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Spinocerebellar Ataxia Type 2

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1. Introduction

The autosomal dominant cerebellar ataxias (ADCA) are a clinically, pathologically and genetically heterogeneous group of neurodegenerative disorders caused by degeneration of cerebellum and its afferent and efferent connections. The degenerative process may additionally involves the ponto- medullar systems, pyramidal tracts, basal ganglia, cerebral cortex, peripheral nerves (ADCA I) and the retina (ADCA II), or can be limited to the cerebellum (ADCA III) (Harding et al., 1993).

The most common of these dominantly inherited autosomal ataxias, ADCA I, includes many Spinocerebellar Ataxias (SCA) subtypes, some of which are caused by pathological CAG trinucleotide repeat expansion in the coding region on the mutated gene. Such is the case for SCA1, SCA2, SCA3/MJD, SCA6, SCA7, SCA17 and Dentatorubral-pallidoluysian atrophy (DRPLA) (Matilla et al., 2006).

Among the almost 30 SCAs, the variant SCA2 is the second most prevalent subtype worldwide, only surpassed by SCA3 (Schöls et al., 2004; Matilla et al., 2006; Auburger, 2011). The disorder was first recognized in India in 1971 by Wadia and Swami, who was intrigued by the early and marked slowing of saccade movements, associated to the cerebellar syndrome (Wadia & Swami, 1971). Contemporarily, in Cuba some neurologists were describing many families coming from the north-east region of the country with the same distinct clinical picture (Vallés et al., 1978). Subsequent epidemiological surveys in this Cuban region, Holguín province, focusing on the causes of the highest SCA2 prevalence rate worldwide found evidence for a founder effect (Orozco et al., 1989; Auburger et al., 1990; Velázquez-Pérez et al., 2001, 2009a).

2. Epidemiology

The collective worldwide prevalence of SCAs is estimated at about 6 cases per 100,000 people, although much higher figures have been reported in particular populations (Schöls et al., 2004). In the case of SCA2, the global prevalence is unknown because the most of the few existing epidemiological studies have been performed in isolated geographical regions with families not large enough for linkage analysis. Nevertheless, large SCA2 families have been found in India, Martinique, Australia, Tunisia, Germany, Italy, Mexico, Poland and especially in Cuba (Klockgether, 2007; Sulek-Pitkowska, et al., 2010, Velázquez-Pérez et al., 2009a).

SCA2 represents 87% of ADCAs in Cuba, with a national prevalence rate of 6.57 cases per 10^5 inhabitants. If asymptomatic at-risk individuals are included in the prevalence analysis, the prevalence rate increases up to 28.51 cases per 10^5 inhabitants, with remarkable values in various eastern provinces, especially in Holguin (Figure 1A). In fact, there are regions in this province where the prevalence reaches higher values such as Baguanos municipality (141.7 per 10^5 inhabitants) (Figure 1B) (Velázquez-Pérez et al., 2009a).

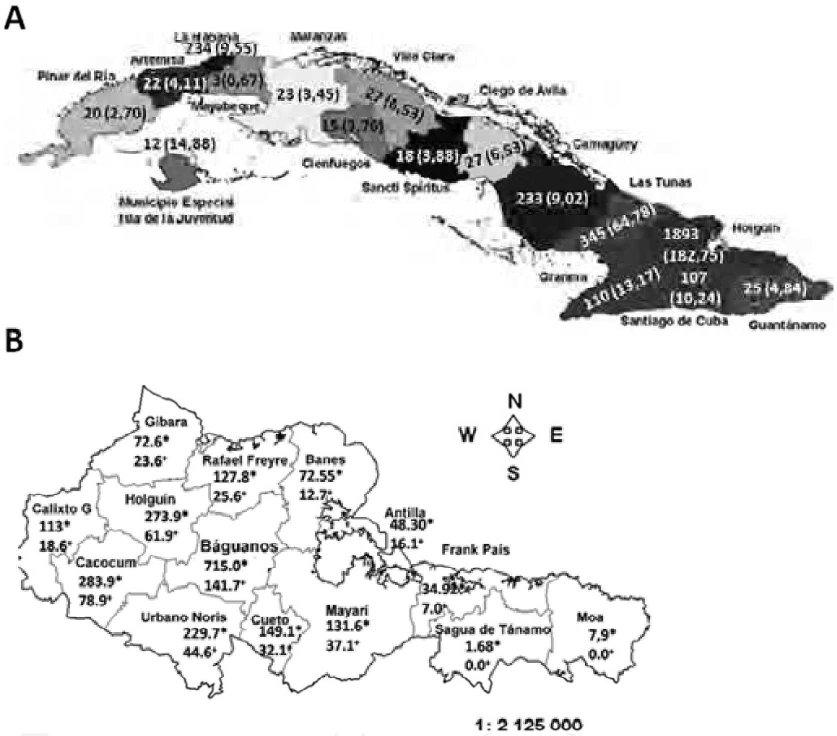

Fig. 1. Epidemiological picture of SCA2 in Cuba. A) Number and prevalence (in parenthesis) of SCA2 mutation carriers in all Cuban provinces. B) Prevalence rates of SCA2 patients ($^+$) and SCA2 mutation (*) in Holguin province, Cuba (2006–2007).

3. Clinical features

The clinical picture of SCA2 includes a cerebellar syndrome in all patients, characterized by ataxic gait, cerebellar dysarthria, dysmetria and dysdiadochokinesia (Orozco et al., 1989; Orozco-Diaz et al., 1990). Patients also exhibit abnormal tandem stance (95%), slow saccadic eye movements (91%), limited voluntary ocular movements (88%), loss of vibration sense (73%), areflexia or hyporeflexia (77%) after initial hiperreflexia and abnormal swallowing (76%) (Velazquez-Pérez et al., 2009a).

Autonomic abnormalities (urinary dysfunction, hypohidrosis, constipation, and sexual dysfunction) are present in 78% of the cases and are accentuated in late stages of the disease

(Sánchez-Cruz, et al., 2001; Velázquez-Pérez et al., 2009a, Montes et al., 2010), together with dysphagia, ophthalmoplegia and distal amyotrophy. Sleep disturbances are frequent complaints of SCA2 patients and their relatives. The most prominent sleep disorders are restless legs syndrome (Trojano et al., 1998; Schöls et al., 1998; Abele et al., 2001; Irazno et al., 2007), muscle cramps, insomnia and reduced dream recalls (Velázquez-Pérez et al., 2011a).

Other clinical manifestations of SCA2 are the cognitive dysfunctions, which include frontal-executive impairment, verbal short-term memory deficits as well as reduction of attention and concentration (Storey et al., 1999; Reynaldo-Arminan et al., 2002; Bürk et al., 1999a; 2003). Although neuropsychological pattern of cognitive disturbances of SCA2 patients not necessarily resembling dementia, some studies have reported high frequency of demented patients (Durr et al., 1995, Burk et al., 1999a), but in the SCA2 Cuban population this neuropsychological state is rare (Reynaldo-Arminan et al., 2002; Orozco et al., 1989; 1990). Depression/anxiety/suicide attempts are found in a third of cases (Reynaldo-Arminan et al., 2002). In comparison to other SCAs, the frequency of slowed ocular movements, postural and action tremor and hyporeflexia are distinctive features of SCA2 (Schöls et al., 1997).

Extrapyramidal manifestations are common in SCA2 patients. Myoclonuses are reported in 13.7% whereas dystonia is present in 14.2%. Chorea may appear in approximately 7%. These symptoms are accentuated in patients with larger CAG repeats. Parkinsonian signs appear in some patients with low-range expansions containing CAA interruptions (Gwinn-Hardy et al., 2000; Payami et al., 2003; Lu et al., 2004; Charles et el, 2007). Among these manifestations, resting tremor (14,9%) and rigidity (7,9%) are the most common (Schmitz-Hubsch, et al., 2008). Recently it was reported an unusual case of SCA2 presenting as an ataxia-parkinsonism-motor neuron disease syndrome in a 46-year-old Brazilian man with 40 CAG repeats in the SCA2 gene (Braga-Neto et al., 2011).

The age at onset varies from 3 to 79 years (mean 33). Usually, the first symptom of the disease is the gait ataxia (97%), followed by the cerebellar dysarthria (3%). However some extracerebellar manifestations may occur a decade or more before the onset of gait instability or dysarthria, such as painful muscle cramps in the calf, sleep disturbances, problems with hand writing (Globas et al, 2008), as well as autonomic alterations, consisting in constipation (19.4%) and pollakiuria (17.7%) (Montes-Brown et al, 2011). In the Cuban SCA2 population the anticipation of clinical manifestation age in successive generations is observed in 80% of transmissions, usually upon transmission from an affected father (Velázquez-Pérez et al., 2009a).

Clinical features develop progressively with an increase in cerebellar syndrome, saccade slowing, and other features which confine the patients first to a wheelchair and following to a bed, where they die approximately 15–20 years after the initial symptoms. Nevertheless patients with larger CAG repeats have earlier age at onset, more saccadic slowing, axial tremor, pyramidal-dystonic-choreic signs, mental deficit and in general a faster progression to death (Filla et al 1999, Cancel et al 1997; Schöls et al., 1997; Sasaki et al., 1998; Filla et al., 1999; Velázquez-Pérez et al., 2009a) and the total disease duration from onset to death may vary between 6 and 50 years (Klockgether et al., 1998; Maschke et al., 2005). Also, the female gender is associated with shortened survival (Klockgether et al., 1998). The main cause of death is bronchopneumonia (63%), followed by bronchial aspiration and cardiovascular incidents, among others (Velázquez-Pérez et al, 2011b).

Pediatric-onset SCA2 is associated with large CAG expansions. Infantile phenotype includes rare symptoms such as retinitis pigmentosa, myoclonus-epilepsy, tetraparesis, developmental delay and facial dysmorphism (Babovic-Vuksanovic et al 1998; Rufa et al., 2002; Tan et al., 2004; Di Fabio et al., 2011). Ramocki and coworkers describe a female child who met all developmental milestones until age 3 years, deterioration of expressive language, comprehension, memory, graphomotor skills, and dysarthria. Cranial nerve examination showed bilaterally restricted lateral gaze with oculomotor apraxia (Ramocki, et al., 2008). Abdel-Aleem and Zakiwith reported a male child with progressive extrapyramidal manifestations, developmental delay, slow eye movements and cognitive impairment, trophic changes, vasomotor instability and dysphagia (Aleem and Zakiwith, 2008)

4. Molecular genetics

The underlying mutation of SCA2 consists in the unstable expansion of the trinucleotide repeat $(CAG)_8CAA(CAG)_4CAA(CAG)_8$ within the ATXN2 gene exon 1 located on chromosome 12q24.1. This repeat encodes a polyglutamine (polyQ) tract in the protein ataxin-2 (Gispert et al., 1993; Pulst et al., 1996; Imbert et al., 1996; Sanpei et al., 1996). In normal individuals, the trinucleotide repeat length varies and contains between 13 and 27 units. Intermediate expansions between 28 and 33 units may predispose the individual to an elevated risk for the motor neuron disease ALS or the Parkinson plus syndrome PSP (Elden et al., 2010; Ross et al., 2011). The prevalence of large normal alleles potentially acting as unstable premutation is particularly high in the Cuban province Holguín (Velázquez-Pérez et al., 2009a). Family planning can be aided by presymptomatic molecular genetic diagnostics, but care has to taken to offer psychological treatment together with the genetic counseling.

Pathological alleles in SCA2 have more than 32 CAG repeats, although the repeats range between 32 and 36 units has incomplete penetrance (Pulst et al., 1996; Cancel et al., 1997; Geschwind et al., 1997). The most frequent expanded allele is 37 (72%). The expanded alleles have lost interrupting CAA-triplets, a factor thought to promote the length instability. Expansions occur in 89% and contractions in 11% of the offspring of affected patients. Paternal transmissions show higher variability in repeat lengths compared with the maternal transmissions. (Velázquez-Pérez et al., 2009a). The presence of CAA interruptions in expanded alleles appears to predispose to a phenotype with Parkinson or with motor neuron disease (Charles et al., 2007; Kim et al., 2007; Modoni et al., 2007; Corrado et al., 2011, Yu et al., 2011), although both CAG and CAA code for glutamine, indicating that the neuronal population affected by the pathogenesis is determined by RNA toxicity rather than protein toxicity.

As in other polyQ diseases, in SCA2 the age at onset and symptom severity correlate inversely with the length of the trinucleotide repeat, which accounts for ~80% of variance, whereas the remaining variability suggests the existence of modifier genes, genetic polymorphisms, epigenetic factors and unknown environmental determinants modulating age of onset (Velázquez-Pérez et al., 2009a). Supporting the above mentioned, long normal CAG repeats in the CACNA1A (Pulst et al., 2005) and RAI1 genes (Hayes et al., 2000) as well as the 10398G polymorphism in the mitochondrial complex I gene (Simon et al., 2007) are associated with earlier manifestation age, also in the Cuban SCA2 population.

4.1 The physiological role of ataxin-2 in cell biology

The ataxin-2 protein (ATXN2) is a polypeptide containing 1312 amino acids encoded by 25 exons of the SCA2/ATXN2 gene encompassed within 130 kiloBases of genomic DNA (Sahba et al., 1998), with at least five human isoforms produced by allelic splicing (Nechiporuk et al 1998; Affaitati et al., 2001; Lastres-Becker et al., 2008a) and an expression in many organs, but only selected neurons of the brain (Huynh et al., 1999). It is phosphorylated, but not glycosylated (Turnbull et al., 2004). Currently, the function of ATXN2 is not clear, but several lines of evidence evoke its involvement in RNA metabolism. For example, the protein have sequence motifs related to mRNA processing, most of ATXN2 is associated to polyribosomes, at the rough endoplasmic reticulum (Satterfield and Pallanck, 2006; van de Loo et al., 2009), and this polypeptide interacts with RNA binding proteins such as A2BP1 and PABPC1 (Shibata et al., 2000; Ralser et al., 2005a; Satterfield and Pallanck, 2006).

Interestingly, ATXN2 and its orthologues in other organisms relocalize during periods of cellular stress to mRNP granules where mRNA is stored during translation repression, promote the formation of these stress granules and inhibit cell growth (Swisher and Parker, 2010; Nonhoff et al., 2007). Furthermore, the expression of ATXN2 is induced by specific stressors (Klinkenberg et al., submitted) and ATXN2 levels increase with old age (Huynh et al., 1999). The indirect effects of ATXN2 on RNAs appear to be mediated partially by its interactor DDX6, a RNA helicase (Nonhoff et al., 2007). Also the formation of P-bodies, mRNP granules implicated in RNA degradation, appears to depend on ATXN2, which may localize to these structures and influence the microRNA-mediated deadenylation of silenced RNAs (Nonhoff et al., 2007; Kozlov et al., 2010). There is preliminary evidence that ATXN2 co-sediments and co-localizes with neuronal mRNPs which are responsible for the transport of mRNAs to synaptic sites of local protein synthesis, and indeed ATXN2 is thought to modulate mRNA translation similar to its yeast orthologue Pbp1 (Siddiqui et al., 2007). Thus, ATXN2 might be important for stimulus-dependent local mRNA translation and influence in this way both synaptic strength and long-term potentiation, an electrophysiological finding which was indeed detected in ATXN2-knock-out mice in the amygdala, but not in the hippocampus (Huynh et al., 2009).

Some ATXN2 is also demonstrable at the plasma membrane, and within its protein sequence several proline-rich domains are able to interact with SH3-motif containing proteins. Such an interaction was demonstrated for endophilin A, CIN85 and Src, three components of the endocytosis complex that modulates trophic factor signaling through receptor tyrosine kinases (Ralser et al., 2005b; Nonis et al 2008). In these reports, ATXN2 was found to antagonize the internalization of the receptor for Epidermal Growth Factor. Interestingly, two other neurodegenerative disease proteins are also interactors of this complex, namely Huntingtin and Parkin, which was shown to ubiquitinate ATXN2 directly and to rescue ATXN2-toxicity (Ralser et al., 2005b; Huynh et al., 2007). Furthermore, the deficiency of ATXN2 in knock-out mice was observed to modulate the levels of insulin receptor, resulting in insulin resistance, altered fat metabolism and obesity (Kiehl et al., 2006; Lastres Becker et al., 2008b). Interestingly, the protein family A2D which shares sequence homology with ATXN2 also shows interaction with the cytoplasmic domain of the thrombopoietin and the erythropoietin membrane receptors which lack intrinsic tyrosine kinase activity, but is also internalized to modulate downstream events of cytokine signaling (Meunier et al., 2002). Of course, this physiological influence of ATXN2 on trophic signaling may be important for neural atrophy in SCA2. Finally, recent evidence suggests a localization and role of ATXN2 in the nucleus, acting as interactor of the transcriptional regulator ZBRK1 (Hallen et al., 2011).

4.2 ATXN2 role for different diseases

SCA2 is thought to be caused by a toxic gain-of-function of the ATXN2 protein, but it is not clear to which degree the physiological function of ATXN2 is enhanced and to which degree unspecific toxic effects such as the aggregation of polyQ domain proteins dominate in the pathogenesis. Since polyQ expansions in different disease proteins affect different neuronal populations, and since the overexpression of wild-type ATXN2 and its orthologues in lower species, which lack the polyQ domain completely, is neurotoxic, the specific properties of ATXN2 regarding expression, subcellular localization and interactors seem to be relevant in disease. Intermediate-length expansions of the ATXN2 trinucleotide repeat below the threshold of SCA2 manifestation were shown to have a pathogenic role, increasing the individual risk to manifest the motor neuron degeneration disease ALS (Amyotrophic Lateral Sclerosis) and the basal ganglia degeneration disease within the Parkinson-plus group of disorders PSP (Progressive Supranuclear Palsy) (Elden et al., 2010; Daoud et al., 2011; Ross et al., 2011; Sorarù et al., 2011; Lee et al., 2011; van Damme et al., 2011). The RNA metabolism function of ATXN2 may explain this phenomenon, since ALS pathogenesis appears to be mediated mainly by altered mRNA processing (Lagier-Tourenne et al., 2010). ATXN2 gain-of-function also potentiates toxicity of ATXN1 and ATXN3 (the SCA1 and SCA3 disease proteins, respectively) and even toxicity of Tau (the frontotemporal lobar degeneration disease protein) in the fly model (Shulman and Feany, 2003; Al-Ramahi et al., 2007; Lessing and Bonini, 2008; Elden et al., 2010). Conversely, reducing ATXN2 levels is sufficient to mitigate the neurotoxicity triggered by TDP-43, ATXN1 and ATXN3 (Al-Ramahi et al., 2007; Lessing et al., 2008; Elden et al., 2010) in yeast and flies, indicating that these effects are mediated by the physiological function of ATXN2, but not by the polyQ domain which characterizes human ATXN2 and is not conserved until mouse.

Large expansions of ATXN2 were reported to exert a profound effect on intracellular calcium levels through specific binding to the carboxy-terminal region of the type 1 inositol 1,4,5-trisphosphate receptor (IP(3)R1), an intracellular Ca(2+) release channel (Liu et al., 2009), an effect mediated by ATXN2 at its major localization in the cytoplasm.

Several lines of evidence suggest that other alterations of the physiological ATXN2 function influence additional neuron populations and diseases. In neuroblastoma tumors, an upregulation of ATXN2 was found to be a decisive factor to induce apoptosis of the aberrant cells and spontaneous tumor remission (Wiedemeyer et al., 2003). In individuals who reached an age over 100 years, a single nucleotide polymorphism within ATXN2 intron 1 contributes to the genetic signature of exceptional longevity. Moreover, in the general human population the same ATXN2 intron 1 polymorphism determines high blood pressure levels (Levy et al., 2009; Newton-Cheh et al., 2009; Sebastiani et al., 2010).

4.3 Animal models

Animal models have been useful tools to study the polyQ expansion diseases, in particular the brain tissue of early stage pathology. Specifically ATXN2 orthologues are highly conserved until Saccharomyces cerevisiae, permitting high-throughput genetic screens into the function of ATXN2 and revealing the role of ATXN2 as a risk factor for TDP-43 toxicity and motor neuron degeneration (Elden et al., 2010). Again, Drosophila melanogaster studies demonstrated the association of dATX2 with PABP and with polysomes (Satterfield and Pallanck, 2006). The use of RNA interference in Caenorhabditis elegans demonstrated an essential role of the atx-2 gene for early embryonic development (Kiehl et al., 2000).

Taking advantage of the mouse as an organism with genetic versatility and with similarity to man in brain structure, two transgenic models of SCA2 have been generated to date. The first one was produced by Huynh et al., 2000, who reported the use of the murine PcP2 (L7) promoter to direct a strong overexpression of the human ATXN2 gene with an expanded allele of 58 CAG repeats specifically to the cerebellar Purkinje neurons. Using the rotarod test, they found that the animals became ataxic at 26 and 16 weeks for the heterozygous and homozygous transgenic mice, respectively. Also, they described progressive incoordination and morphological alterations of Purkinje cells in this animal model. In 2005, Aguiar and coworkers (Aguiar et al., 2006) generated transgenic mouse lines overexpressing the full-length human ATXN2 gene with 75 CAG units under the control of the human self promoter. A neurological phenotype was reported after 12 weeks for heterozygous and 6 weeks for homozygous mice.

5. Imaging

Magnetic resonance imaging shows early cerebellar and brainstem atrophy (Figure 2) with marked involvement of the cerebellar cortex and the pons/inferior olive region in SCA2, in excellent agreement with the traditional neuropathological nomenclature of olivopontocerebellar atrophy (OPCA). Also, frontotemporal atrophy is observed in advanced disease (Bürk et al., 1996; Giuffrida et al., 1999). Voxel-based morphometry studies have revealed the atrophy of the cerebellar and brainstem white matter as well as the symmetric loss of gray matter in the cerebellar vermis (Brenneis et al., 2003; Brenneis et al., 2005; Della Nave et al., 2008a, b, Goel et al., 2011). Positron emission tomography (PET) studies showed a reduced regional glucose metabolism in the cerebellum, brainstem and parietal cortex, which may occur years before the clinical onset of SCA2 (Inagaki et al., 2005). PET analyses also revealed the loss of striatal dopamine transporter function with nigrostriatal atrophy, similar to the pattern observed in idiopathic Parkinson's disease (Boesch et al., 2004; Wüllner et al 2005; Inagaki et al., 2005). Imaging by proton magnetic resonance spectroscopy demonstrated the loss of choline-containing compounds in SCA2 cerebella, suggesting the decreased production and/or the loss of cell membranes as well as the reduced synthesis of precursors of acetylcholine. The same study demonstrated the increase of lactate levels in the cerebellum suggesting an impairment of glycolysis and mitochondrial function (Boesch et al., 2001).

6. Neuropathology

The macroscopic examination of nervous structures in *post-mortem* samples of SCA2 patients shows a significant atrophy of the cerebellum, brainstem, frontal lobe, as well as pallor of the midbrain *substantia nigra* and a reduction of the cerebral and cerebellar white matter. Microscopically, the cerebellum is characterized by an early and marked neuronal loss in Purkinje cell layer with reduction in the number of dendritic arborizations and torpedo-like deformations of their axons. The number of granular neurons is diminished, usually toward

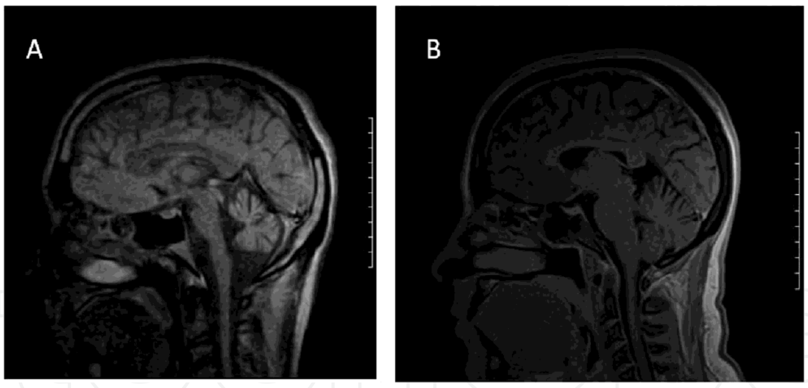

Fig. 2. MRI scans of a SCA2 patient (age 40 years; disease duration 8 years, CAG repeat size 39 units, SARA score 19) (A) and a healthy control (age 40 years, SARA score 0) (B). Note the severe atrophy of cerebellum and brainstem in the SCA2 subject.

late stages of the disease whereas the dentate nucleus is relatively spared. Parallel fibers are sparse and no climbing fibers are observed in the Purkinje cell dendritic trees (Orozco et al., 1989; Ihara et al., 1994; Estrada et al., 1999; Ying et al., 2005). In the brainstem, the most noteworthy microscopic findings are the marked loss of inferior olivary neurons in addition to the degeneration of pontine and other precerebellar brainstem nuclei (Rüb et al., 2005a; Lastres-Becker et al 2008a). The neuropathological evaluation of brainstem and cranial nerves shows that oculomotor, somatomotor, somatosensory, auditory, vestibular and autonomic nuclei are notably affected by neuronal loss and their associated fibers are atrophied and undergo demyelinization (Rüb et al., 2004a, 2004b; Rüb et al., 2006; Gierga et al., 2005; Hoche et al., 2008). Another important neuropathological marker of SCA2 is the notable reduction of neurons of the substantia nigra in the mesencephalon and the extensive degeneration of several thalamic nuclei, such as the reticular, fasciculosus, ventral anterior and posterior, lateral geniculate body and the anterior nuclei (Rüb et al., 2003a, 2003b, 2005b). In the spinal cord, an early and progressive demyelination of the posterior and spinocerebellar columns together with neuronal loss in cuneate and gracile nuclei, dorsal roots and ganglia as well as a reduction of motor neurons, usually in the cervical level and the Clarke's column, are observed (Rüb et al., 2007). Demyelination is severe (Armstrong et al., 2005). The selective neurodegeneration of large neurons affecting multiple regions of the brain with some glial inclusions is quite similar to the pattern of multiple-system atrophy (MSA) (Yagishita and Inoue 1997; Berciano and Ferrer 2005). Polyglutamine inclusion bodies appear to be much less prominent than in Huntington's disease or in SCA3 (Huynh et al., 2000; Uchihara et al., 2001; Koyano et al., 2002; Pang et al., 2002). Also, it is observed a significant loss of giant Betz pyramidal cells in the primary motor cortex. (Hoche et al., 2010). A recent study suggested that either the age at onset or the CAG repeat expansions influence on the distribution pattern of SCA2 neurodegeneration (Ishida et al., 2011).

7. Neurochemistry

The neurochemical findings in SCA2 patients were first recognized by Orozco and co-workers in 1989, (Orozco et al., 1989) who called attention to the significantly decrease of dopamine metabolites such as 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in cerebrospinal fluid (CSF), likely as result of neuronal depletion in the substancia nigra of autopsied patients. However, the mean concentration of Gamma-amino-butyric acid (GABA), as well as metabolites of noradrenalin and serotonin were similar to normal subjects. Additionally, N-acetyl-aspartate and glutamate are markedly reduced in these patients (Oz et al., 2010).

A pathologically relevant biochemical finding is the significant reduction of zinc, iron and copper levels in the CSF and serum of Cuban SCA2 patients. The reduction of zinc levels could be associated with phenotypic features such as nerve conduction slowing, cognitive dysfunction, and immune-depression at final stages of the disease and could accentuate the dysfunction of cerebellar circuits, based on the important role of this element in the control of synapses in the cerebellum (González et al., 2006). Furthermore, most biomarkers of the antioxidant-prooxidant balance are significantly modified in Cuban SCA2 patients with an increase in malondialdehyde (MDA) as evidence of lipid peroxidation, as well as signs of oxidative damage to protein and DNA and significant reduction of the reduced glutathione (GSH). Also, the activity of glutathione S-transferase (GST), superoxide dismutase (SOD) and catalase (CAT) are depressed in these patients with a disruption of the balance CAT/SOD (Velázquez-Pérez et al, 2003; Almaguer, et al., 2005). A third interesting finding is the decrease of erythropoietin levels in the CSF with a compensatory increase of this molecule in the serum of Cuban SCA2 patients, suggesting the existence of reduced capabilities of neuroprotection in the nervous system (Velazquez-Pérez et al., 2011b). We believe that these biochemical features may contribute to the high phenotypic variability of SCA2 and that they could constitute potential therapeutical targets to design future clinical trials.

8. Neurophysiology

8.1 Nerve conduction and electromyography studies

The most common electrophysiological finding in SCA2 patients is a predominantly sensory axonal neuropathy, expressed by the early and progressive reduction of sensory amplitudes, suggestive of dorsal root ganglionopathy. These alterations are associated with slowing of nerve conduction as sign of demyelination. The progression rate of sensory axonal neuropathy is notably accentuated in patients with large CAG expansion sizes. Motor nerve conduction parameters are usually normal, but in patients with 10-15 years of disease duration it is possible to observe a reduction of motor amplitudes (Kubis et al., 1999; van de Warrenburg et al., 2004; Velázquez-Pérez et al., 2007, 2010). Electromyographical findings reveal motor unit potentials (MUP) with light polyphasic alterations, increased amplitudes and isolated contraction pattern in the first stage of the evolution. In advanced stages of the disease signs of denervation can appear (fibrillations and fasciculations) and the contraction pattern becomes simple oscillations, indicating the loss of motor neurons in the anterior horn of the spinal cord (Velázquez-Pérez et al, 2009b).

8.2 Somatosensory evoked potentials (SSEP)

Tibial nerve SSEPs are characterized by a marked prolongation of the P40 component and central conduction time latencies. In the median nerve SSEP there is a latency prolongation of N20 and N13 components in addition to a reduction of amplitude of Erb potentials. In almost all cases, the SSEPs show abnormal morphology and reduced reproducibility. These alterations get worse quickly in patients with larger CAG repeat number and may be detected even in presymptomatic subjects (Velázquez-Pérez et al., 2007, 2008).

8.3 Brain Stem Auditory Evoked Potentials (BSAEP)

BSAEPs have poor reproducibility and unstable morphology in 95% of the patients, in addition to the increase of latency of the waves III and V and the prolongation of the I–III interpeak interval. These abnormalities are common in patients with disease duration above 10 years but the abnormal reproducibility and morphology can be detected since preclinical stage (Velázquez-Pérez et al., 2007, 2008).

8.4 Visual Evoked Potentials (VEP)

VEP are frequently normal in SCA2 patients, but some patients in advances stages of the disease have prolonged P100 latencies with normal amplitudes. These findings reflect the integrity of the visual pathway in Cuban SCA2 patients, allowing us to distinguish SCA2 from other spinocerebellar ataxias such as SCA1, SCA3 and in particular SCA7 (Velázquez-Pérez et al., 2007, 2008).

8.5 Event-related evoked potentials (ERPs)

ERPs revealed prolongation of visual P300 latencies in 40% of cases with a significant correlation of this variable with the disease duration and clinical affectation (Kremlacek et al., 2011).

8.6 Motor evoked potentials

The study of the corticospinal tract by transcranial magnetic stimulation in SCA2 patients reveals an increase of central motor conduction time and motor threshold. Also, intracortical facilitation may be reduced and the induced cortical silent period prolonged. The progression of these abnormalities is dependent on the disease duration and ataxia severity. They probably reflect the reduced excitability of the motor cortex, disturbed conduction along the pyramidal tract and the loss of facilitatory influences of the cerebellum on the primary motor cortex (Yokota et al., 1998; Restivo et al., 2000, 2004; Schwenkreis et al., 2002)

8.7 Electrooculography

The main oculomotor abnormality in SCA2 is the slowing of horizontal saccadic movements, which is probably the result of early pontine brainstem degeneration. This feature is electrooculographically detectable in 99% of the patients and in several presymptomatic subjects. The maximal saccade velocity is negatively correlated with the polyQ expansion and the ataxia score, but is not significantly influenced by the disease duration. (Rivaud-Pechoux et al., 1998; Bürk et al., 1999b; Velázquez-Pérez et al., 2004, 2008, 2009c). The prolongation of saccadic latency is observed in 46% of the cases, reflecting the cortical/subcortical involvement in SCA2. Although this saccadic feature is not directly influenced by the CAG repeats or the disease duration it is close related with the frontal-executive dysfunctions, identifying it as a promising cognitive biomarker (Rodríguez-Labrada et al., 2011a). Additionally, SCA2 patients showed saccadic dysmetria reflecting the cerebellar involvement (Velázquez-Pérez et al., 2008) although saccades made for short target amplitudes are usually accurate due to the visual feedback might be continuously available during the slow movements (Federighi et al., 2011). Furthermore, gain measurements in smooth pursuit movements and horizontal optokinetic nystagmus are slightly reduced in SCA2 patients, whereas the vestibulo-ocular reflex is normal (Buttner et al., 1998).

8.8 Videopolysomnography and electroencephalography

Sleep disorders are common complaints of SCA2 patients, fundamentally towards the final stages of the disease. Clinically, the most prominent findings are a restless legs syndrome and muscle cramps, which appear in 45 % of the cases. Patients with REM (rapid eye movements) sleep behavior disorder; bruxism and excessive daytime sleepiness are scarse. The polysomnographical evaluation reveals a reduction of REM sleep with decreased REM density in 70% of patients. These REM sleep abnormalities appear before the disease onset and their progression rates depend on ataxia severity and disease duration. (Velazquez-Pérez et al., 2011a; Rodríguez-Labrada et al., 2011b). REM sleep without atonia appears in 31% of SCA2 patients and showed a significant correlation with the ataxia score and CAG expansions (Velazquez-Pérez et al., 2011b). Periodic legs movements (PLMs) are also observed, in the 38% of SCA2 patients (Figure 3). They are directly associated with the clinical severity of the disease and their progression rate is notable (Velazquez-Pérez et al., 2011a). Other less prominent sleep abnormalities are the decrease of sleep efficiency, increase of arousal index and central apnea index. (Boesch et al., 2006; Tuin et al., 2006).

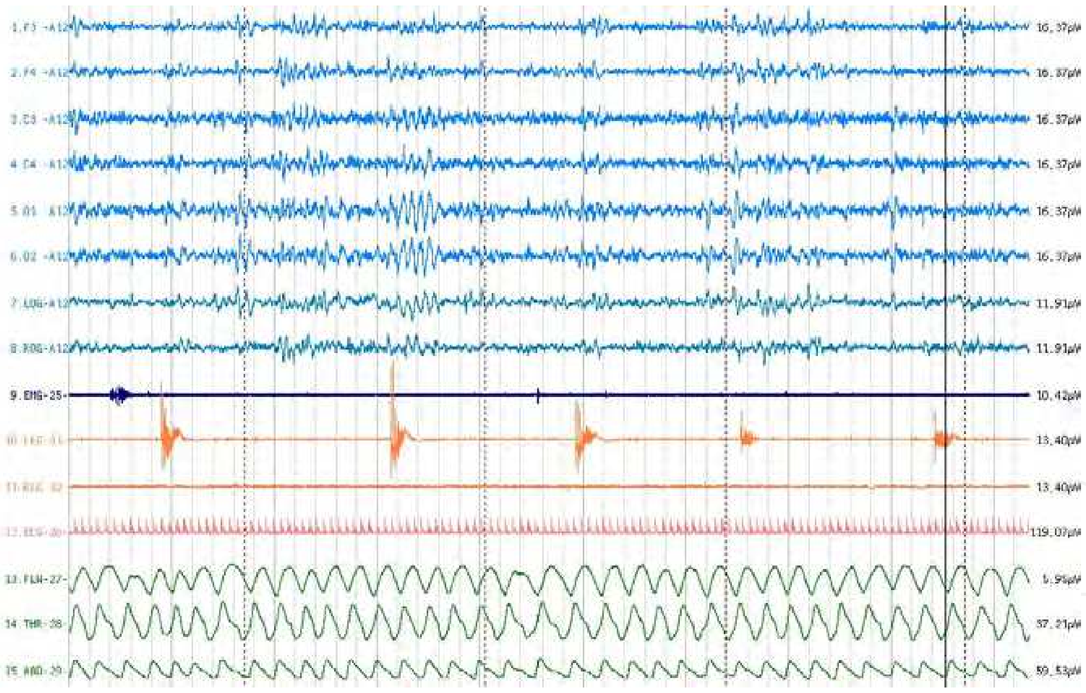

Fig. 3. Two-minute epoch of stage 2 sleep showing periodic leg movements in a SCA2 patient with 44 years old, 12 years of disease duration, 39 CAG repeats in the SCA2 gene and ataxia score in 15 units.

The conventional EEG in SCA2 patients shows a predominantly diffuse theta activity with reduced reactivity to eye opening in 72 % of the cases. In the brain electrical activity mapping a significant increase of absolute power for the theta band with reduction of absolute power for the alpha band is observed (Figure 4).

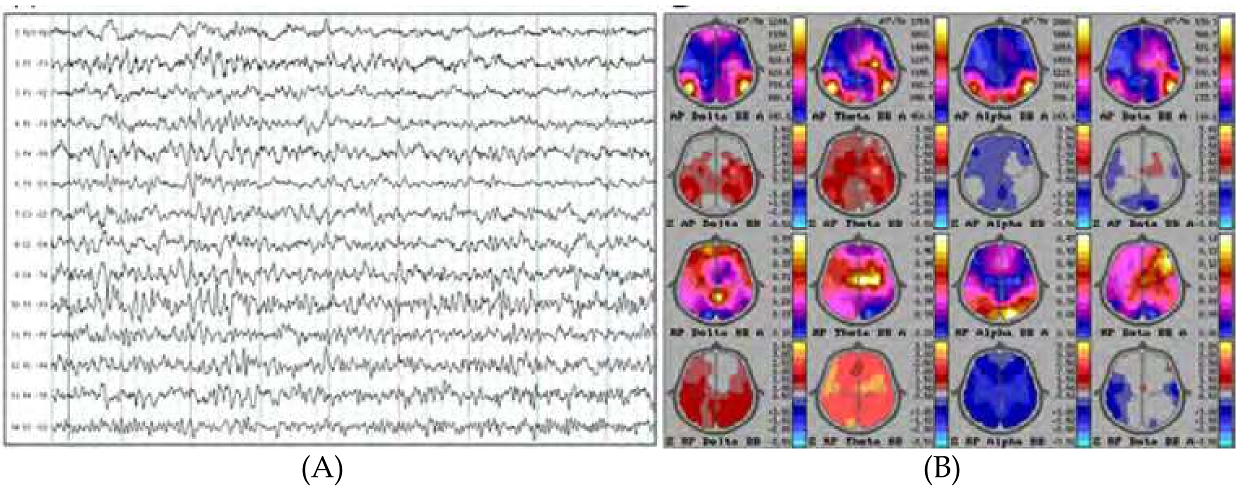

Fig. 4. Conventional (A) and quantitative (B) EEG from a SCA2 patient with age 40 years, 10 years of disease duration, a repeat expansion to 40 CAG in the SCA2 gene and an ataxia SARA score of 17.

8.9 Other neurophysiological alterations

The study of autonomic control of cardiovascular function by heart rate variability (HRV) in a large group of SCA2 patients reveals the presence of cardiovascular autonomic dysfunction associated to SCA2 (Pradhan et al, 2008; Montes-Brown et al., 2010). Additionally, SCA2 patients show a significant impairment of olfactory threshold, identification and discrimination capabilities. The score of the *University of Pennsylvania smell identification test* (UPSIT) is significantly reduced and it correlates positively with ataxia score but it is not influenced by the age, age at onset, disease duration and CAG repeats (Velázquez et al, 2006).

The prism adaptation task let us identify the impaired adaptation decrement. This alteration is accentuated in patients with larger expansions. Also, the deterioration in the adaptation correlates with the motor performance and saccade velocity, suggesting that structures that degenerate in this disease may contribute to both adaptation and motor performance (Fernandez-Ruiz et al, 2007; Velázquez-Pérez et al, 2009d).

9. Early preclinical signs

The earliest subclinical sign appears even 15 years before the onset of ataxia by the slowing of horizontal saccades at 60^0 of target displacement, with amplitudes and latencies normal. This electrophysiological abnormality is accentuated in subjects with larger CAG repeats and reflects probably the early dysfunction or degeneration of paramedian pontine reticular formation (Velázquez-Pérez et al., 2009c). This alteration is followed by the reduction of REM sleep percentage with decreased rapid eyes movements' density, which may precede the ataxia onset by 10 years although its progression during this stage is insidious (Rodríguez-Labrada et al., 2011b). Other preclinical alterations include decrease of sensory amplitudes (Velázquez-Pérez et al., 2010), increased P40 latency (Velázquez-Pérez et al., 2007), motor performance deficits, shown by the prism adaptation task (Velázquez-Pérez et al., 2009d) and reduced capabilities to identify specific odors in a sensible smell identification test (UPSIT). The comprehensive analysis of these early signs in SCA2 suggests the necessity for revisit the current criteria to define the disease onset delineating the boundaries between presymptomatics and symptomatic states.

10. Therapeutical options

Till now, there is no specific treatment for SCA2. Physiotherapy and neuropsychological rehabilitation have palliative effects on motor and cognitive symptoms. Therefore, Cuban SCA2 patients receive a specialized neurorehabilitation program (Pérez-Avila et al., 2004) since 1998, which has been applied to more than 400 patients and has allowed some recovery of motor, cognitive and antioxidant functions in about 75% of the treated patients (Rodríguez et al., 2008).

Regarding clinical trials, few studies have been conducted. For example, muscle cramps are successfully treated with magnesium and levodopa treatment alleviates the parkinsonian signs in SCA2 patients (Lastres-becker, 2008a), whereas severe myoclonus at advanced stage could be dramatically improved by piracetam (De Rosa et al., 2006). Recently, a randomized, double-blind, placebo-controlled pilot trial using riluzole resulted effective to SCA2 and other subjects with cerebellar ataxias (Ristori et al., 2010). Additionally, a double-blinded and placebo-controlled clinical trial with 50 mg zinc sulphate in 36 Cuban SCA2 patients was effective in increasing the zinc levels in serum and CSF of treated subjects and some benefit of this treatment for the cerebellar syndrome, the peripheral neuropathy and the restoration of antioxidant functions was apparent (Velázquez-Pérez et al., 2011c).

Deep brain stimulation with novel patterned low-frequency stimulation (PLFS) was effective in localizing the tremor generator at a subthalamic-thalamic electrode position, suppressing a coarse postural tremor for several postoperative years in one case (Freund et al., 2007; Barnikol et al., 2008).

11. Conclusions

In conclusion, although we have learnt much since SCA2 was described as a distinct clinical entity (Wadia and Swami, 1971) and since its cause was identified and genetic counseling became available (Imbert et al 1996; Pulst et al., 1996; Sanpei et al 1996), until today we have only taken the first steps towards understanding the pathogenic mechanisms and validating neuroprotective therapies.

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