Visual oculomotor abnormalities and vestibulo-ocular reflex dynamics in polyglutamine spinocerebellar ataxias (Review)

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Abstract. Spinocerebellar ataxias (SCAs) are a group of autosomal dominant neurodegenerative diseases that are characterized by cerebellar ataxia. The most common types of SCAs are caused by polyglutamine (polyQ)-encoding cytosine-adenine-guanine repeat expansions. Autosomal dominant SCAs share similar pathophysiological mechanisms. The cerebellum plays an important role in the generation and control of eye movement, and neuropathological findings indicate that cerebellar degeneration is commonly present in polyQ-SCAs. As a result, various patterns of oculomotor impairment are present in most SCA subtypes. The present review summarizes the visual oculomotor abnormalities and vestibulo-ocular reflex dynamics of the most common polyQ-SCAs, as well as their genetic, clinical and neuropathological features. In conclusion, the systemic evaluation of eye movement features is useful in the differential diagnosis of polyQ-SCAs.

Contents

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Abbreviations: SCA, spinocerebellar ataxia; ADCA, autosomal dominant cerebellar ataxia; CAG, cytosine-adenine-guanine; polyQ, polyglutamine; OKN, optokinetic nystagmus; VOR, vestibulo-ocular reflex; HIT, head impulse test; SARA, scale for the assessment and rating of ataxia; SWJs, square wave jerks; GEN, gaze-evoked nystagmus; ALS, amyotrophic lateral sclerosis; MRI, magnetic resonance imaging; UGP, upward gaze palsy; SPEM, smooth pursuit eye movement; VORr, regression of VOR; VVOR, visually enhanced VOR; DBN, downbeat nystagmus; pHSN, perverted head-shaking nystagmus

Key words: spinocerebellar ataxias, polyglutamine, oculomotor abnormalities, vestibulo-ocular reflex dynamics, cerebellum

1. Introduction

Spinocerebellar ataxias (SCAs) are a genetically heterogeneous group of autosomal dominant inherited neurodegenerative diseases (1). The estimated global prevalence of SCAs was ~2.7 per 100,000 individuals between 1983 and 2013 (2). The most common clinical characteristic of SCA is progressive cerebellar ataxia. Notably, SCAs also present with variable non-ataxia clinical manifestations, including a variety of movement abnormalities (parkinsonism, dystonia and chorea), brainstem and cerebellar oculomotor signs, pyramidal tract signs, sensory symptoms, autonomic symptoms, cortical symptoms (cognitive impairment, speech disturbance, epilepsy and myoclonus), pigmentary retinopathy and peripheral neuropathy (1,3). For the majority of SCAs, ataxia appears in the third or fourth decade of life, but there are some differences between and within genotypes and families (1). According to a previous study (4), SCA can be classified as autosomal dominant cerebellar ataxia (ADCA) type I, II or III. The clinical presentation of ADCA type I involves cerebellar ataxia associated with ophthalmoplegia, dementia, extrapyramidal signs, optic atrophy and amyotrophy; that of type II involves cerebellar ataxia, retinal degeneration with or without ophthalmoplegia and extrapyramidal features, while at present SCA 7 is the only member of type II that has been revealed; and type III is defined as pure cerebellar ataxia (4).

SCAs are heterogeneous and encompass numerous genetically distinct subtypes. To date, ~50 clinically distinct SCA subtypes have been identified (4). SCAs can be grouped into two major types according to their genetic mutations, those caused by microsatellite repeat expansions and those caused by point mutations (5). A number of SCAs share similar pathophysiological mechanisms, with at least 12 subtypes caused by repeat expansion mutations (1). The most universal SCAs (SCA1, SCA2, SCA3, SCA6, SCA7 and SCA17) result from similar polyglutamine (polyQ)-coding

cytosine-adenine-guanine (CAG) trinucleotide repeat expansions; these SCAs are referred to as polyQ-SCAs (6,7).

Patients with polyQ-SCAs exhibit increased disease severity and shorter survival (8), and their symptoms typically begin in adulthood. Gait difficulty has been reported as the first abnormality in the majority of cases of SCA1, SCA2 and SCA3 (9). Moreover, various clinical signs and symptoms are key characteristics of certain polyQ-SCAs, as follows: i) Prominent slow saccades are hallmarks of SCA2; ii) dystonia and spasticity are often observed in SCA3; iii) SCA6 is characterized by slowly progressive cerebellar ataxia and extracerebellar symptoms are rarely observed; iv) visual loss due to retinal and macular degeneration is typical of SCA7; and v) pyramidal signs and seizures are prominent features of SCA17 (4).

In repeat expansion SCAs, there is a negative correlation between the onset age of the first symptoms and the CAG expanded repeat length, meaning that longer polyQ expansions are associated with earlier disease onset and increased severity of symptoms (10,11). CAG repeat length has also been revealed to be a significant predictive factor of conversion to ataxia in non-ataxic SCA1 and SCA2 mutation carriers (12).

The most frequent site of degeneration in SCAs is the cerebellum and its connections, and other pathological regions include the brainstem, basal ganglia and spinal cord (1,13). Although repeat expansions are the main cause of polyQ-SCAs, each subtype is attributed to distinct mutations in their respective genes (Table I), which is the primary factor underlying the different pathological characteristics of the diverse SCA subtypes (6). Neuropathological studies provide evidence that SCA6 is characterized by pure cerebellar atrophy, while marked degeneration involving several brainstem and cerebellar structures has been observed in patients with SCA1, SCA2, SCA3 or SCA7 (13). In addition, patients with SCA17 display degeneration of the cerebrum, brainstem and cerebellum (13). Severe loss of Purkinje cells in the cerebellum is one of the principal features of SCA1, SCA2 and SCA6 (13,14), whereas Purkinje neurons are relatively preserved in SCA3 (14). Results from a prospective, longitudinal observational study indicated that cerebellar atrophy in SCA1 and SCA2 and brainstem atrophy in SCA2 are present even in the preclinical stage (15).

The cerebellum plays an important role in the coordination of eye movements; hence, abnormal eye movements are common in patients with SCA (16-18) and are considered diagnostic markers of cerebellar involvement. Cerebellar oculomotor disturbances include nystagmus, slow saccades, saccadic hypometria/hypermetria, saccadic intrusions, abnormalities of smooth pursuit and impaired optokinetic nystagmus (OKN). A retrospective study indicated that oculomotor impairments are universal, even in the initial stages of SCAs (19).

The vestibulo-ocular reflex (VOR) is a normal physiological reflex that maintains gaze stability during rapid head rotation. The head impulse test (HIT) is widely used to detect high-frequency VOR function of six semicircular canals (20). It has been demonstrated that central vestibular lesions involving the brainstem or cerebellum are associated with specific patterns of HIT abnormalities (21).

The present article summarizes and reviews the visual oculomotor abnormalities and VOR dynamics associated with the most widespread polyQ-SCAs. Their genetic, clinical and neuropathological manifestations are also described. A summary of genetic, neuropathological, visual oculomotor and VOR findings in the six polyQ-SCA subtypes is presented in Table I.

2. SCA type 1

An unstable CAG nucleotide repeat expansion mutation in *ATXN1*, the gene encoding the ataxin-1 protein residing on chromosome 6p22.3, is the genetic cause of SCA1 (22). The normal range of the CAG repeat size is 6-39 repeats, whereas pathological SCA1 alleles contain 41-83 triplet units (7).

Among polyQ-SCAs, SCA1 has the most rapid progression rate (3,23,24) and the shortest survival rate (8). Longer CAG repeat lengths (23,24), earlier age at onset (23) and older age at trial inclusion (24) are associated with faster clinical progression in patients with SCA1; the longer the repeat length, the faster the disorder progresses. Moreover, a higher baseline Scale for the Assessment and Rating of Ataxia (SARA) score and dysphagia are predictors of shorter survival in patients with SCA1 (25).

SCA1 involves moderate to severe neuronal cell loss in the cerebellar Purkinje layer, dentate, nucleus pontis, olivary complex, red nucleus, dorsal accessory nucleus, middle cerebellar peduncle and restiform body (26). Data from a multicenter cohort study have suggested that posture and gait impairments are associated with brainstem atrophy in these patients (27).

SCA1 is characterized by progressive gait impairment and, as the disease progresses, clinical extracerebellar presentations include dysarthria, dysphagia, spasticity, cognitive impairments and sensory deficits (28). Brisk deep tendon reflexes (29) and pyramidal tract signs are more common in patients with SCA1 compared with patients with other SCA subtypes (3,30), and older age is correlated with cognitive deficiencies and urinary dysfunction (3).

Visual oculomotor impairments in SCA1 are common, but not specific. Normal saccadic latency (31), reduced saccadic velocity and saccadic dysmetria have been documented in SCA1-affected individuals (16,19,30,31). Other eye movement abnormalities include an increased number of square wave jerks (SWJs) (19,31,32), gaze-evoked nystagmus (GEN) (16,27,30,32), impaired smooth pursuit (16,19,27,30) and vertical OKN (29,33). Moreover, VOR impairment has been revealed in several reports of low-frequency (34) and high-frequency (35) VOR examinations. However, there is no correlation between the extent of VOR impairment and CAG repeat length (34,35).

3. SCA type 2

SCA2 is caused by a glutamine-encoding CAG repeat expansion in the coding region of *ATXN2* localized on chromosome 12q24.12 (36). The normal range of repeats is 14-32 units (5), and sequence analysis has revealed that the majority of normal *ATXN2* alleles have 22 CAG repeats (37), whereas long length expansions (≥33 pure CAG repeats) cause SCA2 (38,39). Intermediate length polyQ expansions (27-33 repeats) in *ATXN2* have been reported to increase the risk of amyotrophic

Table I. Genetic features, neuropathological findings, oculomotor abnormalities and VOR dynamics in polyglutamine-SCAs.

Subtype	Gene	Location	Normal range (expanded repeats)	Neuropathology	Oculomotor abnormalities	VOR dynamics	(Refs.)
SCA1	*ATXN1*	6p22.3	6-39 (41-83)	Cerebellum, brainstem, basal ganglia and cortex	Normal saccadic latencies, slow saccadic speed, increased number of SWJs, saccadic dysmetria, impaired smooth pursuit and OKN, GEN	Significantly impaired VOR gain	(16,19,27,29-35)
SCA2	*ATXN2*	12q24.12	14-32 (>33)	Cerebellar cortex, pontine nuclei, red nucleus, substantia nigra and thalamus	Slow saccades, prolonged saccadic latency, saccade hypometria, increases of anti-saccadic errors	Normal VOR function	(15,16,27,29,32,34,35,50-57)
SCA3	*ATXN3*	14q32.12	12-44 (45-86)	Dentate nuclei, pontine nuclei, basal ganglia, substantia nigra, red nuclei and spinal cord	Ophthalmoplegia, vergence abnormalities, SWJs, saccadic intrusions/ oscillations and saccadic dysmetria, increased total anti-saccadic error rate, impaired smooth pursuit, GEN, positional horizontal nystagmus	Reduced instantaneous VOR and VORr gain, prolonged VOR latency, VVOR and SHIMP deficit	(9,12,15,16,27,30-32,35,64-80)
SCA6	*CACNA1A*	19p13.13	4-18 (20-33)	Cerebellar Purkinje cells	SWJs, saccadic dysmetria, severe impairment of smooth pursuit, GEN, DBN, pHSN, PAN, rebound nystagmus	Normal or increased VOR gain during low-frequency stimuli, decreased VOR gain during high-frequency stimulation	(16,27,30,32, 91-98)
SCA7	*ATXN7*	3p14.1	7-34 (>36)	Cerebral and cerebellar cortex, thalamus, subthalamic nucleus, pallidum, substantia nigra and cervical spinal cord	Saccadic slowing, saccadic dysmetria, saccadic intrusions, impaired smooth pursuit, GEN	Not reported	(19,30,105,109,110)
SCA17	*TBP*	6q27	25-42 (41-66)	Cerebellum, brainstem, cerebral cortex and caudate nucleus	Saccadic dysmetria, increased anti-saccades and memory-guided saccades error rates, impaired smooth pursuit and OKN, GEN, DBN, reboundnystagmus, central positional nystagmus, headshaking and vertical pendular nystagmus	Reversed catch-up saccades, increased gains during the VVOR test	(113,120-122)

DBN, downbeat nystagmus; pHSN, perverted head-shaking nystagmus; GEN, gaze-evoked nystagmus; OKN, optokinetic nystagmus; PAN, periodic alternating nystagmus; SHIMP, suppression head impulse test; SWJs, square wave jerks; VOR, vestibulo-ocular reflex; VVOR, visually enhanced VOR; SCAs, spinocerebellar ataxias; *ATXN*, ataxin; VORr, regression of VOR; *CACNA1A*, calcium voltage-gated channel subunit α1 A; *TBP*, TATA-binding protein.

lateral sclerosis (ALS) (40) and are correlated with an earlier age of onset (40) and shorter survival (41) in patients with ALS.

The cerebellar cortex, pontine nuclei, red nucleus, substantia nigra and thalamus are severely affected in SCA2, whereas the deep cerebellar nuclei are relatively less affected (13). Brain magnetic resonance imaging (MRI) in a previous study revealed that the majority of patients with SCA2 exhibit cerebellar and pontine atrophy even in the early phase (30), as well as a significant reduction in the midbrain and frontal lobe volumes (42).

SCA3 is the most common SCA (7,43), while SCA2 is the second most prevalent subtype in the world (43), with a mean age of onset in the early 30 s (44). A lower age of onset (23,24) and longer repeat expansions (24) are associated with faster disease progression in SCA2. A multicenter study of 163 patients with SCA2 revealed that longer repeat expansions and earlier age of onset increases the possibility of muscle atrophy and brainstem ocular movement signs (3).

Parkinsonism is a relatively frequent syndrome in SCA2 (45) and is associated with short-interrupted CAG expansions between 33 and 43 repeats (46). Patients with parkinsonism-predominant SCA2 exhibit fewer asymmetrical signs and less rigidity compared with individuals with autosomal dominant parkinsonism caused by the G2019S mutation in leucine rich repeat kinase 2, and they are significantly less severely affected compared with those with other genetic causes (39). Other common movement disorders in patients with SCA2 include myoclonus, dystonia and chorea (45).

Peripheral neuropathy is relatively frequent in SCA2, and several studies have demonstrated that hyporeflexia or areflexia are the most frequent signs, even in the early stages (29,30); however, motor sensory axonal neuropathy is the most common electrophysiological presentation (47). The most frequent complaint in non-ataxic mutation carriers is muscle cramps (48), which seems to be a special incipient symptom in patients with SCA2. Other reported prodromal symptoms include dysautonomia, cognitive disorders and olfactory dysfunction (49).

Early-onset slowing of saccades is the predominant ocular feature of SCA2 (50-52). It is estimated that a substantial maximal saccadic velocity reduction at large target amplitude can be detected even in SCA2 pre-symptomatic expansion carriers (51). In addition, saccade slowing exhibits high familial aggregation (52) and is inversely correlated with the length of the CAG expanded repeats in both patients with SCA2 (50) and preclinical carriers (51). Notable increases in saccade latency are observed in individuals with SCA2 and have been associated with impaired frontal-executive functions (53). Furthermore, a prospective study monitoring saccadic eye movements over a period of 5 years indicated a high annual progression rate of saccade, a massive decline in saccade velocity and saccade accuracy and prolongation of saccadic latency in 30 patients with SCA2 (54). However, there may be no evident oculomotor disorders during the preclinical stage of SCA2 (15).

The anti-saccade task provides an objective tool for investigating executive functions such as inhibitory control, working memory and sustained attention abilities. Lower corrected anti-saccadic errors (55), higher directional anti-saccadic error rates, prolonged latencies of pro-saccades and corrective anti-saccades (55,56) have been revealed in patients with SCA2. CAG expansions demonstrate a positive relationship with the inhibitory anti-saccadic error rate and a negative relationship with the percentage of corrected inhibition of anti-saccadic errors (55).

GEN and dysmetric saccades are less frequent in patients with SCA2 (16,27,32). Moreover, hypometric saccades are more common compared with hypermetric saccades and are associated with a decreased functional status (16). By contrast, a prospective cross-sectional observational study in patients with SCA2 observed vertical OKN impairment in all patients, indicating that, compared with measuring saccadic slowing, OKN testing may have a higher sensitivity for detecting early oculomotor dysfunction (29).

To the best of our knowledge, few studies have measured vestibular function in SCA2 mutation carriers, and the preservation of VOR function has been described in these studies (34,35,57). A recent study demonstrated that prominent dynamic visual acuity impairment is highly prevalent even in patients with normal vestibular function and has a statistically significant correlation with VOR deficits (57).

4. SCA type 3

SCA3 arises from expanded CAG repeats in *ATXN3* on chromosome 14q32.12 (58), and is the most common subtype of polyQ SCA globally (7,43), with an average age at onset of 30-40 years (9).

Normal alleles contain <44 CAG repeats, whereas affected alleles in the majority of SCA3 cases usually contain 56-86 repeats (5). However, it has been revealed that intermediate length (53 or 54 repeats) expansions in *ATXN3* may manifest as restless legs syndrome, polyneuropathy and fasciculations (59).

There is marked degeneration of the dentate nuclei, pontine nuclei, basal ganglia, substantia nigra and red nuclei, as well as neuronal loss in multifarious cranial nerve nuclei, anterior horns and Clarke's columns of the spinal cord in patients with SCA3; however, the inferior olive and cerebellar Purkinje cells are relatively preserved (6,13,14). *In vivo* MRI brain scans depict the steepest decline in pontine volume throughout the course of the disease, which is related to CAG repeat length, severity of ataxia and time of life (60). Furthermore, significant hypothalamic atrophy has been observed in a recent report (61).

The predominant clinical feature of SCA3 is progressive ataxia associated with variable extrapyramidal syndrome, pyramidal signs, peripheral neuropathy and various oculomotor abnormalities (6,62). Dystonia is a frequent symptom (29,45) and a predictor of shorter survival (25) in patients with SCA3. Previous studies have recognized that a larger CAG repeat length is associated with a pyramidal phenotype and dystonia (3,63), whereas peripheral motor signs are independent of repeat length and are mainly influenced by age at onset and disease duration (3).

Various types of ophthalmoplegia are more ubiquitous in SCA3 compared with other SCA subtypes (16,64), while vertical gaze palsy is more common compared with horizontal gaze palsy (16). A recent study established that upward gaze palsy (UGP) and bulging eyes signs are common in

SCA3, while UGP shows a positive relationship with CAG expansions, age and disease duration (64). Furthermore, diplopia has been reported as the initial complaint preceding gait ataxia, and is more frequent among patients with SCA3 (9). Double vision is the strongest predictive factor for conversion to ataxia in SCA3 mutation carriers (12). Other non-motor symptoms include emotional and executive disorders, dysautonomia, sleep disturbances and memory deficits (30,65).

Abnormal oculomotor disturbances are common in patients with SCA3. Common eye movement impairments include gaze-evoked nystagmus, impaired smooth pursuit, saccadic intrusions and saccadic dysmetria (27,66,67). Furthermore, the number of different types of ocular motor abnormalities, including impaired smooth pursuits, increased SWJs and GEN, is positively associated with ataxia severity (66) and is not related to the length of CAG repeats (68).

Nystagmus has been described in both symptomatic (27,32,69) and pre-symptomatic carriers (12,15,69). Moreover, nystagmus can be the sole neurological sign of the early phase in clinical patients with SCA3 (70). A central oculomotor study has indicated that frequent SWJs during fixation and gaze holding, lower vertical smooth pursuit eye movement (SPEM) gain, decreased upward peak saccade velocity and increased total anti-saccadic error rate are common characteristics in pre-SCA3, while patients with ataxic SCA3 usually manifest as GEN, impaired horizontal SPEM and saccadic dysmetria (68). These results have been confirmed by a recent ongoing single-center prospective study, which revealed that GEN, broken-up smooth pursuit and alteration of reflexive and volitional vertical saccades can be detected in the pre-symptomatic stages (71).

SWJs are also common among individuals with SCA3 (16,30-32) and have been revealed to be a sensitive positive predictor for the diagnosis of SCA3 in a Korean cohort (32). Certain patients with SCA3 also present with vergence abnormalities even in the early stage (72), and a high frequency of exotropia and multi-axial micro-saccadic oscillations have also been described in a small cohort (73). Conversely, another study on static ocular motor disorders suggested that patients with SCA3 exhibit esodeviation at distance and exhibit more pronounced esodeviation in lateral gaze; adducting saccades demonstrate higher velocities and amplitudes and larger vertical displacement compared with abducting saccades (67). Another abnormality observed in patients with SCA3 is the existence of alternating monocular adducting saccade pulses (74,75).

Abnormal HITs are frequently observed in patients with SCA3. Horizontal VOR dysfunction detected using bedside (76-78) and video (35,67) HITs has been confirmed in several studies. These results are supported by other studies that recorded ocular movements using the magnetic search coil technique (77,79). Luis *et al* (35) provided evidence that patients with SCA3 generally demonstrate reduced instantaneous VOR and regression of VOR (VORr) gain with prolonged VOR latency in the horizontal semicircular canal, whereas VORr gain is significantly negatively correlated with disease severity. Another study further confirmed significant VOR impairment in horizontal and vertical semicircular canals (80). By contrast, abnormal visually enhanced VOR (VVOR) (79) and suppression head impulse test deficits (80) have also been revealed in individuals with SCA3.

5. SCA type 6

SCA6 is considered to be the only polyQ disorder caused by membrane protein mutations (81). It is caused by a CAG expansion in the calcium voltage-gated channel subunit α1 A gene encoding the α1A-subunit of the P/Q-type voltage-dependent calcium channel (82) and is the smallest polyQ expansion SCA (5). SCA6 has the slowest progression and a good prognosis among polyQ SCAs (23,24). The lengths of the CAG expansion range from 20-33 repeats (28), and a larger normal allele size confers an earlier disease onset (10) and faster disease progression (23) in patients with SCA6.

SCA6 has distinctive pathological characteristics that restrict neuronal loss to Purkinje cells in the cerebellum, especially in the vermis and lobules, while other central nervous system structures are often preserved (83). Moreover, the clinical manifestation severity correlates best with total cerebellar atrophy (84).

SCA6 usually shows relatively pure cerebellar ataxia and rarely presents with extracerebellar symptoms, with a median age at onset of 50 years (85). A longitudinal cohort study has revealed an association between a lower baseline SARA score and faster progression in patients with SCA6 (24).

Gait difficulty is one of the most common initial abnormalities in patients with SCA6 (9). Increased step width and step time variability (86), as well as reduced sensorimotor adaptive ability (87), have been reported in the pre-symptomatic stage, and these motor disabilities are correlated with disease severity (86,87). Dysarthria and episodic vertigo can also be early symptoms preceding gait disturbance (9). In addition, clinical signs, including hyperreflexia, basal ganglia signs and parkinsonism signs, are relatively common in SCA6 (45,88). Cognitive dysfunction, such as impairment in the retrieval of memorized information (89), visual memory and verbal fluency (90), can also be present.

Diverse types of visual oculomotor deficits can be encountered in SCA6. Dysmetric saccades (16,27) and decreased saccadic mean gains (91) may be observed. Although saccade velocity is often preserved, increased frequency of SWJs and slowing of upward saccades have been revealed in both symptomatic (91) and pre-symptomatic (92) patients with SCA6. Severe impairment of smooth pursuit is one of the prominent features of SCA6 (16,27,91,93), and downward smooth pursuit is more severely affected compared with upward smooth pursuit (91). Furthermore, SCA6 is characterized by the frequent appearance of various patterns of nystagmus. Horizontal (16,27) and vertical (30) GEN are frequently revealed in these individuals, and it has been reported that low-amplitude horizontal GEN occurs before the onset of clinical symptoms (92).

Downbeat nystagmus (DBN) is a distinguishable characteristic of eye movement (27,32) and may be the initial neurological sign (94) in patients with SCA6. There is evidence that spontaneous and positional DBN and perverted head-shaking nystagmus (pHSN) are strong predictive factors, while pHSN is the most sensitive parameter (32). Periodic

alternating nystagmus (95,96) and rebound nystagmus (96) have also been noted in SCA6.

VOR abnormalities depend on vestibular stimulation at different frequencies in SCA6. VOR gains during relatively low-acceleration/low-frequency stimuli are normal or increase regardless of disease severity; by contrast, the vestibular response to high-acceleration/high-frequency stimulation decreases with disease progression and is strongly negatively associated with disease severity (97). Furthermore, a study on the temporal evolution of the findings of HITs has revealed that the evolution patterns of VOR gain differ among the semicircular canals (98).

6. SCA type 7

SCA7 is caused by CAG repeat expansion in the *ATXN7* gene located on chromosome 3p14.1 (1). The shortest CAG expansion causing definite SCA7 is 36 repeats, but abnormal repeat length is variable, ranging from 37-306 repeats (99), and can even reach 460 repeats in the infantile phenotype (100).

The size of the CAG repeat is strongly negatively correlated with the age at onset in SCA7. Smaller CAG repeats cause ataxia symptoms without visual impairments, whereas large repeats result in early onset of SCA7 with visual disturbances as the initial manifestation (101). The typical alleles have 50-55 CAG repeats and are characterized by ataxic and visual disorders (102).

Individuals with SCA7 show severe atrophy in the brainstem, cerebellar and cerebral regions, including the cerebral and cerebellar cortex, thalamus, subthalamic nucleus, pallidum and substantia nigra (103). Degeneration in the cervical spinal cord is another marked feature of SCA7 and is highly associated with disease duration and severity (104).

Progressive cerebellar ataxia and visual disturbances due to pigmentary retinal degeneration are conspicuous features of SCA7. The majority of patients present with macular deterioration with varying degrees of severity (105), and visual disorders are the initial neurological sign in certain individuals (106). Electroretinogram is considered as a valuable indicator for predicting disease onset and progression in symptomatic carriers with SCA7 (103), while visual fields and macular thickness in optical coherence tomography are putative biomarker candidates for pre-symptomatic carriers (105). Furthermore, the central vision is compromised first, and SCA7 is the only SCA subtype that may manifest as permanent blindness (107). By contrast, patients with SCA7 frequently suffer from dysarthria, dysphagia, ophthalmoplegia, hyperreflexia and pyramidal signs (1). Impairment of executive control and motor-sensory peripheral neuropathy have also been reported (108).

Visual oculomotor examination has revealed that saccadic slowing is prevalent in patients with SCA7, even in its early stages (30,109). Other eye movement disorders, including saccadic dysmetria, saccadic intrusions, GEN and ophthalmoplegia (19,109,110), as well as impaired smooth pursuit, can also be present (109).

7. SCA type 17

SCA17 is a rare autosomal dominant disorder induced by abnormal CAA/CAG repeat expansions in the TATA-box binding protein gene localized on chromosome 6q27 (111).

A narrow gap between normal and abnormal CAG sizes has been reported in SCA17. Typical normal repeat numbers range from 25-42 units (112). However, an expansion of 41 repeats has been reported as a pathological cause in certain patients with SCA7 (112). Intermediate alleles (43-48 repeats) have incomplete variable penetrance, while >48 repeat expansions are fully penetrant (112,113). To date, the largest number of repeat sizes that has been reported is 66 CAG/CAA repeats, to the best of our knowledge (114). A large ataxic cohort study of the frequency distribution of SCA17 allele sizes has demonstrated that the most common pathological alleles have 41 repeats (115).

MRI images of patients with SCA17 display atrophy in the cerebellum, brainstem, cerebral cortex and caudate nucleus (13). An observer-independent approach has indicated that the degree of cerebellar atrophy inversely correlates with the length of the CAG repeats (116).

SCA17 is typically characterized by cerebellar ataxia, cognitive impairment, psychiatric dysfunction and involuntary movements (4,62). Although cognitive dysfunction seems to be a common symptom in certain SCA phenotypes, dementia is uncommon in the early-stages of the majority of SCAs (30); however, it can occur in SCA17 (113). Cognitive decline is recognized as the first clinical manifestation (117). Chorea and dystonia are particularly common symptoms (45), and parkinsonism can commonly be observed in a number of patients with SCA17 (62). Small-range expansions (43-46 repeats) tend to present as a parkinsonian phenotype (118), while Huntington's disease-like syndromes, such as typical chore, psychiatric dysfunction and dementia, are more common in patients with 43-50 repeats (119). Conversely, dystonia and pyramidal signs are observed more frequently in large range expansions (112). Other relatively uncommon symptoms include epilepsy (113,114), autonomic symptoms (113) and peripheral neuropathy (114).

There have been reports of visual eye movement abnormalities in patients with SCA17. The vast majority of mutation carriers showed impaired smooth pursuit (120-122), even in non-symptomatic cases (121). Saccadic dysmetria with normal saccade velocity is another common abnormal oculomotor finding (120,121). However, there are also case reports of individuals with SCA17 presenting with saccadic slowing (113) and prolonged saccadic latencies (121). By contrast, increased anti-saccade and memory-guided saccade error rates have been documented in SCA17 (120).

Diverse types of nystagmus are also revealed in these patients, including GEN, DBN, rebound nystagmus, central positional nystagmus, headshaking and vertical pendular nystagmus (120,122). Another less common oculomotor dysfunction that has been reported is impaired optokinetic nystagmus (121).

In a previous study, normal VOR function detected using rotatory chair tests was considered a characteristic feature of patients with SCA17 (121). By contrast, VOR impairment in rotatory chair tests and video HITs have been described in a recent study (122). VVOR is a useful tool for vestibular assessment at low frequencies and can only be elicited if both smooth-pursuit eye movements and VOR are deficient (123). The majority of individuals with SCA17 exhibit impaired

cerebellar and vestibular function during the VVOR test, including those who are non-symptomatic (87,121,122).

8. Conclusions

Visual and vestibular oculomotor abnormalities are among the most frequent manifestations of polyQ-SCA. Genetic tests are widely used to screen for the abnormal repeat expansions in all polyQ-SCA genes (5). As polyQ-SCA accounts for the most common type of SCAs, combining PCR and capillary electrophoresis in targeted gene tests for SCA1, SCA2, SCA3, SCA6, SCA7 and SCA17 are generally used (3). For the patients with negative result of polyQ-SCA, whole-exome sequencing for other SCAs is used (1).

Certain subtypes of polyQ-SCAs are associated with abnormal eye movements and this may be useful for the differential diagnosis of SCAs, especially when choosing the genetic testing method. For example, patients with SCA2 and SCA7 exhibit prominent saccadic slowing, while those with SCA3 and SCA6 characteristically experience occurrences of GEN and smooth pursuit deficits; therefore, patients with oculomotor abnormalities are preferentially screened for polyQ-SCAs. When considering the diagnosis of SCAs, the combination of oculomotor examination and genetic testing may achieve an improved cost-effectiveness ratio compared with genetic test alone in the diagnosis of SCAs. Advances in precise diagnostic methods for SCAs may facilitate their early diagnosis, especially for patients at the prodromal stage. For instance, oculomotor abnormalities are present in prodromal patients with SCA3, which may encourage patients to access genetic testing earlier, and subsequently participate in future promising clinical trials, such as antisense oligonucleotides therapy. In conclusion, visual oculomotor abnormalities and VOR dynamics are important phenotypes of polyQ-SCAs and may facilitate diagnosis and future clinical trials.

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Not applicable.

Authors' contributions

YP designed the study. YH and CW collected and analyzed the data. YP and QT wrote the first draft of the manuscript. LG reviewed and modified the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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