures present in these patients.

Conclusions

The somatosensorial pathway and the sensory component of the peripheral nerve were the systems most frequently found to be affected in SCA2 patients, corroborating the compatibility of SCA2 with a sensory neuronopathy with central and peripheral axonopathy. To this fact we can add the elevated incidence of alterations detected in the study of the brainstem-encephalic pathways, in consonance with the major anomalies observed in these structures during the pathology and neuroimaging studies of this genotype.

In the SCA3 patients, we detected alterations in the somatosensorial pathway in two thirds of the patients with conservation of the peripheral nervous system. His discrepancy with respect to previous studies might be due to the great phenotypical variability of the SCA3 mutation; in fact, only two cases in our series belonged to sub-type III. In the same way as the peripheral nervous system, the study of the brainstem-encephalic nerve pathways (BSEAP, mandibular reflex and blink reflex) was normal in most SCA3 patients, in line with the relative conservation of the brainstem in this genotype.

Our results suggest that the involvement of the corticospinal pathway is more frequent than reported by other authors in both genotypes, probably because its demonstration requires the assessment of the central motor pathways on the upper and lower limbs.

Comparing the results in SCA2 and SCA3, we have not found any significant differences in the studies of the somatosensorial and corticospinal pathways; the studies of the auditory pathway and the blink reflex showed a higher percentage of alterations in SCA2, but the difference was not significant.

Finally, the alteration in the mandibular reflex in all SCA2 patients versus conservation in all SCA3 patients means that this simple examination may be extremely useful in the differential diagnosis of both genotypes.

Conflict of interest

The authors declare they have no conflict of interest.

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