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Rating Scales and Biomarkers for CAG-Repeat Spinocerebellar Ataxias: Implications for Therapy Development

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Abstract

Spinocerebellar ataxias (SCAs) are a group of dominantly-inherited cerebellar ataxias, among which CAG expansion-related SCAs are most common. These diseases have very high penetrance with defined disease progression, and emerging therapies are being developed to provide either symptomatic or disease-modifying benefits. In clinical trial design, it is crucial to incorporate biomarkers to test target engagement or track disease progression in response to therapies, especially in rare diseases such as SCAs. In this article, we review the available rating scales and recent advances of biomarkers in CAG-repeat SCAs. We divided biomarkers into neuroimaging, body fluid, and physiological studies. Understanding the utility of each biomarker will facilitate the design of robust clinical trials to advance therapies for SCAs.

1. Introduction

Spinocerebellar ataxias (SCA) are a group of dominantly-inherited ataxias. The core clinical features for SCAs are progressive cerebellar ataxia, involving ocular movements, speech,

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Declaration of Interest

The authors declare the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

hand dexterity, gait, and balance. The most common presenting symptom for SCAs is gait abnormality [1], while other symptoms are involved later. In addition, SCA patients often have manifestations other than cerebellar ataxia, including dystonia, tremor, myoclonus, and parkinsonian features [2]. The motor dysfunction invariably leads to impaired daily activities and oftentimes premature death in individuals living with SCAs [3].

To date, 48 SCA subtypes have been identified. The most common SCA subtypes are caused by exonic CAG trinucleotide repeat expansions that encode abnormally long polyglutamine (poly-Q). These CAG-repeat SCAs are SCA1, 2, 3, 6, 7, 17, and dentatorubral-pallidoluysian atrophy (DRPLA), constituting over 50% of SCA patients [4–8]. CAG-repeat SCAs have a very high disease penetrance, implying that the disease process is mostly driven by the genetic mutation. In addition, the clinical progression of SCAs has been characterized in the natural history studies in the United States [9], Europe [10], Japan [11, 12], Brazil [13–15], Portugal [16], Taiwan [17], and China [18], and a linear disease progression has been identified. Given the high disease penetrance and the well-characterized disease progression, CAG-repeat SCAs present a unique opportunity to develop clinical trials for gene therapies or anti-sense oligonucleotides (ASOs). However, several challenges exist for successful clinical trials for SCAs. First, SCAs are rare diseases with a prevalence of 1–6 per 100,000 [19], posing challenges to patient recruitment. Second, despite cerebellar ataxia as the core clinical feature for SCAs, there is still a significant variability of clinical presentations for individuals with different SCAs. Therefore, the development of biomarkers for progression and target engagement, as well as the validation of clinical rating scales for diverse clinical features, are essential to ensure scientific rigor in clinical trials. Specifically, rating scales reflect the disease severity and responsiveness to therapy, capture motor and non-motor features of SCAs, and measure the impact on the activities of daily living. Biomarker development in SCAs can be divided into categories of neuroimaging, fluid, and physiology (Fig. 1). Each biomarker serves a unique purpose. For instance, some neuroimaging findings can track the disease progression, while certain fluid biomarkers are essential to test target engagement. We aim to provide a comprehensive review of existing clinical rating scales and recent advances of biomarker development for SCAs.

2. Rating Scales

Several clinical rating scales for SCAs have been developed. Among these, the measurement of ataxia severity is critical and often serves as the primary endpoint for clinical trials for SCAs. In addition, rating scales for neurological symptoms other than ataxia are important to capture full motor symptoms of SCAs. Finally, cognitive impairment associated with cerebellar dysfunction has been recently identified and can be tracked using a rating scale. We listed the commonly used rating scales in Table 1.

2.1 Scales for motor dysfunction

International Cooperative Ataxia Rating Scale (ICARS) is a commonly used rating scale to measure the severity of ataxia [20]. ICARS has 19 items and a total score of 100, divided into 4 subscales: posture and gait disturbances, limb ataxia (kinetic functions), dysarthria

(speech disturbances), and oculomotor disorders [20]. Another commonly used rating scale for ataxia severity is the Scale for the Assessment and Rating of Ataxia (SARA) [21], which has 8 rating items (gait, stance, sitting, speech, finger chase, nose-finger test, fast alternating hand movements, and heel-shin slide) with a total score of 40. Brief Ataxia Rating Scale (BARS) is derived from a modified version of ICARS. It is a five-item scale with a total score of 30, including gait, kinetic function of legs and arms, speech, and eye movements [22]. While BARS is more concise than ICARS, BARS has finer granularity in each item. Another rating scale for ataxia assessment is the Neurological Examination Score for the Assessment of Spinocerebellar Ataxia (NESSCA), which was originally developed to assess individuals with SCA2 [23] and SCA3 [24]. In addition to ataxia symptoms, NESSCA includes non-ataxia motor symptoms: eyelid retraction, fasciculations, sensory loss, blepharospasm, rigidity, bradykinesia, distal amyotrophy, sphincter dysfunction, vertigo, and optic atrophy. Among these rating scales, SARA is most commonly used and has been extensively validated in the natural history study of SCA1, 2, 3, and 6 in the cohorts in Europe and the United States [3, 9, 10, 25–27], showing linear progression in these diseases. SARA also has excellent inter-rater reliability (interclass coefficient = 0.98) and test-retest reliability (interclass coefficient = 0.90) [21], making it the most widely used scale in the SCA research field.

Apart from the core symptoms of cerebellar ataxia, SCA patients often have additional neurological symptoms. The Inventory of Non-Ataxia Symptoms (INAS) is used to assess spasticity, fasciculations, myoclonus, tremor, dystonia, and vibratory sense, while the oculomotor findings are partially overlapping with typical cerebellar signs such as nystagmus and hypo- or hyper-metric saccades [28]. INAS thus is a useful tool to monitor whether a particular therapy improves the non-ataxia motor symptoms in SCA patients.

Both SARA and INAS have been adopted for tracking disease progression in patients with SCA1, 2, 3, 6, and 17, demonstrating that the rates of disease progression differ between SCAs [9, 10, 12, 15, 17]. Interestingly, even within the same type of SCA, the rate of progression measured by SARA showed a geographical difference (summarized in Supplementary Table 1).

2.2 Performance scales

There are two performance-based rating scales for SCAs: Composite Cerebellar Functional Severity Score (CCFS) [29] and SCA Functional Index (SCAFI) [30]. CCFS contains two different functional tests. One is the 9-peg board test, which measures the time for a patient to place 9 pegs into holes. The other is the click test, which measures the time required for a patient to press two buttons alternatively for 10 times. CCFS assesses the accuracy of hand movements, which is linked to the core symptoms of cerebellar ataxia; however, these measurements are restricted to the upper limbs. SCAFI is similar to CCFS but with the addition of a timed 8-meter walk to assess a composite of lower limb function and balance. However, the timed 8-meter walk can only be measured by patients who can still ambulate either with or without assistive devices, and it is unclear how to adjust for the use of different assistive devices in data analysis. Overall, CCFS and SCAFI may provide better

information on ataxia as it reflects real-world performance in the activities involving coordination.

2.3 Scales for non-motor symptoms

The cerebellum has diverse connections with the cerebral cortex to modulate cerebral function; therefore, SCA patients, not surprisingly, can have a variety of cognitive symptoms in addition to motor impairments. Recently, the Cerebellar Cognitive Affective Syndrome Scale (CCAS) was developed to capture the cognitive dysfunction in ataxia patients, including SCAs [31]. Cognitive dysfunction related to ataxia is assessed in several domains, including semantic fluency, phonemic fluency, category switching, verbal registration, digit span, cube drawing/copying, recalls, similarities, go-no-go, and affect. Because these cognitive dysfunctions can have a major impact on the quality of life in SCA patients, CCAS can be used to monitor cognitive responses to therapies.

Depression is one of the most common non-motor symptoms among SCAs [32], and it has been frequently reported in SCA3 [33–35]. Patient Health Questionnaire-9 (PHQ-9), a self-administered questionnaire to assess the severity of depression [36], has been adopted by clinical studies in both Europe [32] and the United States [37], such as the EUROSCA and CRC-SCA natural history study [32, 37]. PHQ-9 has 9 items, each with scores ranging from 0 (no depression at all) to 3 (depressed nearly every day) [36] with a maximal total score of 27. Cutoffs at 5, 10, 15, and 20 correspond to mild, moderate, moderately severe, and severe depression. PHQ-9 can monitor the temporal progression of depression in SCA patients.

2.4 Scales for functional capacity and quality of life

Two scales are frequently used in ataxia research to measure the functional status of a patient. The first is Part IV of the Unified Huntington’s Disease Rating Scale. This scale (UHDRS IV) measures the functional capacity, including 25 questions to gauge the patient’s ability to accomplish activities of daily living, handle financial matters, and perform at work [38]. Another commonly used scale in ataxia research for the functional outcome is the EQ-5D [29]. This scale has been widely used in clinical trials for various diseases. In addition to measuring the functional level of a patient, EQ-5D also rates the overall health of a patient. EQ-5D-3L includes five 3-level questions to query the patient’s mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a self-reported score between 0 and 100 to represent the patient’s health state [39]. UHDRS IV and EQ-5D are important because they can reflect the clinical meaningfulness of improvements in response to treatment. In fact, a growing concern is that patients may not necessarily perceive a change in their daily activities, despite an improvement in the rating scales based on neurological examinations, such as SARA, ICARS, or INAS. The Food and Drug Administration also requests the inclusion of outcome measurements in clinical trials that reflect functional improvements reported by patients [40, 41].

3. Neuroimaging Biomarkers

The main pathological feature of SCAs is cerebellar degeneration, which can be measured by structural imaging such as magnetic resonance imaging (MRI). Preceding the actual

structural alterations, the metabolism of the cerebellum and related brainstem areas is often found to be altered and can be assessed by positron emission tomography (PET) or magnetic resonance spectroscopy (MRS). Finally, single-photon emission computed tomography (SPECT) is used to assess dopaminergic neurons, GABAergic binding, and cerebral perfusion. We will review each neuroimaging modality in SCAs (Table 2) and also summarize the utility of each imaging tool in designing clinical trials (Table 3). It is important to note that neuroimaging studies have focused on the CAG-repeat SCAs, which are most commonly encountered. It has been challenging to recruit enough patients for such investigations in less common SCAs; therefore, the neuroimaging findings could be SCA subtype-specific and may not be generalizable.

3.1 MRI

Cerebellar atrophy is the hallmark of the neuroimaging finding of SCAs. The reduction of the cerebellum volume has been found to closely correlate with the ataxia severity, either using region of interest (ROI)-based analysis [42–47] or voxel-based morphometry (VBM) [48–54], in SCA1 [42, 48, 51, 54], SCA2 [42, 43, 51], SCA3 [44, 46–52, 54], SCA6 [44, 46, 48, 54], SCA17 [45, 53], and DRPLA [55]. In addition, white matter alterations are identified in SCA2 using diffusion tensor imaging (DTI) [56]. On the other hand, high signal intensity ratio in T2-weighted image was observed in the cerebral white matter, thalamus, midbrain, pontine tegmentum, basis pontis, inferior olive, and cerebellar white matter in patients with DRPLA [57]. While the cerebellum is the predominantly affected brain region in SCAs, other brain areas may be involved. Studies using MRI have demonstrated volume changes in the brainstem [42, 43, 46, 48, 49, 52, 54], basal ganglia [48], and pons [43, 51, 54]. MRI techniques can also be used to detect structural changes before the onset of symptoms in SCA2 [43] and SCA17 [45], as well as the progression of the cerebellar volume reduction from the presymptomatic stage to the symptomatic stage [43]. These findings indicate that MRI is more sensitive than clinical rating scales and can be useful to predict the symptom onset and to test disease-modifying therapies in presymptomatic stages. Interestingly, each SCA studied seems to have its own pattern of cerebellar degeneration (i.e., lobule-specific) [42, 44, 48, 58]. Therefore, a detailed analysis of each lobule will yield additional information regarding the degenerative mapping of each SCA.

Several imaging parameters are shown to correlate with clinical rating scales. For example, SARA correlates with the volume of the cerebellum [54], brainstem [52, 54, 59], caudate [54], and spinal cord [60], as well as the cerebellar white matters [49]. These parameters can be useful markers to track disease progression.

3.2 MRS

MRS is a sensitive imaging modality to detect chemical changes, which may precede the structural alterations seen in MRI. The commonly studied metabolites in MRS are N-acetylaspartate (NAA, a marker of neuronal density and function), creatine/phosphocreatine (Cr, a metabolism marker), choline compounds (Cho, a marker of synthesis and degradation of cell membranes), and myoinositol (mI, a marker for gliosis). In SCA1 [61, 62], SCA2 [62, 63], SCA3 [62, 64], SCA6 [62, 65], and SCA17 [62] cerebellum, a reduction in NAA/Cr and NAA/Cho ratios is identified as a marker for neurodegeneration. An interesting

aspect of MRS as a biomarker is its translatability. A SCA1 mouse model has been shown to have biochemical changes in the cerebellum spanning the presymptomatic and symptomatic stages similar to SCA1 patients [66]. Therefore, therapies that can ameliorate motor symptoms of the SCA1 mouse model with corresponding MRS signal improvement can be studied in clinical trials in SCA1 patients using MRS as a neuroimaging biomarker.

3.3 Functional MRI (fMRI)

Resting-state fMRI can be used to assess the oxygen consumption of the cerebellum. While this technique has not been studied extensively in SCAs, the reduction of fMRI signals in the cerebellar cortex and cerebellar nuclei have been observed in SCA6 [44].

3.4 PET

The most commonly used PET tracer in SCAs is [^{18}F]fluorodeoxyglucose ([^{18}F]FDG), which reflects the overall metabolism. Reduction of the metabolism of the cerebellum can be seen in SCA1 [67, 68], SCA2 [58, 68, 69], SCA3 [58, 68, 70, 71], and SCA6 [58, 68, 69, 72]. Such a reduction can also be observed in the presymptomatic SCA patients [71]. PET can thus be used to track the disease progression in SCA patients [51]. As patients with SCA2, SCA3, SCA17 can present with parkinsonian symptoms, several PET ligands, such as [^{11}C]D-threo-methylphenidate ([^{11}C]dMP) or [^{11}C]raclopride ([^{11}C]RAC), can be useful to interrogate the involvement of the dopaminergic axis. Overall, PET provides important information in metabolic changes, which may be sensitive neuroimaging biomarkers for SCAs.

3.5 SPECT

SPECT is an imaging technique that integrates radioactive tracers to provide functional and metabolic information. SPECT studies in ataxia studies focus on the dopamine axis and overall brain perfusion. Using SPECT techniques, dopaminergic dysfunction is identified in SCA2 [73], SCA3 [74], and SCA17 [73]. [^{99}mTc]ECD SPECT (technetium-^{99}m N,N-1,2-ethylene diylbis-L-cysteine diethyl ester dihydrochloride or ethyl cysteinate dimer) is used to assess brain perfusion and has demonstrated a perfusion reduction in SCA3 [75] and SCA6 [76]. However, it is unclear whether SPECT is more sensitive to PET in identifying perfusion changes in the brain.

4. Fluid biomarkers

Genetic mutations of SCA patients can cause various biological alterations that can be traced either in blood or in cerebrospinal fluid (CSF) (Table 4). These fluid biomarkers can be used to either track disease progression and/or test target engagement in future clinical trials.

Axonal degeneration is commonly seen in neurodegenerative disorders, and SCAs are no exception. Therefore, markers of axonal degeneration have been studied. Specifically, tau protein level is reduced in the CSF of SCA2 patients compared to that in controls [77]. Another axonal maker is the neurofilament light chain, which is increased in the serum of SCA1 [78] and SCA3 [78, 79] patients and in the CSF of SCA3 patients [79]. In addition, the neurofilament light chain level in the CSF of SCA3 patients highly correlates with the

level in the serum [79], indicating a peripheral source can be a reliable indicator for the neurodegenerative process. The increased level of neurofilament light chain in CSF can also be observed in the presymptomatic SCA3 patients [79], indicating this biomarker precedes the symptom onset of SCA3. Another translational study investigated neurofilament levels in SCA3 patients and SCA3 mouse models [80]. This study found a step-wise increase in the serum levels of neurofilament light chain and phosphorylated neurofilament heavy chain in controls, presymptomatic and symptomatic SCA3 patients. Among these markers, serum neurofilament light chain level can reflect disease severity and clinical progression, highlighting its role as a disease progression biomarker. Interestingly, it is estimated that the elevation of serum neurofilament light chain can precede the clinical symptoms by 7.5 years. Similar changes in neurofilament light chain level can be found in the blood and brain of a mouse model of SCA3, providing additional evidence that these changes are the results of a degenerative process driven by mutant *ATXN3* [80]. While the alterations of neurofilament light chain level can be found in other neurodegenerative disorders, SCA patients are often in their thirties to fifties; therefore, they are less likely to have other co-existing late-onset neurodegenerative disorders such as Parkinson disease or Alzheimer disease, which may confound the interpretation of the level of neurofilament light chain.

Since CAG-repeat SCAs are caused by abnormal poly-Q proteins, knocking down such protein expression has been the main goal for gene therapies or ASO-based therapies. To ensure the sufficient efficacy of reducing the Poly-Q protein production, assay development to detect such Poly-Q proteins is essential. By utilizing time-resolved fluorescence energy transfer-based immunoassays, ataxin-3 with abnormally expanded poly-Q can be distinguished from normal ataxin-3 and reliably detected in the peripheral blood mononuclear cells from both presymptomatic and symptomatic SCA3 patients [81]. However, this assay cannot detect ataxin-3 protein in serum or CSF. On the other hand, another group has recently developed an immunoassay to sensitively detect the level of abnormally expanded poly-Q ataxin-3 in the CSF and plasma, which is elevated in both presymptomatic and symptomatic SCA3 patients [82]. Therefore, this new assay may be used to measure expanded poly-Q ataxin-3 level as a fluid biomarker to test target engagement for SCA3.

Besides the direct measurement of ataxin-3 level, endogenous binding partners of mutant ataxin-3 have been investigated as potential biomarkers. The carboxyl terminus of Hsp-70 interacting protein (CHIP) is a co-chaperone protein that can bind to mutant ataxin-3. CHIP protein level is increased in both serum and CSF of SCA3 patients [83].

Neuroinflammation is a common process in neurodegenerative disorders. Along this line, the protein level of eotaxin, a cytokine involved in the chemotaxis of eosinophil, is increased in the serum of symptomatic SCA3 patients compared to presymptomatic SCA3 patients [84], suggesting that eotaxin may be useful to study the phenoconversion from presymptomatic to symptomatic stages of SCA3.

Biomarkers related to glial cells, such as activation of astrocyte and glial loss, have been reported in SCA3. Glial fibrillary acidic protein (GFAP), a type III intermediate filament protein, is increased in the serum of SCA3 patients [85], indicating astrogliosis may occur in

response to the degenerative mechanism. Similarly, the serum level of the astrocytic marker S100B is increased in SCA3 patients [86]. Neuron-specific enolase (NSE) is a peripheral marker of neuronal disruption, and an increased level of NSE has been observed in SCA3 patient serum [86, 87].

Oxidative stress has been reported to be linked to the pathogenesis of SCA3 [88–90]. The activity of catalase [91] (an antioxidant enzyme) and the oxidation of DCFH-DA [92] (an artificial substrate to assess the degree of oxidation) are increased in the serum of SCA3 patients. The oxidation of DCFH-DA is also increased in presymptomatic SCA3 patients compared to controls [92]. Interestingly, serums from symptomatic SCA3 patients oxidize DCFH-DA more than serums from presymptomatic SCA3 patients [92], indicating the oxidative burden increases as the disease progresses. The activities of glutathione peroxidase [92] and superoxide dismutase [92] are decreased in the serum of SCA3 patients. Similar to the oxidation of DCFH-DA, symptomatic SCA3 patients have a more severe reduction in the activities of glutathione peroxidase [92] and superoxide dismutase [92] compared to presymptomatic SCA3 patients [92], further supporting the role of oxidative stress in the disease progression.

Insulin resistance has been observed in patients with poly-Q disorders. The mechanism is still unclear, but it has been hypothesized that poly-Q peptides may interfere with the expression of insulin-related genes, such as insulin-like growth factor 1 (IGF-1) [93]. Therefore, levels of IGF-1 and its binding partners, IGFBP1 and IGFBP3, have been studied in SCAs. Specifically, SCA3 patients have a higher serum IGFBP1 level and a higher serum IGF-1/IGFBP-3 ratio than those in healthy controls [94]. On the other hand, IGFBP-3 and insulin levels are reduced in SCA3 patients [94].

The biochemical composition of biofluids from SCA patients has also been studied. Levels of amino acids, such as valine, leucine, and tyrosine, are reduced in the plasma of SCA7 patients [95]. Moreover, alterations of various microRNA (miRNA) levels have been identified in serum, plasma, or CSF in SCA1 [96], SCA2 [96], SCA3 [85, 96], and SCA7 [97] patients. However, the sample sizes in these miRNA studies remain small.

To date, most studies on fluid biomarkers have been conducted in SCA3 as it is the most common SCA worldwide, and few studies were done in patients with SCA1, 2, and 7. There is a need to expand the search of fluid biomarkers in other types of SCAs.

5. Physiology biomarkers

SCA pathology involves the cerebellum and associated brainstem areas, leading to brain circuitry re-organization. These defects may be detected using physiological tools such as vestibulo-oculography (VOG) and evoked potentials, including visual-evoked potential (VEP), brainstem auditory-evoked potential (BAEP), somatosensory-evoked potential (SSEP), and motor-evoked potential (MEP). The findings are summarized in Table 5.

The vestibulo-ocular system is often affected in SCAs. SCA3 patients have abnormal vestibulo-ocular reflex with prolonged reflex latency [98]. VOG has been implemented to detect quantitative oculomotor dysfunction in SCAs. Increased gaze-evoked eye movements

(nystagmus, dysmetric saccade, and square-wave jerks) can be seen in SCA1 [99], SCA3 [99, 100], and SCA6 [99] patients when compared to healthy controls. Gaze-evoked eye movements occur more frequently in symptomatic SCA3 patients compared to presymptomatic SCA3 patients [100].

BAEP can be used to study brainstem involvement, and abnormalities have been demonstrated in SCA2 and SCA6 [101, 102]. SSEP has been applied to study the integrity of the posterior column. Specifically, SCA1, 2, and 3 patients have delayed or loss of P40 cortical SEP (from tibial nerve stimulation). Delayed P40 latency was seen in SCA3 (69%) and SCA2 (23%) but not seen in SCA1 patients [103]. Prolonged P100 latency in VEP was more commonly seen in SCA1 than SCA3 patients (78% vs. 25%) [103].

MEP is commonly used to monitor the dysfunction of the descending motor pathway by transcranial magnetic stimulation. Central motor conduction time (CMCT) is prolonged in SCA1 [104–106], SCA2 [104], SCA3 [104, 107], and SCA6 [108], suggesting damages to the descending motor pathways in these SCAs. The resting motor threshold at the motor cortex is also increased in SCA1 [104–106] and SCA3 [104].

These physiological measurements are helpful to probe the abnormalities of the brain circuit. However, whether these sensitive physiological parameters can be implemented in SCA trials to interrogate the relevant neurological symptoms remains undetermined. Specifically, whether the improvement of these measures correlates with clinical improvement remains to be answered. If such correlation is confirmed, incorporating these physiological biomarkers into SCA clinical trial design will be valuable.

A gap still exists between neuroscientists and clinicians. The cerebellum is crucial for motor prediction, error correction, and motor learning, and neuroscientists have been studying these aspects in patients with ataxia *versus* controls. A commonly used test is the hand-reach perturbation, which implements an error in the visual input to subjects when they try to reach a target and measures the rate subjects make the correction [109–113]. Assessments for such error-based learning can potentially be useful in tracking the disease progression but have not been applied in the clinical setting. Similarly, quantitative kinematic-based measurements of limb movements and gait in patients with ataxia have been widely studied [112, 114–122] but not implemented as a standard clinical practice. Such techniques can provide objective and accurate scoring of clinical rating scales, therefore, precisely monitoring the disease progression and treatment effects in clinical trials.

6. Conclusion

This review summarizes the recent development of rating scales and biomarkers in CAG-repeat SCAs. While rating scales provide important information for therapeutic responses and often serve as the primary endpoint for large-scale clinical trials, the integration of imaging and fluid biomarkers can provide additional information for target engagement, disease mechanism, and patient selection. As each biomarker has its distinct characteristic, the combination of biomarkers is likely to yield useful information. Of note, we found a lack of fluid biomarkers for DRPLA, likely owing to the rarity of the disease. Nevertheless,

efforts to find markers for DRPLA, such as neurofilament, is ongoing [7] and will add to our knowledge of the CAG-repeat SCAs.

The understanding of the natural history of SCAs in both the United States [9] and Europe [10] is leading the way towards clinical trial readiness for SCAs [123]. In addition, the advances in the knowledge of the disease pathomechanism of SCAs have identified several therapeutic targets. Finally, the identification of multimodal biomarkers will ensure a rigorous clinical trial design. We are now at the forefront of therapy development for SCAs to eventually bring hope to patients and their families to combat these relentless disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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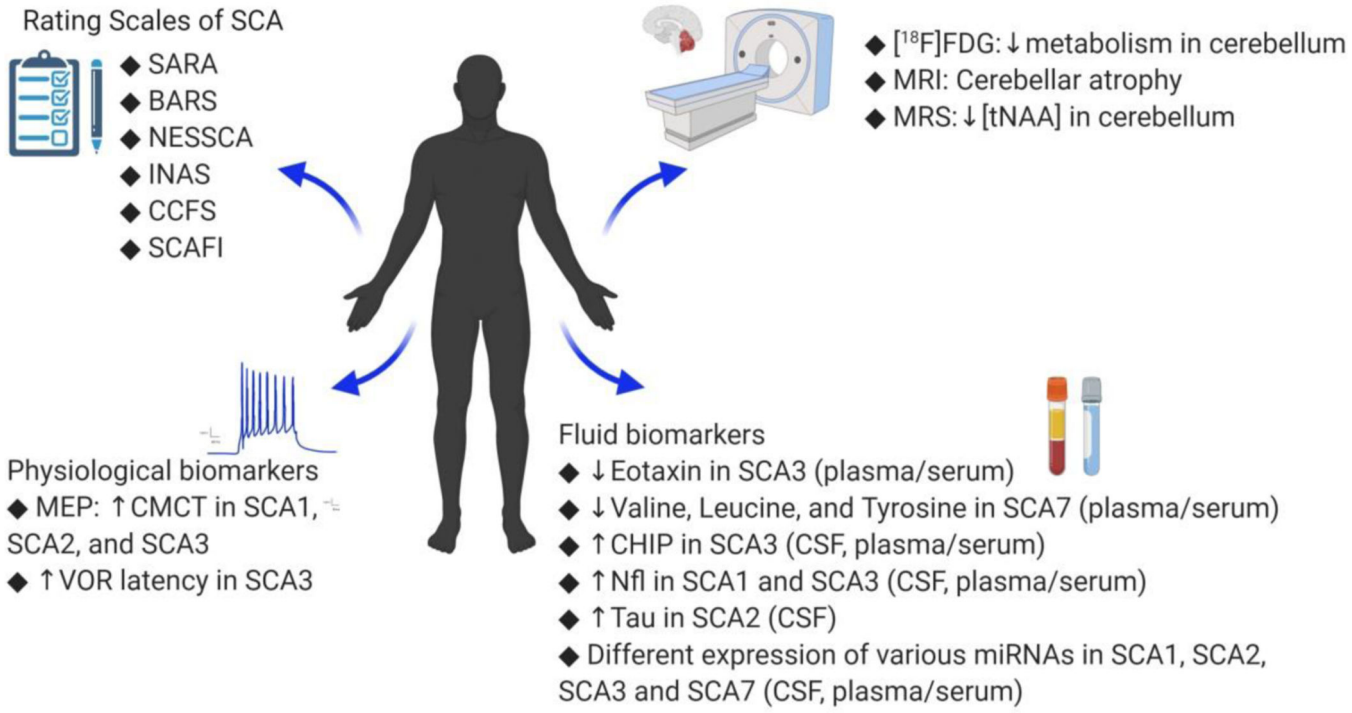

Fig. 1.

The summary of biomarkers of SCAs, including clinical rating scales, neuroimaging, and biofluid biomarkers (see text for abbreviations).

Table 1

Summary of Clinical Scales of Spinocerebellar Ataxias

Methods	Comment	Reference
International Cooperative Ataxia Rating Scale (ICARS)	Evaluate various body part of ataxia motor symptoms, including oculomotor examination (0–100)	[20]
Scale for the assessment and rating of ataxia (SARA)	Most extensively used ataxia scale with only 8 domains assessment without oculomotor evaluation. (0–40)	[21]
Brief Ataxia Rating Scale (BARS)	Only evaluate 5 domains, including oculomotor evaluation (0–30)	[22]
Neurological Examination Score for the Assessment of Spinocerebellar Ataxia (NESSCA)	Originally developed for SCA3 but later validated in SCA2. Including items to assess cerebellar ataxia neuropathy, parkinsonism, and pyramidal signs. (0–40)	[23, 24] [28] [29]
The Inventory of Non-Ataxia Symptoms (INAS)	Evaluate extra-cerebellar symptoms associated with SCA patients. A part of the scale is subjective, patient reported outcomes. (0–16)	[30]
Composite Cerebellar Functional Severity Score (CCFS) and CCFS with writing test	Consisted of two performance-based tasks: nine-hole pegboard test and click test	[31] [38]
SCA Functional Index (SCAFI)	Consists of three functional measures: timed 8-meter walk, 9-hole peg test, and PATA repetition.	[29]
Cerebellar Cognitive Affective Syndrome Scale (CCAS)	Assess the cognition of ataxia patients	[36]
UHDRS IV	Patient reported functional capacity	
EQ-5D	Patient reported functional capacity and overall health	
Patient Health Questionnaire-9 (PHQ-9)	A self-administered questionnaire to assess the severity of depression	

Table 2

Summary of Neuroimaging Findings in Ataxia

Modality	Major Finding
MRI	**SCA1** ROI: ↓cerebellum [42], brainstem [42] VBM: ↓cerebellum [54], brainstem (including midbrain, pons, and medulla) [54], caudate [54], putamen [54], and temporal lobe [54] ↓WM in cerebellar hemispheres [51] ↓GM in cerebellar hemispheres [51], left anterior and posterior cerebellum [48], vermis [51], brainstem [48], right putamen, and pallidum [48] **SCA2** ROI: ↓cerebellum [42, 43], brainstem [42, 43] (mesencephalon [43], pons [43], anteroposterior diameter of the pons [43]) VBM: ↓WM in pons [51], middle cerebellar peduncle [51], cerebellar hemispheres [51] ↓GM in cerebellar hemispheres and vermis [51] DTI: ↓fractional anisotropy and mode of anisotropy in the brain stem, cerebellar peduncles, cerebellum, cerebral hemisphere WM, corpus callosum, and thalami [56] **SCA3** ROI: ↓cerebellum [46, 47], cerebellar nuclei [44], brainstem [46], vermis [47] volume, spinal core area [60], and spinal cord eccentricity [60] VBM: ↓cerebellum [48, 54], basal ganglia [48], brainstem (including midbrain, pons, and medulla) [48, 54], caudate [54], putamen [54], striatal [48], and temporal lobe [54] ↓GM in cerebellum [52], cerebellar hemispheres [49, 51], brainstem [49, 52], vermis [51], bilateral thalamus [49] ↓GMD in cerebellum [50], brainstem [50], frontal [50], occipital lobes [50], parietal [50], subcortical GM [50], temporal lobes [50] ↓WM in cerebellum [52], cerebellar hemispheres [49], brainstem [52], bilateral thalamus [49] DTI: ↓fractional anisotropy in cerebellum [52], brainstem [52];↑radial diffusivity in cerebellum [52], brainstem [52], frontal lobes [52], temporal lobes [52], thalamus [52] ↓cerebellum [124], anterior lobe [124], left posterior lobe [124], right posterior upper lobe [124] **SCA6** ROI: ↓cerebellum [44, 46], cerebellar nuclei [44], brainstem [46], superior vermis [65] VBM: ↓cerebellum [48, 54], basal ganglia [48], brainstem [48, 54], caudate [48] **SCA17** ROI: ↓cerebellum [45], vermis, caudate nucleus [45] VBM: ↓cerebellum, limbic system (parahippocampus, cingulate) and parietal precuneus [53] **DRPLA** ROI: ↓midbrain [55], pontine tegmentum [55], basis pontis [55], cerebellar vermis [55] SIR: ↑cerebral WM [57], thalamus [57], midbrain [57], pontine tegmentum [57], basis pontis [57], inferior olive [57], and cerebellar WM [57] Atrophy of the cerebrum [57], midbrain tegmentum [57], pontine tegmentum [57], basis pontis [57], superior cerebellar peduncle [57], and cerebellum [57]
MRS	**SCA1** ↓[Glu] in cerebellar hemisphere [125, 126], pons [125–127], vermis [125, 126] ↓[NAA] in cerebellar hemisphere [42], cerebellar WM [127], pons [42, 127], vermis [125, 127] ↓[NAAG] in cerebellar WM [127], pons [127] ↓[tNAA] in cerebellum [128], cerebellar hemisphere [125, 126], cerebellar WM [127], parietofrontal lobe WM [128], pons [125–127], sensory cortex [128], vermis [125–127], visual cortex [128] ↓Cho/Cr ratio in cerebellar hemisphere [62], basis pontis [61] ↓Glu/Gln ratio in vermis [125] ↓NAA/Cho ratio in cerebellar hemisphere [62] ↓NAA/Cr ratio in cerebellar hemisphere [61, 62], basis pontis [61], vermis [62] ↑[Asc] in vermis [127] ↑[Glc] in vermis [127] ↑[Gln] in cerebellar white matter [127], vermis [125, 126] ↑[mI] in cerebellar hemisphere [125, 126], pons [125–127]

Modality	Major Finding
	↑[Tau] in cerebellar WM [127] ↑[tCr] in cerebellar hemisphere [125, 126], cerebellar WM [127] ↑[Glc + Tau] in cerebellar hemisphere [125, 126], cerebellar WM [127], vermis [127] **SCA2** ↓[Cho] in cerebellum [129], vermis [129] ↓[Glu] in cerebellar hemisphere [126], pons [126], vermis [126] ↓[NAA] in cerebellar hemisphere [42, 63], cerebellum [129], pons [42], vermis [129] ↓[tNAA] in cerebellar hemisphere [126], pons [126], vermis [126] ↓Cho/Cr ratio in cerebellar hemisphere [62], vermis [62] ↓NAA/Cho ratio in cerebellar hemisphere [62], vermis [62] ↓NAA/Cr ratio in cerebellar hemisphere [62], basal ganglia [63], frontal lobes [63], pons [63], vermis [62, 63] ↑[Gln] in cerebellar hemisphere [126], cerebellar WM [127], vermis [126] ↑[GSH] in cerebellar WM [127], vermis [126] ↑[mI] in cerebellar hemisphere [63], cerebellar WM [127], pons [63, 127], vermis [126, 127] ↑[Tau] in cerebellar WM [127], vermis [126, 127] ↑[tCr] in cerebellar hemisphere [126], cerebellar WM [127], pons [126], vermis [126, 127] ↑[Glc + Tau] in cerebellar hemisphere [126], cerebellar WM [127], pons [127], vermis [127] ↑mI/Cr ratio in cerebellar hemispheres [63], basal ganglia [63], frontal lobes [63], pons [63], vermis [63] **SCA3** ↓[NAA] in cerebellum [124, 129], pons [127], vermis [124, 129] ↓[NAAG] in cerebellar WM [127] ↓[tNAA] in cerebellar WM [127], vermis [127] ↓NAA/Cho ratio in cerebellar hemisphere [62], dentate nucleus [64], vermis [62, 64] ↓NAA/Cr ratio in cerebellar hemisphere [62], cortex [64], dentate nucleus [64], middle cerebellar peduncle [64], vermis [62, 64] ↑[mI] in pons [127] ↑[Tau] in cerebellar WM [127] ↑[tCr] in cerebellar WM [127] ↑[Glc + Tau] in vermis [127] **SCA6** ↓[GABA] in cerebellar WM [127], vermis [127] ↓[NAA] in cerebellum [63, 129], vermis [127, 129] ↓[tNAA] in vermis [127] ↓NAA/Cho ratio in cerebellar hemisphere [62, 65], vermis [62, 65] ↓NAA/Cr ratio in cerebellar hemisphere [62], vermis [62] ↑[Lac] in vermis [126] ↑[mI] in cerebellar hemisphere [126], vermis [126] ↑[Glc + Tau] in cerebellar hemisphere [126], vermis [127] **SCA17** ↓NAA/Cho ratio in vermis [62] ↓NAA/Cr ratio in cerebellar hemisphere [62], vermis [62]
fMRI	↓cerebellar cortex [44], cerebellar nuclei [44]
PET	**SCA1** [^{18}F]FDG:↓metabolism in cerebellum [68], cerebral cortex [67], cerebellar hemispheres [67], vermis [67], brainstem [67, 68], caudate nucleus [67], putamen [67], thalamus [67], whole brain cortex [67] **SCA2** [^{18}F]FDG:↓metabolism in cerebellum [58, 68, 69], anterior-posterior lobe ratio [69], brainstem [68], parietal cortex [68], pons [58], parahippocampal gyrus [58], frontal cortex [58] [^{11}C]dMP:↓Dopamine transporter levels in putamen [68], caudate nucleus [68] **SCA3** [^{18}F]FDG:↓metabolism in cerebellum [58, 68], cerebellar hemispheres [70, 71], cerebellar vermis [70], occipital cortex [70, 71], brainstem [68, 70, 71], putamen [68], thalamus [68], parahippocampal gyrus of the limbic system [58], lentiform nucleus [58];↑metabolism in parietal and temporal cortices preclinically [71] [^{11}C]dMP:↓Dopamine transporter levels in putamen [68], caudate nucleus [68] [^{11}C]MP4P:↓thalamus [130] **SCA6** [^{18}F]FDG:↓metabolism in cerebellum [58, 68, 69], cerebellar hemispheres [72], anterior-posterior lobe ratio [69], basal ganglia [72], brainstem [72], caudate [72], putamen [68], frontal cortex [58, 72], prefrontal cortex [58], occipital cortex [72], temporal cortex [72];↑temporal cortex [68] **SCA17** [^{18}F]FDG:↓metabolism in caudate nucleus [45], putamen [45] [^{11}C]dMP:↓Dopamine transporter levels in caudate nucleus and putamen [45] [^{11}C]Raclopride:↓D2 receptor levels in caudate nucleus and putamen [45]

Modality	Major Finding
SPECT	**SCA2** [^{99}mTc]TRODAT-1 SPECT:↓striatal DAT binding [73] [^{123}I]β-CTT SPECT:↓striato-cerebellar ratio [131] [^{123}I]IBZM SPECT:↓striato-frontal IBZM binding ratio [131] [^{123}I]FP-CIT SPECT:↓uptake in caudate, putamen [132] **SCA3** [^{99}mTc]TRODAT-1 SPECT:↓nigrostriatal ratio [74] [^{99}mTc]HMPAO SPECT:↓perfusion in cerebellar hemispheres [47], inferior [47] and superior [47] frontal lobe [47], lateral temporal lobe [47], parietal lobe [47], vermis [47] [^{99}mTc]ECD SPECT:↓perfusion in bilateral cerebellum [75], vermis [75] [^{123}I]iomazenil SPECT:↓binding in cerebellum [133], cerebral cortex [133], thalamus [133], striatum [133] **SCA6** [^{99}mTc]ECD SPECT:↓perfusion in cerebellar hemisphere[76], cerebral vermis[76] **SCA17** [^{99}mTc]TRODAT-1 SPECT:↓striatal DAT binding [73]

Asc: ascorbate; Cho: Choline; Cr: Creatine; [^{123}I]β-CIT : [^{123}I]2β-carbomethoxy-3b-(4-iodophenyl)tropane; [^{11}C]dMP: [^{11}C]D-threo-methylphenidate; DAT: dopamine transporters; DTI: diffusion tensor imaging; [^{99}mTc]ECD: technetium-99m N,N-1,2-ethylene diylbis-L-cysteine diethyl ester dihydrochloride; [^{18}F]FDG: [^{18}F]fluorodeoxyglucose; 3D-FD: three-dimensional fractal dimension; fMRI: functional magnetic resonance imaging; [^{123}I]FP-CIT: [^{123}I]N-fluoropropyl-2b-carbomethoxy-3b-(4-iodophenyl) nortropane ([^{123}I]ioflupane); GABA: gamma-aminobutyric acid; Glc: glucose; Gln: glutamine; Glu: glutamate; GM: gray matter; GMD: gray matter density; GSH: glutathione; [^{99}mTc]HMPAO: technetium-99m hexamethylpropylene amine oxime; [^{123}I]IBZM SPECT: [^{123}I](S-)-2-hydroxy-3-iodo-6-methoxy-N[(l-ethyl-2-pyrrolidinyl) methyl]-benzamide; [^{123}I]IMZ: [^{123}I]iomazenil; Lac: lactate; mI: myo-Inositol; [^{11}C]MP4P: N-[^{11}C]-methyl piperidine-4-propionate; MRI: magnetic resonance imaging; MRS: magnetic resonance spectroscopy; NAA: *N*-acetyl aspartate; NAAG: *N*-acetylaspartylglutamate; PET: positron emission tomography; [^{11}C]RAC: [^{11}C]Raclopride; ROI: region of interest; SIR: signal intensity ratio; SPECT: single photon emission computed tomography; Tau: taurine; tCr: total creatine; tNAA: total *N*-acetyl aspartate; VBM: voxel-based morphometry; WM: white matter.

Table 3

The utility of each imaging technique for SCAs

Utility	Method
Differentiating symptomatic SCA patients from healthy controls	MRI [42–50, 52–54, 56, 60, 61] MRS [42, 61–65, 124–129, 134–137] PET [45, 58, 67–72] SPECT [47, 74–76, 131–133]
Differentiating presymptomatic SCA patients from healthy controls	MRI: SCA2 [43], SCA17 [45] PET: SCA3 [71], SCA17 [45]
Differentiating presymptomatic SCA patients from symptomatic SCA patients	MRI: SCA2 [43], SCA17 [45] PET: SCA3 [71], SCA17 [45]
Differentiating different SCA subtypes	MRI [42, 44, 48, 54, 58] MRS [42, 62, 126, 127, 129, 134, 136, 138] PET [48, 51, 58, 68, 69, 130]
Differentiating SCA patients with mild ataxia from severe ataxia	MRI [46, 49, 54, 59, 60] PET [51]

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Table 4

Summary of SCA fluid biomarkers

Biomarker	**SCA cases *vs.* controls**	**Presymptomatic SCA cases *vs.* controls**	**Presymptomatic SCA cases *vs.* symptomatic SCA cases**	**Adult-onset SCA cases *vs.* early-onset SCA cases***
Poly-Q expanded ataxin-3	↑ in PBMC of SCA3 [80] ↑ in plasma and CSF of SCA3 [82]	↑ in PBMC of presymptomatic SCA3 [80] ↑ in plasma and CSF of presymptomatic SCA3 [82]	↑ in CSF of symptomatic SCA3 *vs.* presymptomatic SCA3 [82]	
Catalase activity	↑ in serum of SCA3 [91]			
CHIP	↑ in serum of SCA3 [83] ↑ in CSF of SCA3 [83]			
Oxidation of DCFH-DA	↑ in serum of SCA3 [92]	↑ in serum of presymptomatic SCA3 [92]	↑ in serum of symptomatic SCA3 *vs.* presymptomatic SCA3 [92]	
Eotaxin			↑ in serum of symptomatic SCA3 *vs.* presymptomatic SCA3 [84]	
GFAP	↑ in serum of SCA3 [139]			
Glutathione peroxidase activity	↓ in serum of symptomatic SCA3 [92]		↓ in plasma of symptomatic SCA3 *vs.* presymptomatic SCA3 [92]	
IGFBP-1	↑ in serum of SCA3 [94]			
IGFBP-3	↓ in serum of SCA3 [94]			
IGF-1/IGFBP-3 molar ratio	↑ in serum of SCA3 [94]			
Insulin	↓ in serum of SCA3 [94]			
miRNA	↑ miR-34b [85] in serum of SCA3			Alterations of miRs in plasma of early onset SCA7 *vs.* adult onset SCA7 [97]
	↑miR-7014 in CSF of SCA1, SCA2, and SCA3 [96] ↑71 miRs in plasma of SCA7 [97] ↓miR-25 [85], miR-29a [85], miR-125b [85] in serum of SCA3 ↓ miR-7014 [96] in plasma of SCA3 Different expression of various exosomal miRs in plasma and CSF of SCA3 [96]			

Biomarker	SCA cases *vs.* controls	Presymptomatic SCA cases *vs.* controls	Presymptomatic SCA cases *vs.* symptomatic SCA cases	Adult-onset SCA cases *vs.* early-onset SCA cases*
Neurofilament light chain	↑ in serum of SCA1 [78] and SCA3 [78–80] ↑ in CSF of SCA3 [79]	↑ in serum of presymptomatic SCA3 [79, 80]		
NSE	↑ in serum of SCA3 [86, 87]			
Phosphorylated neurofilament heavy chain	↑ in serum of SCA3 [80]			
S100B	↑ in serum of SCA3 [86]			
Superoxide dismutase activity			↓ in serum of symptomatic SCA3 vs. presymptomatic SCA3 [92]	
Tau	↑ in CSF of SCA2 [77]			
Valine, leucine, and tyrosine	↓ in plasma of SCA7 [95]			

CHIP, carboxyl terminus of the Hsp70-interacting protein; DCFH-DA, 2',7'-dichlorofluorescein diacetate; GFAP, glial fibrillary acidic protein; GSH-Px, glutathione peroxidase; IGFBP, insulin-like growth factor-binding protein; IGF, insulin-like growth factor; miRNA, microRNA; NSE, neuron-specific enolase; S100B, protein S 100 B; SOD, superoxide dismutase.

*Adult-onset ≧ 20 years old, early-onset < 20 years old

Table 5

Physiological biomarkers of SCAs

Biomarker	SCA *vs.* controls	Presymptomatic SCA *vs.* controls	Presymptomatic SCA *vs.* Symptomatic SCA	Comparisons between different SCA subtypes
Auditory evoked potential	Reduced suppression of P50 in SCA3 [140]			
BAEP	prolonged absolute III and V latencies and interpeak I–III latency in SCA2 [101] prolonged I and III latency in SCA6 [102]			
EEG	↓ late bereitschaftspotential with dominant (right) hand movements in SCA3 [141]			
F wave amplitudes of ulnar nerve	↑ in SCA1, SCA2, SCA3 [106]			
MEP	↑ CMCT in SCA1 [104–106], SCA2 [104], SCA3 [104, 107]	↓ intracortical facilitation in presymptomatic SCA3 [107]		↑ CMCT in SCA1 *vs.* SCA2 [104] ↑ RMT in SCA1 *vs.*
	↑ RMT in SCA1 [104–106], SCA3 [104] ↑ amplitude in SCA3 [105] ↓ intracortical facilitation in SCA2 [106], SCA3 [106, 107] ↓ SICI in SCA3 [107]	↓ SICI in presymptomatic SCA3 [107]		SCA2 [104] Prolonged latency more commonly seen in SCA1 than SCA2 or SCA3 [103]
SSEP	Loss of cortical SEP in SCA1, SCA2, and SCA3 [103] Prolonged latency of P40 in SCA2 [101]			Delayed P40 seen in SCA3 (69%) and SCA2 (23%) but not in SCA1 [103]
VEP				Prolonged P100 more commonly seen in SCA1 than SCA3 [103]
VOG	Gaze-evoked nystagmus and dysmetric saccade ↑ in SCA1 [99], SCA3 [99, 100], and SCA6 [99] SWJ/SWO ↑ in SCA3 [99, 100] Downward nystagmus in SCA6 [99] pHSN in SCA6 [99] ↑ VOR latency in SCA3 [98] ↓ VORr, VOR40, VOR60, and VOR80 in SCA3 [98]	SWJ and impaired smooth pursuit ↑ in presymptomatic SCA3 [100]	Gaze-evoked nystagmus ↑ in symptomatic SCA3 vs. presymptomatic SCA3 [100]	

BAEP: brainstem auditory evoked potentials; CMCT: central motor conduction time; EEG: electroencephalography; MEPs: motor evoked potentials; pHSN: perverted head shaking nystagmus or vertical nystagmus after horizontal head shaking; RMT: resting motor threshold; SICI: short-interval intracortical inhibition; SSEPs: somatosensory evoked potentials; VOG: video-oculography; VOR: vestibulo-ocular reflex; VOR40, VOR60, and VOR80: the median of the eye and head velocity ratio during 35–45, 55–65, and 75–85 ms after head-turning impulse starts.