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Eye Movement Abnormalities in Spinocerebellar Ataxias

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1. Introduction

Spinocerebellar ataxias (SCAs) are a heterogeneous group of autosomal dominant neurodegenerative disorders characterized by a progressive cerebellar syndrome, variably associated to signs of brainstem involvement, pyramidal or extrapyramidal manifestations and cognitive dysfunctions, among other features that confer a remarkable wide range in phenotypes (Harding, 1983; Durr, 2010).

SCAs are associated with at least 31 different genetic loci, but the responsible gene is known in only 19 of them. Causative mutations include coding CAG expansions leading to a long polyglutamine (polyQ) tract in the respective proteins (SCA1, 2, 3, 6, 7 and 17), non-coding trinucleotide or pentanucleotide expansions (SCA8, 10, 12 and 31), as well as conventional mutations (SCA5, 11, 13, 14, 15/16, 20, 27 and 28) (Durr, 2010). The worldwide prevalence of SCAs is estimated near to 5-7 cases per 100 000 inhabitants but it can be higher in some regions due to foundational effects such as SCA2 in Holguín, Cuba (Velazquez-Pérez et al., 2009a) and SCA3 in Azores islands, Portugal (Vale et al., 2010).

Oculomotor disturbances are prominent features of SCA patients as result of cerebellar and brainstem neurodegeneration (Zee et al., 1976; Pula et al., 2010). The study of eye movement abnormalities give us valuable tools to search disease biomarkers because they can be easily accessible to clinical and/or electrophysiological evaluations and their dynamic properties and neurobiological basis are well known (Leigh & Kennard, 2004; Leigh & Zee, 2006; Reilly et al., 2008). The focus of this chapter is to review the state of the art of the eye movement deficits in SCAs, emphasizing in the usefulness of these features as disease biomarkers.

2. Brief overview of eye movements

Eye movements contribute to the clear vision stabilizing images on the retina, especially against movements of the head and body, capturing and keeping particular stimuli on the fovea and aligning the retinal images in the two eyes to guarantee the single vision and stereopsis. These functions can be achieved by 5 basic types of eye movements. For example, the image stabilization on the retina is promoted by the vestibuloocular and optokinetic reflexes; the foveation occurs thorough the saccadic and smooth pursuit movements, whereas the binocular alignment is guaranteed by the vergence eye movements (Bruce & Friedman, 2002).

Eye movements differ in many aspects, such as their velocity, reaction time, reflexivity/volitional degree and their neurobiological substrate (Sparks, 2002). Nevertheless all have generic kinematic properties and share a common final path represented by three cranial nerve nuclei and the three pairs of eye muscles that they control (Bruce & Friedman, 2002; Leigh & Zee, 2006). Cranial nerve III (oculomotor) innervates superior, inferior and medial rectus muscles as well as the inferior oblique muscle, whereas trochlear (IV) and abducens (VI) nerves innervate the superior oblique and lateral rectus respectively (Leigh & Zee, 2006).

Main features and neurophysiological bases of the 5 basic types of eye movements will be briefly addressed as follow.

2.1 Vestibuloocular reflex (VOR)

The vestibuloocular reflex (VOR) is elicited by the vestibular system in response to body/head rotations and consists in compensatory eye movements in opposite direction to body/head movement to guarantee the image stabilization on the retina (Aw et al., 1996). VOR depends of two neural circuits: *a)* Basic three neurons circuit and, *b)* Neural integrator circuit.

In the basic three neurons circuit, the head/body rotations are detected and transduced by vestibular ganglion neurons in the semicircular canal. Then, the transduced information is projected to neurons of the vestibular nuclei, located in the pons, and from there to oculomotor neurons (OMN) in one of the three oculomotor nuclei. Nevertheless, the three neurons circuit by itself is unable to adequately stabilize the image on the retina because it only generates phasic innervations of the oculomotor muscles, causing the return of the eye back to the central position due to the pulling of elastic forces. The neural integrator serves to exactly overcome this elastic force producing tonic innervations of oculomotor muscles. It is located in the *prepositus hypoglossi* and medial vestibular nuclei, which receive projections from the vestibular nuclei and have recurrent connections onto themselves. Some vestibular afferents go directly to the flocculus/paraflocculus cerebellar lobe, which is involved in VOR adaptation (Bruce & Friedman, 2002).

2.2 Optokinetic reflex (OKR)

When head/body rotations are very large and continued the VOR is depressed and thus it is complemented by the optokinetic reflex (OKR), in which the speed and direction of a full-field image motion is computed to develop eye movements with two phases, an slow phase that alternates with resetting quick phase (Tusa & Zee, 1989). Pathway underlying OKR includes the nucleus of the optic tract, which receives visual motion signals from the contralateral eye and striate/extrastriate cortical areas. This information is send to the vestibular nuclei and to the inferior olivary nucleus, and then to the floccular/parafloccular Purkinje cells via their climbing fibers (Bruce & Friedman, 2002).

2.3 Saccadic eye movements

Saccades are ballistic, conjugate eye movements that redirect fovea from one object of interest to another, allowing to explore accurately the visual scenes. For that, the saccadic system processes information about the distance and direction of a target image from the

current position of gaze. Saccades are the fastest eye movements, reaching up to $600^{\circ}/s$. There are close relationships between saccadic peak velocities, durations and amplitudes, which represent the saccadic main sequence (Bahill et al., 1975, Ramat et al., 2007).

Behaviourally, the saccades may be classified as reflexive guided saccades and intentional or volitional saccades. The first ones are evoked by the suddenly appearing targets, whereas the second ones, called also higher-order saccades, are made purposely, involve high cognitive processing and include voluntary, memory guided and delayed saccades as well as antisaccades (Müri & Nyffeler, 2008; Leigh & Kennard, 2004).

The neural basis of saccadic eye movements system comprises some cortico-cortical and cortico-subcortical networks (Müri & Nyffeler, 2008). Visual information processed in the primary visual cortex is sent to higher cortical areas, such as parietal eye field (PEF) and frontal eye field (FEF), which are involved in the preparation and triggering of reflexive and intentional saccades respectively (Pierrot-Deseilligny, et al., 2004). These cortical areas project their output directly or through the basal ganglia, to superior colliculus, a midbrain structure that identifies the target in retinotopic coordinates, generates trigger signal to the brainstem premotor oculomotor circuitry and encodes the magnitude and direction of the desired eye movement. This information is projected to the cerebellum, via a pontine pre-cerebellar nucleus, which guarantees the saccadic accuracy. Premotor burst neurons (PBN) for horizontal saccades lie within the paramedian pontine reticular formation (PPRF) while burst neurons for vertical and torsional saccades lie within the rostral interstitial nucleus of the medial longitudinal fasciculus. Saccade-related cerebellar areas include the oculomotor vermis (lobules VI and VII) and the caudal region of the fastigial nucleus which send saccade commands to the contralateral PBNs leading the activation of motoneurons and oculomotor muscles related with the desired saccadic movement (Leigh & Zee, 2006; Robinson & Fuchs, 2001; Prsa & Their, 2011; Voogd et al., 2011).

2.4 Smooth pursuit movements

Smooth-pursuit eye movements enable us to maintain the image of a moving object relatively stable on or near the fovea by matching eye velocity to target velocity (Leigh & Zee, 2006). Smooth pursuit performance is optimal for target speeds ranging between $15^{\circ}/s$ and $30^{\circ}/s$ but pursuit velocity can reach up to $100^{\circ}/s$ (Lencer & Trillenber 2008; Bruce & Friedman, 2002). Smooth pursuit system is closely related to other oculomotor systems such as OKR and saccadic system. In fact, the small position errors raised when the tracking velocity is not properly matched to the target are corrected by saccadic movements named “catch up” saccades (Lencer & Trillenber, 2007).

Neuronal pathways for smooth pursuit movements involve a complex network of cortical and subcortical structures. Extrastriate visual area V5 (divided into middle temporal visual area (MT) and the medial superior temporal visual area (MST)) play a crucial role for motion perception and smooth pursuit control. This area receives visual motion information from the primary visual cortex in a retinotopic and ipsilaterally organized fashion. The MT area encodes image motion in a retinal coordinate system whereas MST area converts the signals into a spatial coordinate system. The signals generated in the V5 area are projected to other cortical areas in the parietal and frontal lobes. Among them, the frontal eye field (FEF) is involved in the generation of oculomotor command for smooth pursuit. Both visual motion

signals and oculomotor commands are relayed to oculomotor parts of the cerebellum, through the dorsolateral and medial pontine nuclei. Smooth pursuit-related areas of the cerebellum comprise the paraflocculus, the flocculus, the oculomotor vermis and the uvula, which control the initiation and maintenance of smooth pursuit. Finally, the cerebellar output is projected, via the vestibular nuclei, to the oculomotor nuclei (Lencer & Trillenber, 2007; Mustari et al., 2009).

2.5 Vergence eye movements

Vergence eye movements are disjunctive movements that provide the binocular alignment in response to changing fixation target distances, requiring that both eyes point in contrary directions (Zee & Levi, 1989). Vergence movements are elicited by retinal disparity (when a fixation target is not on both foveae) and retinal blur (when a target is not in focus) and are closely related to the lens accommodation and pupillary reflexes. Although the neural basis of vergence eye movements are not well understood, it is known that both the retinal disparity and the retinal blur signals are processed by cortical visual areas such as primary visual cortex (V1) and an anterior region of the FEF. Additionally, it is presumed an important role of the oculomotor nucleus (III) for vergence movements, due to its known relation to lens accommodation and pupillary reflexes (Vilis, 1997; Bruce & Friedman, 2002). The cerebellum is involved in the processing of dynamic vergence eye movements (Sander et al., 2009). Cerebellar regions related with these disconjugate eye movements lie on the dorsal paraflocculus, and the floccular lobe, which project to the lateral portion of the posterior interposed nucleus (Voogd et al., 2011).

2.6 Oculomotor disturbances

Oculomotor disturbances can be topographically classified as peripheral or central disturbances. Peripheral abnormalities result from lesions in the oculomotor muscles or nerves, whereas the central disturbances are caused by lesions in the brainstem, cerebellum or other higher-level centers (Karatas, 2009). Oculomotor signs of cerebellar impairment include pathological nystagmus such as downbeat, rebound and periodic alternating nystagmus, as well as abnormal pursuit, VOR/OKR abnormalities and saccadic dysmetria (Robinson & Fuchs, 2001; Strupp et al., 2011). Whereas, brainstem involvement produces slowed vertical, torsional or horizontal saccades, ophthalmoplegia, VOR/OKR impairments and gaze-evoked nystagmus (Rüb et al., 2008, Strupp et al., 2011). Affectations in the basal ganglia can lead to reduced ability to initiate voluntary eye movements and to suppress unwanted saccades, in addition to deficits in memory-guided saccades, eye-head coordination and eye-hand coordination (Hikosaka et al., 2000; Shires et al., 2010). Frontal cortex lesions produce prolongation of saccadic latency, impaired ability to make saccades to remembered target locations and errors on the antisaccade task, as well as delayed initiation of smooth pursuit and increase of catch up saccades (Pierrot-Deseilligny et al., 2004; Thurtell et al., 2007; Karatas, 2009).

3. Oculomotor findings of spinocerebellar ataxias

3.1 Spinocerebellar ataxia type 1 (SCA1)

The main eye movement abnormalities of SCA1 patients include saccadic dysmetria, gaze evoked nystagmus and depressed smooth pursuit (Matilla-Dueñas et al., 2008). Saccadic

hypermetria is observed in majority of the cases, appears at an early stage of the disease and progresses quickly (Klostermann et al., 1997; Rivaud-Pechoux et al., 1998; Buttner et al., 1998). The overshoot of saccades may reach values greater than 30% in comparison with normal subjects (Buttner et al., 1998).

Brainstem oculomotor signs such as saccadic slowing or ophthalmoparesis are observed in 74% (Schmitz-Hübsch, et al., 2008). Reduction of saccade velocity can be detected in mildly affected patients and it is accentuated with the disease duration. Advanced patients may show ophthalmoparesis or severe saccadic slowing, so that saccadic hypermetria is less noticeable in comparison to early stages (Klostermann et al., 1997). Abnormal prolongation of saccadic latency occurs in 67% of cases (Buttner et al., 1998), whereas the execution of the antisaccadic task shows increased error rates, suggesting the presence of neurodegenerative changes in the frontal cortex (Rivaud-Pechoux et al., 1998).

Reduced gain of smooth pursuit and OKN is noticed in 92% of SCA1 cases with the lowest smooth pursuit gains in comparison to SCA2 and SCA3 patients and comparable values of OKN gains to SCA2 (Burk et al., 1998). The progressive saccadic slowing causes the diminution of catch up saccades during visual tracking, leading to decrease of the smooth pursuit amplitudes on advanced disease (Buttner et al., 1998, Klostermann et al., 1997). Regarding vestibular functions, SCA1 patients are usually characterized by reduced VOR gains, which distinguish this SCA subtype from SCA2 but neither from SCA3 nor SCA6 (Burk et al., 1998; Buttner et al., 1998).

No oculomotor abnormalities of SCA1 patients correlate with the number of CAG repeats (Burk et al., 1999; Rivaud-Pechoux et al., 1998), suggesting that they are not under significant genetic control but are more dependent on disease duration.

3.2 Spinocerebellar ataxia type 2 (SCA2)

The most common oculomotor sign in patients with SCA2 is a significant reduction in horizontal saccadic eye velocity owing to brainstem involvement. This feature called attention to Wadia and Swami when made the first report of SCA2 in 1971, so that they described the disease as "*a new form of heredofamilial spinocerebellar degeneration with slow eye movements*" (Wadia & Swami, 1971). Several clinical and epidemiological studies have confirmed the high frequency of this saccadic alteration in more than 80% of cases (Velazquez-Pérez et al., 2009a; Orozco et al., 1989; Cancel et al., 1997, Wadia et al., 1998; Schmitz-Hübsch, et al., 2008).

The first electronystagmographical evaluation of SCA2 patients was conducted by Kulkarni & Wadia in 1975 who found a relative decrease of saccadic velocity up to 25% in comparison with controls (Kulkarni & Wadia, 1975). Furthermore, comparative studies of oculomotor phenotypes among patients with cerebellar ataxias demonstrated that saccadic slowing is more prominent in SCA2 patients in comparison with SCA1, SCA3, SCA6 (Burk, et al; 1999; Buttner et al., 1998; Rivaud-Pechoux et al., 1998) and late onset cerebellar ataxia (Rufa & Federighi, 2011) giving an important diagnostic value to this oculomotor feature for SCA2.

A comprehensive electronystagmographical study developed in 82 SCA2 Cuban patients showed little overlap between maximal saccadic velocity (MSV) values of SCA2 patients and controls. This study demonstrated a high sensitivity for SCA2 diagnosis assessed by a

receiver operating characteristic (ROC) yielding an area under the curve of 0.99. The most important finding of this work was the significant influence of the number of CAG repeats, but not of disease duration, on saccadic velocity (Figure 1). According to this relationship, patients with larger expansions showed more saccadic slowing, identifying the saccadic velocity as the main variable endophenotype of the SCA2, which is under strong genetic control and therefore it may be considered as a sensitive biomarker for the study of polyglutamine toxicity. Also, MSV was negatively correlated with the total score of a cerebellar ataxia scale suggesting its association with the severity of the cerebellar syndrome (Velázquez et al., 2004). Other study performed in Cuban SCA2 patients revealed a closer relationship between the saccadic velocity and the visuomotor learning capabilities assessed by a prism adaptation task (Fernandez-Ruiz, et al., 2007).

A preliminary follow-up evaluation of saccadic slowing after one year in 30 SCA2 patients revealed no significant changes of MSV (Seifried et al., 2004). Nevertheless, other follow-up study during a larger period time it is being conducted in a large Cuban SCA2 cohort.

The saccadic slowing appears during the presymptomatic stage of the disease only for 60° target amplitude, but asymptomatic subjects carrying full-penetrant CAG expansions (≥ 36) show reduced MSV values even for 30°. In fact, the MSV reduction is stronger in carriers of large expansions. This preclinical feature progresses insidiously and it correlates with predicted time to clinical manifestation, which classifies this variable as a preclinical biomarker of high values for diagnosis and prognosis of the disease (Velázquez-Pérez et al., 2009b).

The neuroanatomical basis of this disorder has been elucidated by post-mortem studies that demonstrated the marked loss of excitatory PBN in the PPRF (Buttner-Ennever, et al., 1985; Geiner et al., 2008), the structure that coordinates the horizontal saccades (Leigh & Zee, 2006). Early, Gierga et al, 2005 had reported a significant neuronal death in the abducens (cranial nerve VI) and oculomotor nucleus (cranial nerve III), which innervate the oculomotor muscles responsible for eye movements in the horizontal plane (Leigh & Zee, 2006).

Hypometric saccades to extreme gaze positions are usual in SCA2 patients (Velázquez, 2008), nevertheless for short target amplitudes the saccade accuracy is maintained, although some patients can make hypermetric saccades. It has been suggested that as SCA2 patients having slow saccades that are no longer ballistic, visual feedback might be continuously available during the movement execution to guide the eye to its target rendering accurate short saccades (Federighi et al., 2011).

A recent electronystagmographical study in 110 SCA2 patients demonstrated the significant prolongation of saccadic latency in 46% of SCA2 patients. This variable was neither influenced by the CAG repeats, disease duration nor ataxia score, but it was close related with the neuropsychological performance of frontal-executive tasks, which highlights the saccadic latency as sensitive biomarker of cognitive disorders in SCA2 (Rodríguez-Labrada, et al., 2011a). Additionally, SCA2 patients show increased antisaccadic error rate (Rivaud-Pechoux et al., 1998). The delayed saccade onset and antisaccadic deficits could be explained by the severe gyral atrophy and neuronal loss in the frontal lobes and neurodegenerative changes in caudate nucleus and substantia nigra (Orozco et al., 1989; Durr et al., 1995; Estrada et al., 1999; Gierga et al., 2005), as well as deficits in the processing

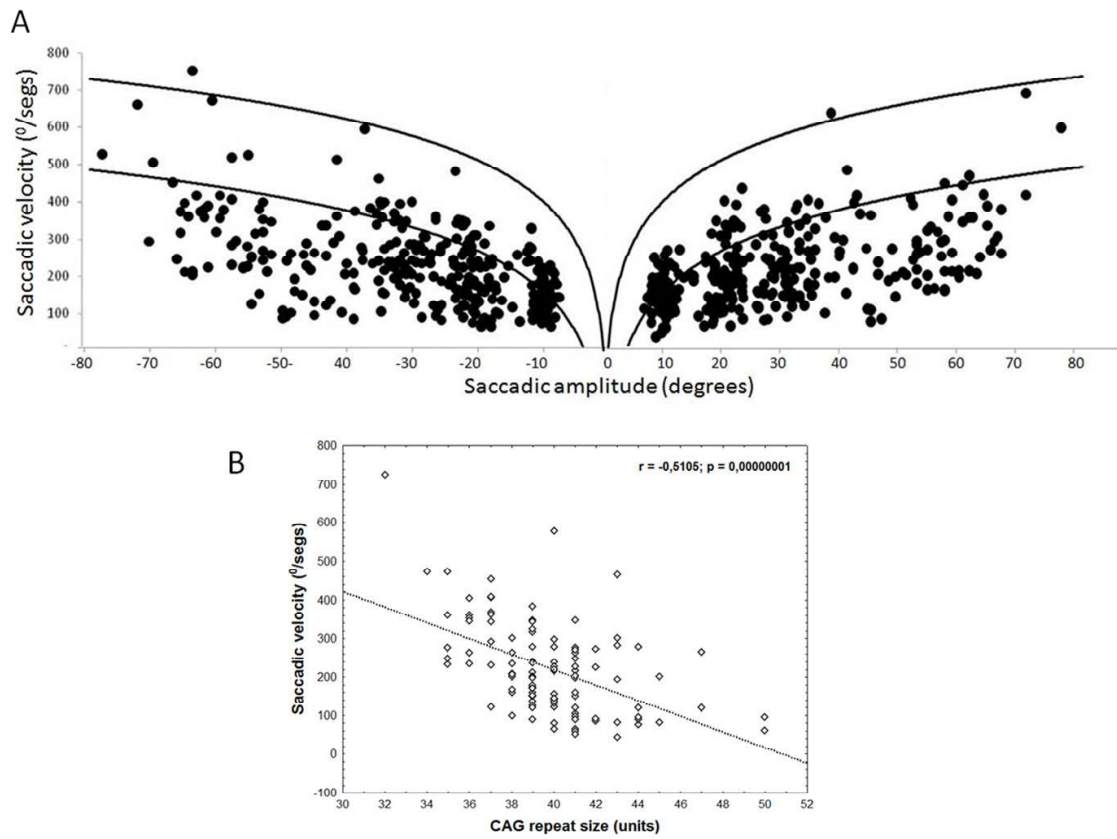


Fig. 1. Saccadic slowing in SCA2. A) Relationship of saccadic velocity and amplitudes in SCA2 patients. Show the significant reduction of saccadic velocity in almost all subjects. Dark lines represent the saccadic velocity ± 2 SD of controls. B) Influence of CAG repeat size on the saccadic velocity.

of visual information (Kremlacek et al., 2011) or in the visual-spatial attention (Le Pira et al., 2002).

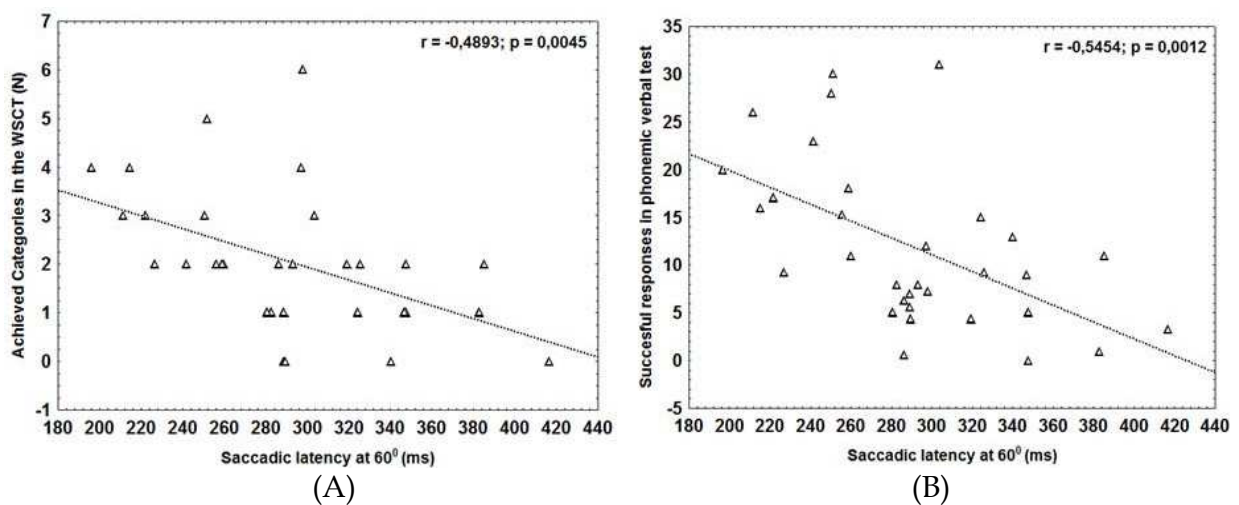


Fig. 2. Saccadic latency correlates with frontal-executive dysfunctions in SCA2 patients. Correlation analyses of saccadic latency with achieved categories in the Wisconsin sort card test (WSCT) and the number of correct responses in the phonemic verbal test.

Other oculomotor alterations include ophthalmoplegia, which usually appears at advanced disease in the 45% of the cases, although the severe saccadic slowing might overlook the frequency of ophthalmoplegia in SCA2. These patients have mild reduction of smooth pursuit gain in correspondence with the atrophy of cerebellar flocculus (Ying et al., 2006) and the decrease of catch up saccades. The physiological and pathological nystagmus are very rare in SCA2 due to impaired ability to produce saccadic corrective phases. Some SCA2 patients have VOR responses with reduced gain (Burk et al., 1999; Rivaud-Pechoux et al., 1998; Buttner et al., 1998).

Saccadic eye movements have also been used to evaluate the efficacy of therapeutical alternatives in Cuban SCA2 patients, such as neurorehabilitation (Rodríguez et al., 2008) and oral supplementation with zinc-sulphate (Velázquez-Pérez et al., 2011a). In both cases the saccadic latency decreased significantly after the therapies, but saccadic velocity and dysmetria were unchanged.

For SCA2, the oculomotor function has not only evaluated in wake state, since the density of rapid eye movements (saccadic) during REM sleep was recently assessed. Both symptomatic and presymptomatic subjects show a marked decrease in this parameter, which is negatively correlated with the ataxia score in the patients (Velázquez-Pérez, et al., 2011b; Rodríguez-Labrada et al., 2011b). These findings suggest the usefulness of saccadic density during REM sleep as progression marker of the disease and reflect the extension of the oculomotor brainstem involvement to the sleep.

3.3 Spinocerebellar ataxia type 3 (SCA3)

Pathological nystagmus are prominent oculomotor signs of SCA3 patients. The frequency of gaze evoked and rebound nystagmus is approximately 90% (Jardim et al., 2001) being higher than those in SCA1, SCA2 and SCA6. Square wave jerks are usually reported in SCA3 subjects, unlike SCA1 and SCA2 individuals (Buttner et al., 1998; Burk et al., 1998). This oculomotor sign results from cerebellar disease and consists in small, horizontal, saccade-like movements that lead the eye away from the target trajectory and, after a delay, bring it back onto the target (Leigh & Zee, 2006).

Decreased VOR gain can be detected in majority of SCA3 patients and correlates with the CAG repeats, suggesting the pathologic involvement of the vestibular nuclei in the lateral brainstem. Furthermore, these patients show reduction of smooth pursuit and OKR gains with a presentation frequency above 70% in both cases (Buttner et al., 1998; Burk et al., 1998).

Upon saccades, the main abnormality is saccadic dysmetria. Nevertheless, there are apparently conflicting data regarding the predominant type of dysmetria. Buttner et al., 1998 reported hypermetric saccades in 86% of the cases, while Rivaud-Pechoux et al., 1998, observed a predominance of hypometric (56%) over hypermetric saccades (18%). The disagreement can be explained by differences in the clinical stage of studied patients. In fact, the 81% of the patients recruited by Rivaud-Pechoux and colleagues had a moderate to severe motor disability, which could explain the higher prevalence of saccadic hypometria.

Different to SCA2 and SCA1, decreased saccadic velocity is not a common feature of SCA3 patients (Burk et al., 1999; Rivaud-Pechoux et al., 1998; Buttner et al., 1998). This oculomotor feature appears in advanced disease, perhaps in correspondence with the degenerative

changes seen in the raphe interpositus nucleus (Rub et al., 2003), a key structure of the brainstem premotor network that contains the omnipause neurons, a group of cells that play an important role in determining the size of the velocity command for saccades, beside their well-known role as gating saccades (Miura & Optican, 2006). Also, internuclear and nuclear ophthalmoplegia is observed in 53% and 10% of the cases respectively. The latter is associated with a more severe disease course (Jardim et al., 2001).

Finally, the prolongation of saccadic latency occurs late in few cases (14%) (Buttner et al., 1998) and the performance in the antisaccadic paradigm shows an increase in the number of errors (Rivaud-Pechoux et al., 1998).

3.4 Spinocerebellar ataxia type 6 (SCA6)

Oculomotor function of SCA6 patients is characterized by signs of cerebellar and vestibular impairments such as horizontal and vertical nystagmus, abnormal smooth pursuit, saccadic dysmetria and abnormal VOR (Buttner et al., 1998; Christova et al., 2008; Bour et al., 2008). In comparison with other SCAs, the spontaneous downbeat nystagmus and square-wave jerks have the higher incidence in SCA6 subjects, whereas gaze-evoked nystagmus, rebound nystagmus and periodic alternating nystagmus are common features too (Buttner et al., 1998; Colen et al., 2008; Kim et al., 2010).

Patients with SCA6 have the more severe pursuit, OKN and VOR-fixed deficits among other polyglutamine SCAs but these oculomotor signs are not directly associated to CAG repeats or disease duration (Buttner et al., 1998). Vertical pursuit is impaired more than horizontal whereas downward pursuit more than upward (Bour et al., 2008).

The pattern of saccadic dysmetria in SCA6 is variable since these patients can show both hypometric and hypermetric saccades (Buttner et al., 1998; Bour et al., 2008). Although the decrease of saccadic velocity is not a prominent sign in these patients, it has been reported a mild saccadic slowing in some subjects both for the horizontal and vertical planes (Bour et al., 2008). These findings suggest functional extracerebellar impairment in the saccadic system and therefore are opposed to the paradigm of SCA6 as a "pure cerebellar syndrome." In fact, the screening of non-ataxia signs reveals a 25% of brainstem oculomotor signs (Schmitz-Hübsch, et al., 2008). In these patients the saccadic latency is normal (Buttner et al., 1998).

In 2009, Christova and co-workers studied the eye movement's abnormalities in both symptomatic and asymptomatic SCA6 cohorts and noticed that square-wave jerks, saccadic abnormalities and depressed smooth pursuit can be detected even before the disease onset. Among them, the square-wave jerks were the most prominent with an apparition frequency of 80% (Christova et al., 2008).

3.5 Spinocerebellar ataxia type 7 (SCA7)

The major saccadic alteration in this SCA is the slowing of saccades, together with saccadic dysmetria (Miller et al., 2009; Manrique et al., 2009). The decrease in saccadic velocity in SCA7 is associated with marked pontine atrophy that characterizes these patients from early stages of the disease and progresses to produce significant external ophthalmoplegia in patients with longer disease history (Bang et al., 2004; Martin et al., 1999). These alterations

may precede cerebellar and retinal manifestations and are among the earliest signs of the disease (Oh et al., 2001). In addition, some cases have difficulties to initiate the saccadic eye movements and may develop gaze evoked nystagmus (Miller et al., 2009; Manrique et al., 2009).

3.6 Spinocerebellar ataxia type 17 (SCA17)

The patients with SCA17 show hypometric saccades in correspondence with the marked reduction of Purkinje cells in the cerebellum (Hubner et al., 2007). The saccadic hypometria is increased with disease duration but neither with ataxia score nor the number of CAG repeats. In 26% of cases, there are transient saccadic decelerations and accelerations causing hypometric saccades with multiple steps. Clinical assessments have reported normal (Nakamura, 2001) or slowed saccades (Rolfs et al., 2003), although the hypometria or prematurely terminated saccades may conduce to the erroneous classification of slowed saccades. In these patients, the saccadic latency is normal, while antisaccades have a significant increase in the error rate (Hubner et al., 2007).

Smooth pursuit abnormalities in SCA17 patients include decrease of initial eye acceleration, which appears even in the asymptomatic and mildly affected SCA17 mutation carriers, reduced steady state velocity and prolongation of smooth pursuit latency. Smooth pursuit gain decreases with the disease duration and ataxia score, whereas the latency prolongation correlates positively with the ataxia score. Gaze-evoked nystagmus is not a prominent feature in SCA17 patients (Hubner et al., 2007).

3.7 Other spinocerebellar ataxias

With the exception of polyglutamine expansions SCAs, the oculomotor function of remaining SCAs has not been systematically studied while most of data result for clinical assessment. SCA5 is characterized by eye abnormalities owing to cerebellar impairments such as downbeat nystagmus and impaired smooth pursuit movements (Ranum et al., 1994; Ikeda et al., 2002). Similar features occur in SCA8, in addition to saccadic dysmetria (Day et al., 2000; Koob et al., 1999), and SCA10 (Zu et al., 2000; Grewal et al., 2002; Lin & Ashizawa, 2005). SCA11 is associated with horizontal and vertical nystagmus as well as jerky pursuit (Worth et al., 1999), while approximately one third of SCA12 patients can develop saccadic slowing, abnormal smooth pursuits or pathological nystagmus (Worth et al., 1999, Fujigasaki et al., 2001). Besides, in subjects affected with SCA13 is usual to observe horizontal nystagmus (Stevanin et al., 2005; Waters & Pulst, 2008).

Regarding SCA14, the main oculomotor disturbance is the hypermetria of downgaze and horizontal saccades, even from the early stages of the disease. Additionally, upwards gaze evoked nystagmus are common in patients with longer disease duration. Smooth pursuit movements and VOR are also impaired (Yamashita et al, 2000; Brkanac et al, 2002a; Fahey et al., 2005). Eye movement abnormalities of SCA15/16 and SCA18 include nystagmus for all these SCA subtypes associated to saccadic dysmetria in the first one (Miyoshi et al., 2001; Brkanac et al, 2002b; Gardner et al., 2005). In addition, hypermetric saccades into downgaze and lateral gaze are detected in some patients with SCA20 (Knight et al., 2004).

SCA22 patients show nystagmus and impaired smooth pursuit with intermittent corrective saccadic (Chung et al., 2003), while in SCA23 the ocular dysmetria and slowed saccades can

be noted (Verbeek et al., 2004; Verbeek, 2009). SCA25, SCA26 and SCA27 are characterized by pathological nystagmus in some patients, associated with slow eye movements in SCA25, abnormal pursuit in SCA26 and saccadic dysmetria in SCA27 (van Swieten, et al., 2003; Stevanin et al. 2004; Yu et al., 2005). SCA28 patients develop gaze-evoked nystagmus at early disease, while subjects with advanced disease have slowed saccades and ophthalmoparesis with frequency estimates of 60% and 80% respectively (Cagnoli et al., 2006). SCA29, which overlap with SCA15, is characterized by bilateral horizontal nystagmus (Dudding et al., 2004). In the case of SCA30, hypermetric saccades and gaze evoked nystagmus can be detected (Storey et al., 2009), as well as abnormal pursuit in SCA31 (Ishikawa et al., 2004). Finally, in a new SCA subtype recently identified by Wang et al., 2010 in two Chinese families, it was observed ocular dysmetria as main oculomotor sign.

4. Conclusions

Eye movement abnormalities are among the most common phenotypic manifestations of patients with SCAs. The most prominent oculomotor feature is the presence of pathological nystagmus in almost all subtypes, which is generally associated to abnormal smooth pursuit, saccadic dysmetria, impaired VOR/OKR, saccadic slowing and ophthalmoplegia. These oculomotor phenotypes are useful, but not determinant, for the differential diagnosis of SCAs. For example, the early and severe saccadic slowing with rare pathological nystagmus distinguishes SCA2 from SCA1, SCA3, SCA6, SCA17 and other SCA subtypes, whereas the marked abnormalities of smooth pursuit, VOR and OKR; in association with pathological nystagmus and rare saccadic slowing may help to define a SCA6 phenotype. Nevertheless, the notable overlapping of oculomotor features between SCA subtypes implies the requirement of other clinical criteria or the genetic testing for sensitively discriminating among these diseases.

The study of eye movement abnormalities allows the identification of several biomarkers useful in the clinical and research practice of SCAs. Some of the oculomotor disturbances precede the ataxia onset, being important preclinical markers to detect the early stages of the neurodegenerative process, to evaluate the genetic susceptibility of the asymptomatic relatives and to identify individuals close to ataxia onset for enrollment in preventive clinical trials and as potential outcome variables in these same trials. As most of the oculomotor abnormalities of SCAs are significantly accentuated with the advance of the disease, these can be used in monitoring clinical progression and therefore to assess the response to symptomatic treatments at short, medium or long term. The number of CAG repeats influences significantly on the saccadic slowing in SCA2 and the reduced VOR gain in SCA3 classifying these oculomotor features as sensitive biomarker of genetic damage, useful to evaluate the effect of modifying factors and therapeutic alternatives on the polyglutamine toxicity.

Despite the above, still is necessary to deep more into the study of oculomotor function in SCAs. For example, vergence movements have not been studied, in spite of the known role of the cerebellum in these eye movements (Robinson & Fuchs, 2001) and the correspondent vergence deficits in patients with circumscribed cerebellar lesions (Sender et al., 2009). Moreover, further neuropathological, imaging and transcranial magnetic stimulation studies are required to focus the oculomotor system in order to provide more

insight on eye movement abnormalities and its potential role as therapeutic biomarkers in SCAs.

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6. References

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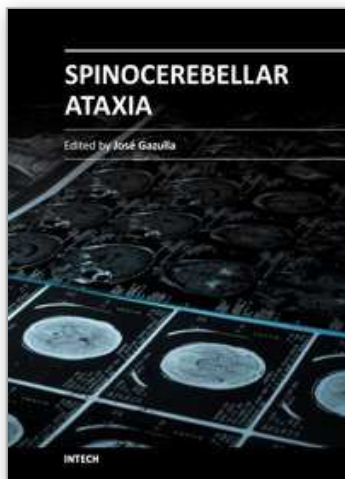
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