Chapter

Rehabilitation for Spinocerebellar Ataxia

Akiyoshi Matsugi, Kyota Bando, Yutaka Kikuchi, Yuki Kondo and Hideki Nakano

Abstract

Rehabilitation is an important treatment for spinocerebellar ataxia (SCA). The lack of improvement in ataxia, deficit of motor learning, and unstable balance causes disability for activities of daily living and restricts participation in social activities, further resulting in a disturbance of the restoration of quality of life. This narrative review describes physical rehabilitation, including measurement of movement disorder, associated with ataxia and possible interventions. Several lines of evidence suggest that high-intensity individualized physical rehabilitation programs, especially for gait and balance training, improve motor function. Continuous exercise at home contributes to the maintenance of the gait and balance function. Moreover, videography and mechanical technology contribute to the evaluation of ataxia and motor learning ability, and assistive robotic systems may improve gait stability. Neuromodulation montages, such as repetitive transcranial magnetic stimulation and transcranial electrical stimulation, can enhance the effect of physical rehabilitation. Further research aimed at developing a more-effective physical rehabilitation for these patients is expected.

Keywords: spinocerebellar ataxia, rehabilitation, physical therapy, ataxia, assessment, gait training, balance training, motor learning, assistive technology, neuromodulation, noninvasive brain stimulation

1. Introduction

Spinocerebellar ataxia (SCA), which is included in spinocerebellar degeneration (SCD), is a genetically heterogeneous group of autosomal dominantly inherited progressive disorders [1]. Cerebellar atrophy is the most prominent clinical feature of this condition and is accompanied by spinal cord and sequential brain stem and basal ganglion damage. Therefore, coordinated movement of the eyes, head, trunk, and extremities is impaired. Therefore, the activities of daily living (ADL) and participation in social activities are limited, and the quality of life (QOL) is undisputedly impaired in these patients [2].

The effects of medication and surgery in this clinical setting depend on the cause of ataxia and the extent of neuronal damage [3, 4]; however, there is no rational effective treatment for SCA and it is difficult to slow the progression of the disease. Rehabilitation [5, 6], including physical therapy [7, 8], aimed at improving/maintaining motor function, ADL, and QOL [5] is an important intervention for patients with SCA. Here we provide a narrative review of physical rehabilitation for SCA.

2. General features

For the clinical diagnosis of cerebellar ataxia, specific blood studies and magnetic resonance imaging (MRI) have been performed [9]. Furthermore, genetic techniques improve the diagnosis of degenerative cerebellar ataxia [10]. Although the details of the findings of these genetic and blood studies are beyond the scope of this review of rehabilitation, cerebellar atrophy and cerebellar motor deficits are traditionally common observations in patients with degenerative cerebellar ataxia [9]. Furthermore, recently, the absence of motor cerebellar symptoms has also been recognized as being important for rehabilitation [11].

The cerebellum is the motor-control system in humans [12]. Clinically, the oculomotor deficit, speech deficits, ataxia in the trunk and extremities, balance disorder, and gait disturbance are the targets of rehabilitation in SCA [9, 13]. The possible underlying pathogenetic mechanisms include distorted timing, abnormal sensory acquisition, impaired sensory motor synchronization, impaired triggering of corticomotor excitability, and abnormal visuokinesthetic cerebro-cerebellar interactions [13].

Oculomotor deficits cause deoptimized vision. The vestibulo-ocular reflex and smooth pursuit [14] partially depend on motor prediction in static and dynamic movement and contribute to dynamic gazing [15]; moreover, the cerebellum contributes to the trainability of eye-head coordinated movements [16].

Abnormal excitability and modulation in the motor cortex and corticospinal tract causes a voluntary contraction deficit in [17, 18]. Cerebellar stimulation modulates the motor-evoked potential induced by transcranial magnetic stimulation (TMS) of the primary motor cortex [19–21]; however, this modulation is absent in patients with SCA [22, 23]. Furthermore, the cortical silent period, which reflects the excitability of the inhibitory GABAergic neural circuit in the primary motor cortex, is abnormal in these patients [24–29], and this cerebellar effect on the cortical silent period is characteristic of the healthy population [30]. Before muscle contraction for movement, the corticospinal excitability increases in healthy individuals; in contrast, this facilitation is insufficient in SCA [31]. In addition, in patients with SCA, muscle tones are decreased [11] and the spinal reflex excitability is facilitated by cerebellar stimulation [32–34]. The long latency spinal reflex, which is correlated with the cortical circuit, is disturbed in SCA [35]. Although this functional cerebellum-spine connection may contribute to the preparation for muscle contraction, there is insufficient evidence that these connections contribute to motor control in healthy and cerebellar ataxia populations.

In simple movements, such as extension of the elbow, coordinated activity of the biceps and triceps is needed. For ballistic elbow-extension movement practice, the triphasic muscle agonist and antagonist contraction patterns contribute to the smooth movement, but under/overshooting appears during the uncoordinated contraction pattern of patients with SCA [36, 37]. Furthermore, this contraction pattern may be obtained by temporal electrical stimulation in these individuals [37].

The cerebellar internal model contributes to predictable/online/offline motor control and motor learning/adaptation [38]. The symptoms associated with motor learning do not appear at the onset of the cerebral atrophy [39], because several brain areas, i.e., the prefrontal cortex, primary motor cortex, and basal ganglia, compensate for cerebellar function in early-stage SCA [5, 6, 39]. Recently, the motor learning deficit at the early stage of the disorder was reportedly detected using an adaptation task [40]. Therefore, the assessment of the capacity for motor learning may be important to strategize the interventions that are concretely described in the following sections.

Representative nonataxia symptoms include hyperreflexia, areflexia, extensor plantar, spasticity, paresis, muscle atrophy, fasciculations, myoclonus, rigidity, chorea/dyskinesia, dystonia, resting tremor, sensory symptoms, urinary dysfunction, cognitive impairment, and brain stem oculomotor signs [41]. The Inventory of NonAtaxia Symptoms (INAS) [41] is used to estimate these nonataxia symptoms. The appearance of these symptoms depends on the type of SCA [41].

3. Assessment format

We should conduct assessment to detect the degree of motor dysfunction and consider more effective intervention of physical rehabilitation. The first, the imaging technology such as MRI provides us with structural information about the atrophic areas of the brain associated with the disease. We described about neuroimaging technique in Section 3.1. The next, we can use some outcome measurement to estimate the motor dysfunction and verification in the physical rehabilitation. Then, we introduce the representable outcome measures for physical rehabilitation in SCA in Section 3.2. However, we had not established method to estimate the remaining of motor learning ability, which is one of the most important factors to predict the effect of physical rehabilitation. Therefore, we propose the possible assessment of motor learning ability in Section 3.3.

3.1 Neuroimaging

Neuroimaging is a technique that is used to visualize the structural and functional activities of the brain. MRI measurements, such as diffusion tensor imaging and surface-based morphometry, visualize the brain structures. Functional activity imaging is achieved using fMRI and NIRS, which are indicators of cerebral blood flow, and electroencephalogram (EEG) and magnetoencephalography, which are indicators of electrical activity. Positron emission tomography and single-photon emission computed tomography with nuclear tracers are also used in this setting. The application of neuroimaging in the rehabilitation of cerebellar disorders includes voxel-based lesion symptom mapping in patients with stroke, to investigate the recovery of upper arm reach [42] and walking ability [43] depending on the lesion site.

Although conventional MRI [44] is widely used for the neuroimaging of spinocerebellar degeneration, to obtain diagnostic findings, few studies have used neuroimaging as a guideline or outcome of rehabilitation. The lack of reports in this context hampers the quantification of cerebellar degeneration in SCA and its correlation with motor dysfunctions. In terms of measurement techniques, the cerebellum exhibits a much tighter folding compared with the cerebral cortex, with individual cortical sheets with a thickness of 1–2 mm and a sheet area of 1500–2000 cm^2, compared with a sheet area of 2200 cm^2 with a thickness of 1.5–4 mm in the cerebral cortex. Therefore, the typical 2–4 mm^3 spatial resolution of neuroimaging techniques is insufficient to capture local cerebellar changes. Patient factors include the difficulty in limiting the brain regions involved in movement disorders to the cerebellum, because the degenerative regions in SCD extend beyond this structure to multiple brain regions [45].

Among the neuroimaging modalities, the role of voxel-based morphometry (VBM) is notable in SCA rehabilitation. VBM is a statistical analysis of the entire brain in voxel units (1 mm^3) that is used to identify the behavioral patterns and related brain morphological characteristics of patients [46]. Burciu et al. assessed the degree of cerebellar atrophy concerning motor and learning functions using VBM to evaluate brain structure changes after 2 weeks of balance training in patients

with SCD; these authors reported the association between an increased volume of the dorsal premotor cortex and increased balance ability [47]. Matsgi et al. reported an association between VBM and neurophysiological markers in cerebellar brain inhibition (CBI), with atrophy of the dentate nucleus at VBM observed in cases of pure cerebellar ataxia that did not show CBI [48]. Bando et al. reported a correlation between adaptive learning ability and gray matter volume of the cerebellar IV-VII lobules and the supramarginal gyrus in a prismatic adaptation task in SCA [49]. Thus, VBM may be a biomarker to explain motor dysfunction in patients with SCA.

Conversely, VBM is not an ideal tool to show a causal relationship between brain structural changes and behavioral differences. As a solution to this problem, we can propose a combination of VBM and neurostimulation [50], as neurostimulation of the brain regions associated with the behavioral patterns obtained by VBM and the observation of behavioral changes before and after stimulation allow us to examine brain degeneration sites and behavior.

3.2 Outcome measurement

Gait disturbance is a major symptom of the cerebellar pathology in SCA [51]. The functional ambulation categories (FAC) is useful for the comprehensive assessment of walking ability; the FAC assesses gait for about 15 m and climbing stairs and classifies gait levels into 6 levels [52]. The FAC is also used in the exercise program created by Research Committee for Ataxia Disease (Research team under the jurisdiction of the Ministry of Health, Labour and Welfare in Japan, http://ataxia.umin.ne.jp/rehabilitation/).

The quantitative assessment of cerebellar ataxia is very important in clinical practice. The International Cooperative Ataxia Rating Scale (ICARS) has been used as a quantitative assessment of ataxia symptoms. However, it has been noted that the test reliability of the eye movement items is low [53]. The Scale for Assessment and Rating of Ataxia (SARA) is an 8-item performance-based scale that yields a total score of 0–40 (most severe ataxia). The minimal detectable change (MDC) for individual score difference from the baseline to the 1-year follow-up in SARA was <3.5 (n = 171; SCA1, n = 43; SCA2, n = 61; SCA3, n = 37; and SCA6, n = 30; mean age, 50.9 ± 13.5 years; mean disease duration, 11.8 ± 5.6 years) [54]. SARA does not include an eye movement section. Schmahmann et al. noted the importance of assessing oculomotor abnormalities and developed the Brief Ataxia Rating Scale, a modification of ICARS [55]. Each SCA genotype exhibits specific symptoms [56]. Therefore, these assessments should be used differently for different symptoms. However, one feature that is consistent among these assessments is that the scoring range is large and does not allow the assessment of minute symptom changes. Honda et al. developed a system to measure the evaluation of SARA using a depth sensor [57]. Using this system, the degree of ataxia can be measured numerically. In addition, because the system is inexpensive, it can be installed at the patient's home, making it a useful tool for telemedicine.

The balance dysfunction in SCA has a significant impact on QOL [58]. The Berg Balance Scale and the Timed Up and Go test are widely used to assess balance dysfunction in SCA [59]. However, despite their widespread use, these assessments have not been examined for reliability and validity in SCA. Kondo et al. examined the test reliability of the Balance Evaluation Systems Test (BESTest) [60]. The BESTest is a multitask balance assessment tool that was developed to identify specific postural control problems (i.e., biomechanical constraints, stability limits, anticipatory postural adjustments, postural responses, sensory orientation, dynamic balance during gait, and cognitive effects) [61]. The MDC for an individual score difference from the baseline to the 4-week follow-up in

BESTest was <8.7 (n = 20; SCA3, n = 4; SCA6, n = 9; SCA31, n = 7; mean age, 63.7 ± 10.1 years; age at onset, 53.9 ± 10.5 years; baseline SARA, 9.9 ± 3.5) [61]. Many types of balance function measures have been reported. However, BESTest is the only scale that is considered to have absolute reliability in SCA.

Gait speed is often used as an outcome of intervention studies in SCA [62, 63]. However, some changes in the gait pattern (e.g., base of support and gait speed) most likely reflect cerebellar-unspecific, compensatory strategies, and a high spatiotemporal gait variability appears to be a distinctive feature of ataxic gait [58, 64]. The Gait Variability Index (GVI) is a measure of gait variability that has been examined regarding reliability and validity [65]. The MDC for an individual score difference from day 1 to day 2 in GVI was <8.6 (Friedreich's ataxia, n = 81; baseline ICARS, 70.4 ± 7.9) [65]. It has been suggested that gait instability in SCA are characterized by a stronger effect of balance-related impairments of cerebellar control during slow walking and a stronger effect of impaired intra-limb coordination during fast walking [58]. Therefore, in clinical practice, it is necessary to evaluate not only the optimal gait speed, but also slow walking and fast walking, to extract the characteristics of gait instability.

3.3 Assessment of motor learning ability

The cerebellum has the ability to compensate for tissue damage and loss of function. This is called the cerebellar reserve [6]. Mitoma et al. suggested that this is important for motor rehabilitation at a time when the cerebellar reserve is functioning [6]. Motor rehabilitation in the early stages may maintain and improve the cerebellar reserve [66, 67]. Therefore, it is important to assess this parameter.

Cerebellar ataxia is the main symptom of SCA. Ataxia symptoms may represent a compensation for predictive control using feedback control [6]. Predictive control requires a mechanism called internal model [38]. The internal model is constantly updated by motor learning [68]. In turn, motor learning is one of the most important functions of the cerebellum. Thus, a measure of motor learning ability may be useful as an assessment of the cerebellar reserve.

Prism adaptation (PA) is widely used as an assessment of motor learning ability in patients with SCA [40, 69]. The basic procedure of PA is shown in **Figure 1**. First, at the "baseline," the task is performed without a prism lens. Subsequently, the prism lens is introduced and the task is performed. In the initial phase, the lens is set off to either the left or right side of the target, but the error is corrected as the number of repetitions increases. This period is called the "initial error correction phase." Thereafter, a spatial realignment phase is performed under the prism lens. The purpose of this phase is to gather visuospatial information including the errors. Next, the prism is removed and an "after-effect phase" is performed. If the spatial information is being re-learned, errors are generated in the opposite direction to the initial error correction phase. Recently, Hashimoto et al. developed the Adaptability Index (AI), which is a composite index computed from several parameters measured PA (**Figure 2**). The clinical efficacy of the AI in discriminating patients with SCA from healthy individuals has been demonstrated [70]. Furthermore, Bando et al. found that a reduced AI was correlated with gray matter atrophy in the cerebellum in the SCA group [49]. In particular, the right lobule VI and the left Crus I showed the most robust correlation. These cerebellar regions are consistent with the correlates of PA detected in previous human and nonhuman primate studies [71, 72]. AI is considered as a motor learning index that reflects the cerebellar reserve (in this case, the degree of cerebellar atrophy).

PA can be implemented using a simple system. In addition, it takes only 20 min to complete a PA. Reaching tasks can be performed even in the period during which

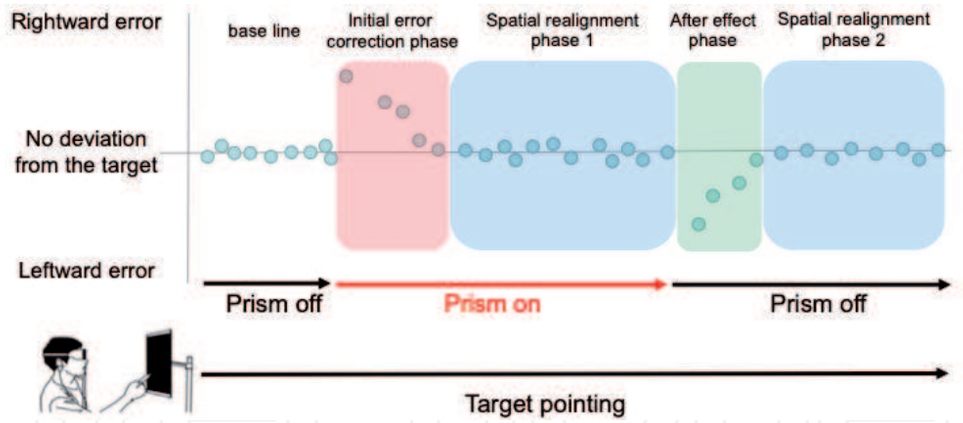

Figure 1.
Overview of prism adaptation. The ordinate shows the finger-touch error represented from the target to the touch point. Three phases are generally used: (1) absence of a prism lens (prism off), (2) presence of a prism lens (prism on), and (3) absence of a prism lens (prism off).

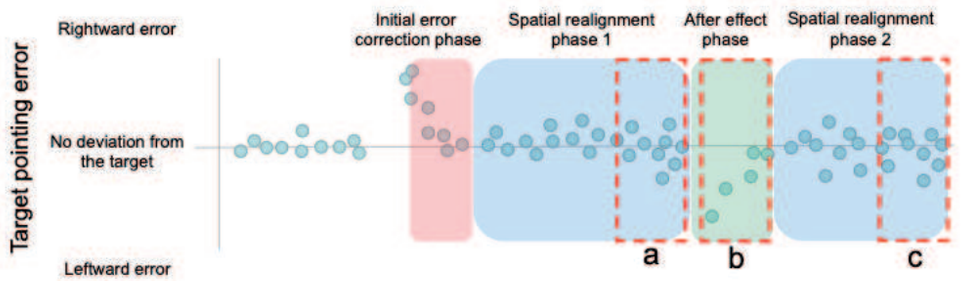

Figure 2.
Calculation of the adaptability index (AI). The AI is calculated as follows: AI = a × b × c, where "a" is the adaptation index defined as the probability of correct touches in the last 10 trials of the spatial realignment phase 1, "b" is the retention index defined as the probability of incorrect touches in the initial 5 trials of the after-effect phase, and "c" is the extinction index designated as the probability of correct touches in the last 10 trials of the spatial realignment phase 2.

the patient is unable to walk, and the fact that the PA can be assessed continuously over a long period is an advantage. However, only cross-sectional studies have been conducted in previous reports [40, 49, 69, 70, 73, 74]. Future studies need to be designed to examine long-term changes and intervention effects.

4. Rehabilitation

The targets of rehabilitation in cerebellar ataxia are mainly disability in ADL, gait, and motor dysfunction. Therefore, GAS, FIM, 10-m walking test, TCA, SARA, ICARS, and BESTest are used as important outcomes in rehabilitation. The most important strategies of rehabilitation for cerebellar ataxia including SCA consists in balance training (see Section 4.3), gait training (see Section 4.2), and muscle strengthening training using a high-intensity program (see Section 4.1). Further, optional possible interventions are using assistive technology (see Section 4.4) and neuromodulation technique (see Section 4.5).

4.1 Intensive and continuous training

Rehabilitation methods for cerebellar ataxia have been reported [75]. The most important strategy is the increase in the intensity of physical training, such as balancing, gait, and strength [76]. Several systematic reviews [77–79] and narrative

reviews [3, 75, 80, 81] introduced and recommended intensive physical therapy for cerebellar ataxia in patients with SCA. Miyai et al. [62] reported that physical and occupational therapies of 2 h × 5 days +1 h × 2 days per week for 4 weeks were applied to inpatients and improved the SARA score and gait speed; however, the effect was carried over only up to 12 weeks after the training, and had disappeared at 24 weeks [62]. Conversely, Ilg et al. reported that intensive coordinative physiotherapy delivered over 4 weeks improved motor performance in degenerative cerebellar ataxia in a study with an intraindividual control design [63].

An outpatient rehabilitation program for 6 weeks applied to 19 participants with Friedreich's ataxia improved the motor domain item in the FIM score and Friedreich's Ataxia Impact Scale, but the posthome program could not maintain the effect [82]. Therefore, this finding indicates that continuous outpatient rehabilitation programs are important for maintaining the ADL in patients with Friedreich's ataxia. Additional large-scale studies are needed to investigate the long-term effect of outpatient rehabilitation programs and identify the characteristics of patients who respond to treatment. Therefore, the development of optimal individual programs is important to obtain the effect of training, regardless of the inpatient, outpatient, or home-self-training setting [83]. The semi-order program of the Research Committee for Ataxia Disease (Research team under the jurisdiction of the Ministry of Health, Labour and Welfare in Japan, http://ataxia.umin.ne.jp/rehabilitation/) can be used for this purpose.

Subsequently, the continuity of the intensive training is an important factor, because degradation in physical function was reported. Therefore, approaches aimed at upkeeping these programs in a way that suits the patients are needed. For example, exergames contribute to the practice of exercise at home. In the future, tele-rehabilitation systems [84] should be tested for the improvement (or maintenance) of the function and continuity of exercise.

4.2 Gait training

Gait training has been reported to improve spatiotemporal gait parameters (cadence, step length/width, gait speed, etc.) [85–87], complex gait (Timed Up and Go test, Dynamic Gait Index) [85], independence (FAC) [86], ataxia (SARA) [88], and adaptive locomotor adjustments (ALA) [88]. Patients with SCA exhibit problems other than the gait disturbance itself, i.e., stiffening of the body in an attempt to avoid the occurrence of gait disturbances. Therefore, it is important to focus on gait disturbances and increasing the number of walking patterns when considering gait training in a person with SCA.

Disturbances of gait are the core features of SCA [89–92], thus leading to a risk of falling down [93]. Patients with cerebellar ataxia walk with a reduced walking speed and cadence, as well as reduced step length, stride length, and swing phase; increased walking base width, stride time, step time, stance phase, and double limb support phase; and increased variability of step length, stride length, and stride time [94]. These items are affected by both balance-related impairments and deficits related to limb control and intra-limb coordination [95]. We believe that balance training and coordination training are key to the improvement of gait disturbances. Regarding the details of balance training, please refer to the Section 4.3.

In addition, stiffening of the body leads to a decrease in the number of walking patterns; as a result, ALA deteriorates [96, 97]. ALA implies that obstacle avoidance is achieved by modifying basic walking patterns in response to obstacle properties, e.g., a sloping road, stepping over an obstacle, or dynamically changing the spaces created by pedestrians in a hallway. In persons with SCA, feelings of anxiety as a result of the frequent experience of falls, as well as deficits related to limb control

by ataxia, could negatively affect their ALA because of increased muscular co-contractions and reduced joint movements [98]. We will describe the approaches to improve ALA in the next paragraph.

The proposals for gait training are as follows: gait training without or with a treadmill. First, in gait training without a treadmill, we refer the reader to Section VI of the BESTest as gait adaptability training [61]. Section VI of the BESTest consists of a 7-item scale: (1) Gait Natural, (2) Change Speed, (3) Head Turns, (4) Pivot Turn, (5) Obstacles, (6) "Get Up & Go" Test, and (7) Cognitive Task "Get Up & Go" Test, aimed at evaluating the stability of the gait. These elements are important to improve ALA. As an example of gait training, persons with SCA are asked to walk while making an effort to change their walking speed according to therapist's instructions to engage is "fast (or slow)" walking as fast (or slow) as possible. If patients need assistance when walking, you might want to change the walking speed with the support of a therapist.

Second, gait training using a treadmill has advantages in that patients can practice a relatively large amount of gait training over a short period and the therapists can control the speed and incline easily. Gait training using a treadmill has been reported as a potentially promising tool for improving ALA in a person with SCA [88], as well as gait disturbances in a person with Parkinson's disease [99, 100]. It has been reported that variability was increased during slow and fast walking, but was normal during the preferred walking speed in a person with cerebellar ataxia [101]. Another study reported that, in ataxia, walking at the preferred speed minimizes the gait abnormalities, and the analysis of gait at a wide range of speeds is recommended [94]. For this reason, when using a treadmill in gait training, we suggest that walking be practiced at the speed at which the gait disturbance increases (i.e., slow or fast walking speed) for specific patients. When the fear of falling increases, the use of a harness is recommended, to provide a safe environment for gait without the fear of falling.

It is important to improve the balance ability and ALA during gait training in a person with SCA. Gait training is a relatively easy method; however, it is left to the therapist's discretion and experience. By changing the task itself or adjusting the difficulty level of the task, gait training may be able to overcome the limited walking patterns of these patients.

4.3 Balance training

All patients with SCA will develop balance difficulties during the course of the disease. Balance is essential for mobility, and is very important for QOL. Although there is no effective pharmacological treatment for decreasing the ataxia or slowing disease progression, physical therapy plays an important role in controlling ataxia and improving or maintaining function through training [76]. In general, the physical therapy programs for degenerative cerebellar ataxia are based on intensive static and dynamic balance and coordination training. There is some evidence that such therapeutic training programs alleviate the ataxic symptoms and improve functional activities in a person with cerebellar ataxia [63, 78, 102]. In these patients, the disease progressively damages the cerebellar structure that plays a crucial role in motor learning [103]; however, these studies have indicated that it is necessary for highly repetitive balance training for balance impairment in SCA. For this reason, highly repetitive balance training in patients with SCA should be the focus of future studies.

More concretely, balance training exercises in early stages of the disease, i.e., ambulation, include the following categories: (1) static balance training, (2) dynamic balance training, and (3) coordination training (**Figure 3**). In addition, combining a

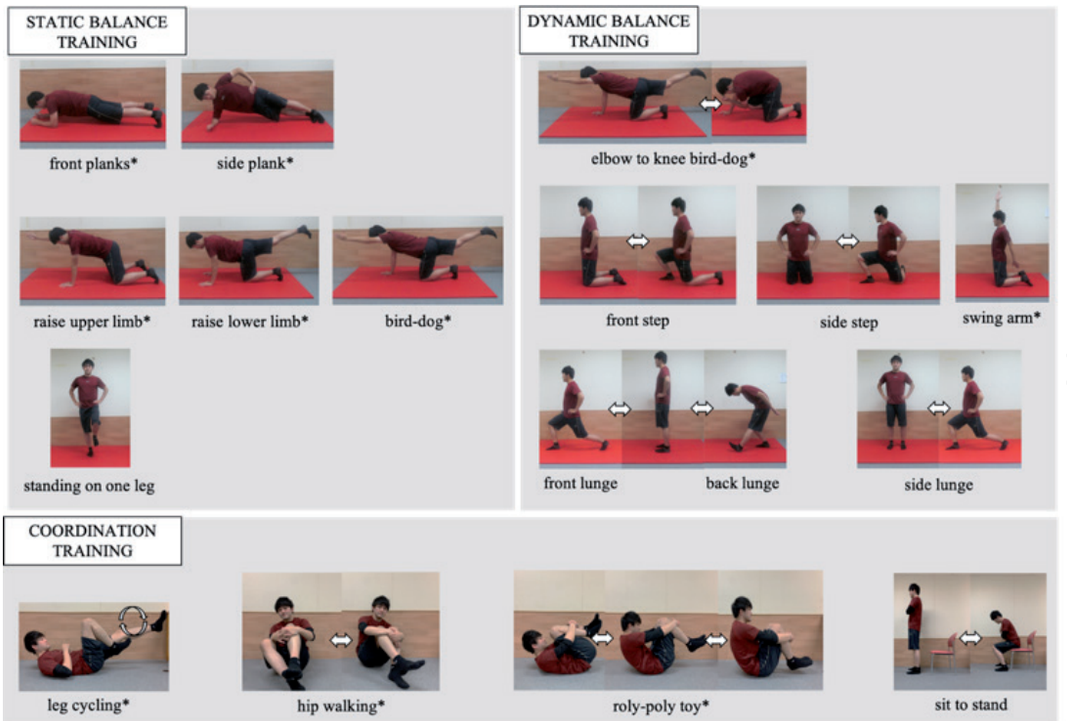

Figure 3.
National Center of Neurology and Psychiatry (NCNP) balance training program. This balance training program was devised through consultations with patients with SCA, medical doctors, and therapists at the NCNP in Japan. In the advanced stage of SCA, it is recommended to perform the programs indicated by an asterisk.

dual task with balance training improves balance and reduces the number of falls in individuals with cerebellar ataxia [104].

Moreover, it is important to provide support for these approaches and make them a habit of exercising. For instance, if the patients with SCA have no habit of exercising, they should start with a small number of exercises (i.e., the minimum necessary) to get used to exercising, followed by the gradual increase in the number of exercises. If the patients with SCA have a habit of exercising, the therapist should teach them to adjust the exercise load (e.g., exercise more slowly and/or provide a small base of support). It is also important to adopt balance training that can be enjoyed, e.g., video games [105] and Tai Chi [106], as a means of continuing balance training.

In advanced stages of the disease (i.e., no ambulation), it is necessary to perform balance training under safe conditions (e.g., prone, supine, crawl, and sitting positions), to prevent the decrease in physical activity. Even in advanced stages, it has been reported that a person with degenerative ataxia may benefit from balance training [107]. In addition, it is necessary to focus on ADL and living infrastructure at this stage. If a patient with SCA requires assistance during transfer, engaging in repetitive transfer training with assistance and/or modification of the living infrastructure (e.g., installation of handrails) are necessary.

Focusing on highly repetitive balance training in patients with SCA might preserve the balance function. There is no scientific basis for the number of balance training exercises that are necessary to achieve this goal; however, we would like to recommend engaging in 30 repetitions at least per balance training session. Furthermore, the balance training must be designed to provide a significant challenge to the person's balance. If a person with SCA wants to preserve the balance function, they have to continue engaging in repetitive balance training, "use it or lose it." However, few studies have reported the effect of gait and balance training in persons with SCA.

Therefore, further studies are needed to clarify the clinical effectiveness of gait and/or balance training.

4.4 Assistive technology

In recent years, various technologies have been used in the assessment of and treatment based on rehabilitation, as well as to support daily life in patients with SCD. Curara, a wearable robotic system, assists both hip and knee movements and supports the wearer's rhythmic gait using a synchronization control based on a central pattern generator [108]. Gait support using the curara system has been reported to improve gait smoothness in patients with SCD [109]. In addition to these findings, a recent study addressed the effects of robotic gait training combined with noninvasive brain stimulation. This report showed that robot gait training using Lokomat-Pro in combination with cerebellar tDCS improved the functional scores on SARA, especially the scores on the subitems of gait, stance, sitting, and heel-shin slide compared with robot gait training alone [110]. Thus, hybrid training using robots and noninvasive brain stimulation will be applied to the rehabilitation treatment of patients with SCD in the future.

Accordingly, the use of walking aids is a complementary method for balance and gait impairment. In general, walking aids such as canes and walkers improve postural stability, but their improper use increases the risk of falling [111]. Because the manipulation of a cane requires coordinated upper limb movements [112], patients with SCD who have upper limb ataxia are likely to experience difficulty in using a cane. Conversely, because a walker does not require much coordinated movement of the upper limbs, technology-based walkers are being developed. Recently, a smart walker for mobility assistance and monitoring system aid, ASBGo, was developed and reported to improve gait parameters and postural stability in patients with SCA [113, 114]. In addition to technology, some studies on walking assistance using dogs and handkerchiefs have also been reported. Walking with a rehabilitation dog that has been specifically trained for goal-directed interventions or with an assistance dog that helps people with physical disability and mobility impairments has been reported to improve balance while walking in patients with SCD [115]. Furthermore, the handkerchief-guided gait, in which the patient with SCD walks along with the caregiver while maintaining light tension on a handkerchief by pulling lightly, has been shown to decrease body swaying and increase stride length and gait velocity during walking [116].

Moreover, technology is also being used as a tool to assess ataxia in patients with SCD living at home. Most of them represent attempts to evaluate SARA, which is a typical measure of ataxia, at home. In recent years, a technology aimed at objectively evaluating the speech, upper and lower limb, balance, and gait functions using wearable inertial sensors and a Kinect camera was developed, which makes it possible to discriminate between normal and abnormal functions and to detect ataxia at an early stage [117]. In addition, SaraHome has been developed to allow the remote evaluation of SARA items using Kinect and Leap Motion Controller [118]. Moreover, a spoon equipped with an inertial sensor, called Ataxia Instrumented Measurement-Spoon, has been developed, which allows the evaluation of upper limb function in ataxia while eating with a spoon [119–121]. Because SCD is an intractable neurological disease, it is difficult for many patients to leave their houses. Therefore, the contribution of technology to home-based rehabilitation is expected to increase in the future if a low-cost and easy method of assessing ataxia at home is established using the technologies and products of daily living described above.

Regarding the support of ADL, BMI studies have been reported. Patients with severe SCA often have difficulty in communicating because of language impairment. The application of BMI using event-related potentials and frequency bands of EEG is being investigated as a solution to this problem. The operational accuracy of BMI using P300 for event-related potentials was 82.9% in patients with SCA, which was similar to the accuracy observed in healthy subjects (83.2%) [122]. There are also reports of BMI manipulation in patients with SCD using the EEG frequency band associated with motor imagery [123]. BMI has a wide range of applications in diseases of the central nervous system, such as communication tools, transportation, and life support, and is expected to contribute to the QOL of patients with SCD.

4.5 Neuromodulation

Neuromodulation via noninvasive brain stimulation (NIBS) is a potential method for the treatment of cerebellar ataxia [19, 124]. A previous systematic review [125] reported the effectiveness of cerebellar neuromodulation using the TMS technique of transcranial direct current stimulation (tDCS). The SARA and ICARS scores in patients with SCA3, multiple system atrophy, and postlesion ataxia, as assessed using real cerebellar rTMS (1 Hz), were significantly lower than those detected in the sham stimulation group [125]. Furthermore, no harmful side effects were noted [125]. Cerebellar rTMS can modulate the plasticity of the vestibular reflex [16, 126]; therefore, cerebellar rTMS has potential for application in balance training to enhance vestibular contributions.

A single session of anodal cerebellar tDCS (2 mA, 20 min) significantly improved SARA, ICARS, 9-hole-peg test, and 8-m walking test scores [127]. Furthermore, combined anodal cerebellar tDCS and cathodal spinal DCS (5 days/week, 2 weeks) improved SARA score, ICARS score, 9-peg test, and 8-m walking time in patients with degenerative cerebellar ataxia [128]. There is insufficient evidence regarding whether simultaneous stimulation is more effective than single stimulation [129]; however, it is possible that this intervention method will produce improvements. Based on these findings, which were gleaned from small-sample studies, we suggest that a neuromodulation montage will improve the ataxia, balance, and gait ability. Therefore, we should perform further studies using a larger population.

5. Conclusion

Individualized physical rehabilitation programs for patients with SCA may improve/maintain their motor function, balance, gait ability, and ADL. In particular, the intensity and continuity of gait and balance training need to be considered to achieve effectiveness. Furthermore, several technologies, such as depth sensors, robotics, and NIBS, have contributed to the development of methods for the assessment and treatment of motor dysfunction in individuals with SCA. We should continue to study populations suffering from dysfunction caused by SCA.

Acknowledgements

This work was supported by Shijonawate Gakuen University and JSPS KAKENHI (Grant Number 20 K11298).

Conflict of interest

The authors declare no conflict of interest.

Author details

Akiyoshi Matsugi[1*], Kyota Bando[2], Yutaka Kikuchi[3], Yuki Kondo[2] and Hideki Nakano[4]

1 Shijonawate Gakuen University, Daito, Osaka, Japan,

2 National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

3 Institute of Brain and Blood Vessels Mihara Memorial Hospital, Isesaki, Gunma, Japan

4 Kyoto Tachibana University, Kyoto-city, Kyoto, Japan

*Address all correspondence to: a-matsugi@reha.shijonawate-gakuen.ac.jp

References

[1] Klockgether T, Mariotti C, Paulson HL. Spinocerebellar ataxia. Nat Rev Dis Primers. 2019;5(1):24. DOI:10.1038/s41572-019-0074-3

[2] Schmitz-Hubsch T, Coudert M, Giunti P, Globas C, Baliko L, Fancellu R, et al. Self-rated health status in spinocerebellar ataxia--results from a European multicenter study. Mov Disord. 2010;25(5):587-595. DOI:10.1002/mds.22740

[3] Pandolfo M, Manto M. Cerebellar and afferent ataxias. Continuum (Minneap Minn). 2013;19(5 Movement Disorders):1312-43. DOI:10.1212/01.CON.0000436158.39285.22

[4] Ilg W, Bastian AJ, Boesch S, Burciu RG, Celnik P, Claassen J, et al. Consensus paper: management of degenerative cerebellar disorders. Cerebellum. 2014;13(2):248-268. DOI:10.1007/s12311-013-0531-6

[5] Mitoma H, Manto M, Gandini J. Recent Advances in the Treatment of Cerebellar Disorders. Brain Sci. 2019;10(1). DOI:10.3390/brainsci10010011

[6] Mitoma H, Buffo A, Gelfo F, Guell X, Fuca E, Kakei S, et al. Consensus Paper. Cerebellar Reserve: From Cerebellar Physiology to Cerebellar Disorders. Cerebellum. 2020;19(1):131-153. DOI:10.1007/s12311-019-01091-9

[7] Mills RJ, Yap L, Young CA. Treatment for ataxia in multiple sclerosis. Cochrane Database Syst Rev. 2007(1):CD005029. DOI:10.1002/14651858.CD005029.pub2

[8] Trujillo-Martín MM, Serrano-Aguilar P, Monton-Alvarez F, Carrillo-Fumero R. Effectiveness and safety of treatments for degenerative ataxias: a systematic review. Mov Disord. 2009;24(8):1111-1124. DOI:10.1002/mds.22564

[9] Manto M, Gandini J, Feil K, Strupp M. Cerebellar ataxias: an update. Curr Opin Neurol. 2020;33(1):150-160. DOI:10.1097/WCO.0000000000000774

[10] Beaudin M, Matilla-Duenas A, Soong BW, Pedroso JL, Barsottini OG, Mitoma H, et al. The Classification of Autosomal Recessive Cerebellar Ataxias: a Consensus Statement from the Society for Research on the Cerebellum and Ataxias Task Force. Cerebellum. 2019;18(6):1098-1125. DOI:10.1007/s12311-019-01052-2

[11] Bodranghien F, Bastian A, Casali C, Hallett M, Louis ED, Manto M, et al. Consensus Paper: Revisiting the Symptoms and Signs of Cerebellar Syndrome. Cerebellum. 2016;15(3):369-391. DOI:10.1007/s12311-015-0687-3

[12] Ito M. Neurophysiological aspects of the cerebellar motor control system. Int J Neurol. 1970;7(2):162-176

[13] Manto M, Oulad Ben Taib N. The contributions of the cerebellum in sensorimotor control: what are the prevailing opinions which will guide forthcoming studies? Cerebellum. 2013;12(3):313-315. DOI:10.1007/s12311-013-0449-z

[14] Sharpe JA. Neurophysiology and neuroanatomy of smooth pursuit: lesion studies. Brain Cogn. 2008;68(3):241-254. DOI:10.1016/j.bandc.2008.08.015

[15] Tang SY, Shaikh AG. Past and Present of Eye Movement Abnormalities in Ataxia-Telangiectasia. Cerebellum. 2019;18(3):556-564. DOI:10.1007/s12311-018-0990-x

[16] Matsugi A, Yoshida N, Nishishita S, Okada Y, Mori N, Oku K, et al. Cerebellum-mediated trainability of eye and head movements for dynamic gazing. PLoS One.

2019;14(11):e0224458. DOI:10.1371/journal.pone.0224458

[17] Manto M, Bower JM, Conforto AB, Delgado-Garcia JM, da Guarda SN, Gerwig M, et al. Consensus paper: roles of the cerebellum in motor control--the diversity of ideas on cerebellar involvement in movement. Cerebellum. 2012;11(2):457-487. DOI:10.1007/s12311-011-0331-9

[18] Buckner RL. The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. Neuron. 2013;80(3):807-815. DOI:10.1016/j.neuron.2013.10.044

[19] Maas R, Helmich RCG, van de Warrenburg BPC. The role of the cerebellum in degenerative ataxias and essential tremor: Insights from noninvasive modulation of cerebellar activity. Mov Disord. 2020;35(2):215-227. DOI:10.1002/mds.27919

[20] Ugawa Y, Uesaka Y, Terao Y, Hanajima R, Kanazawa I. Magnetic stimulation over the cerebellum in humans. Ann Neurol. 1995;37(6):703-713. DOI:10.1002/ana.410370603

[21] Tanaka H, Matsugi A, Okada Y. The effects of imaginary voluntary muscle contraction and relaxation on cerebellar brain inhibition. Neurosci Res. 2017. DOI:10.1016/j.neures.2017.11.004

[22] Ilg W, Branscheidt M, Butala A, Celnik P, de Paola L, Horak FB, et al. Consensus Paper: Neurophysiological Assessments of Ataxias in Daily Practice. Cerebellum. 2018;17(5):628-653. DOI:10.1007/s12311-018-0937-2

[23] Matsugi A, Kikuchi Y, Kaneko K, Seko Y, Odagaki M. Cerebellar transcranial magnetic stimulation facilitates excitability of spinal reflex, but does not affect cerebellar inhibition and facilitation in spinocerebellar ataxia. Neuroreport. 2018;29(10):808-813. DOI:10.1097/WNR.0000000000001036

[24] Teo JT, Schneider SA, Cheeran BJ, Fernandez-del-Olmo M, Giunti P, Rothwell JC, et al. Prolonged cortical silent period but normal sensorimotor plasticity in spinocerebellar ataxia 6. Mov Disord. 2008;23(3):378-385. DOI:10.1002/mds.21847

[25] Restivo DA, Lanza S, Giuffrida S, Le Pira F, Drago MT, Di Mauro R, et al. Cortical silent period prolongation in spinocerebellar ataxia type 2 (SCA2). Funct Neurol. 2004;19(1):37-41

[26] Restivo DA, Lanza S, Saponara R, Rapisarda G, Giuffrida S, Palmeri A. Changes of cortical excitability of human motor cortex in spinocerebellar ataxia type 2. A study with paired transcranial magnetic stimulation. J Neurol Sci. 2002;198(1-2):87-92. DOI:10.1016/s0022-510x(02)00086-2

[27] Schwenkreis P, Tegenthoff M, Witscher K, Bornke C, Przuntek H, Malin JP, et al. Motor cortex activation by transcranial magnetic stimulation in ataxia patients depends on the genetic defect. Brain. 2002;125(Pt 2):301-309. DOI:10.1093/brain/awf023

[28] Oechsner M, Zangemeister WH. Prolonged postexcitatory inhibition after transcranial magnetic stimulation of the motor cortex in patients with cerebellar ataxia. J Neurol Sci. 1999;168(2):107-111. DOI:10.1016/s0022-510x(99)00164-1

[29] Nakashima K, Wang Y, Shimoda M, Sakuma K, Takahashi K. Prolonged silent periods produced by magnetic cortical stimulation in patients with cerebellar ataxia. Psychiatry Clin Neurosci. 1995;49(2):143-146. DOI:10.1111/j.1440-1819.1995.tb01879.x

[30] Matsugi A, Douchi S, Suzuki K, Oku K, Mori N, Tanaka H, et al. Cerebellar Transcranial Magnetic

Stimulation Reduces the Silent Period on Hand Muscle Electromyography During Force Control. Brain Sci. 2020;10(2). DOI:10.3390/brainsci10020063

[31] Nomura T, Takeshima T, Nakashima K. Reduced pre-movement facilitation of motor evoked potentials in spinocerebellar degeneration. J Neurol Sci. 2001;187(1-2):41-47. DOI:10.1016/s0022-510x(01)00522-6

[32] Matsugi A, Mori N, Uehara S, Kamata N, Oku K, Mukai K, et al. Task dependency of the long-latency facilitatory effect on the soleus H-reflex by cerebellar transcranial magnetic stimulation. Neuroreport. 2014;25(17):1375-1380. DOI:10.1097/WNR.0000000000000275

[33] Matsugi A, Mori N, Uehara S, Kamata N, Oku K, Okada Y, et al. Effect of cerebellar transcranial magnetic stimulation on soleus Ia presynaptic and reciprocal inhibition. Neuroreport. 2015;26(3):139-143. DOI:10.1097/WNR.0000000000000315

[34] Matsugi A, Okada Y. Cerebellar transcranial direct current stimulation modulates the effect of cerebellar transcranial magnetic stimulation on the excitability of spinal reflex. Neurosci Res. 2020;150:37-43. DOI:10.1016/j.neures.2019.01.012

[35] Kurokawa-Kuroda T, Ogata K, Suga R, Goto Y, Taniwaki T, Kira J, et al. Altered soleus responses to magnetic stimulation in pure cerebellar ataxia. Clin Neurophysiol. 2007;118(6):1198-1203. DOI:10.1016/j.clinph.2007.03.006

[36] Koster B, Deuschl G, Lauk M, Timmer J, Guschlbauer B, Lucking CH. Essential tremor and cerebellar dysfunction: abnormal ballistic movements. J Neurol Neurosurg Psychiatry. 2002;73(4):400-405. DOI:10.1136/jnnp.73.4.400

[37] Huang YZ, Chang YS, Hsu MJ, Wong AM, Chang YJ. Restoration of Central Programmed Movement Pattern by Temporal Electrical Stimulation-Assisted Training in Patients with Spinal Cerebellar Atrophy. Neural Plast. 2015;2015:462182. DOI:10.1155/2015/462182

[38] Honda T, Nagao S, Hashimoto Y, Ishikawa K, Yokota T, Mizusawa H, et al. Tandem internal models execute motor learning in the cerebellum. Proc Natl Acad Sci U S A. 2018;115(28):7428-7433. DOI:10.1073/pnas.1716489115

[39] Wong AL, Marvel CL, Taylor JA, Krakauer JW. Can patients with cerebellar disease switch learning mechanisms to reduce their adaptation deficits? Brain. 2019;142(3):662-673. DOI:10.1093/brain/awy334

[40] Hanajima R, Shadmehr R, Ohminami S, Tsutsumi R, Shirota Y, Shimizu T, et al. Modulation of error-sensitivity during a prism adaptation task in people with cerebellar degeneration. J Neurophysiol. 2015;114(4):2460-2471. DOI:10.1152/jn.00145.2015

[41] Schmitz-Hubsch T, Coudert M, Bauer P, Giunti P, Globas C, Baliko L, et al. Spinocerebellar ataxia types 1, 2, 3, and 6: disease severity and nonataxia symptoms. Neurology. 2008;71(13):982-989. DOI:10.1212/01.wnl.0000325057.33666.72

[42] Konczak J, Pierscianek D, Hirsiger S, Bultmann U, Schoch B, Gizewski ER, et al. Recovery of upper limb function after cerebellar stroke: lesion symptom mapping and arm kinematics. Stroke. 2010;41(10):2191-2200. DOI:10.1161/STROKEAHA.110.583641

[43] Bultmann U, Pierscianek D, Gizewski ER, Schoch B, Fritsche N, Timmann D, et al. Functional recovery and rehabilitation of postural impairment and gait ataxia in

patients with acute cerebellar stroke. Gait Posture. 2014;39(1):563-569. DOI:10.1016/j.gaitpost.2013.09.011

[44] Meira AT, Arruda WO, Ono SE, Neto AC, Raskin S, Camargo CHF, et al. Neuroradiological Findings in the Spinocerebellar Ataxias. Tremor Other Hyperkinet Mov (N Y). 2019;9. DOI:10.7916/tohm.v0.682

[45] Tada M, Nishizawa M, Onodera O. Redefining cerebellar ataxia in degenerative ataxias: lessons from recent research on cerebellar systems. J Neurol Neurosurg Psychiatry. 2015;86(8):922-928. DOI:10.1136/jnnp-2013-307225

[46] Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage. 2000;11(6 Pt 1):805-821. DOI:10.1006/nimg.2000.0582

[47] Burciu RG, Fritsche N, Granert O, Schmitz L, Sponemann N, Konczak J, et al. Brain changes associated with postural training in patients with cerebellar degeneration: a voxel-based morphometry study. J Neurosci. 2013;33(10):4594-4604. DOI:10.1523/JNEUROSCI.3381-12.2013

[48] Matsugi A, Kikuchi Y, Kaneko K, Seko Y, Odagaki M. Cerebellar transcranial magnetic stimulation facilitates excitability of spinal reflex, but does not affect cerebellar inhibition and facilitation in spinocerebellar ataxia. Neuroreport. 2018. DOI:10.1097/WNR.0000000000001036

[49] Bando K, Honda T, Ishikawa K, Takahashi Y, Mizusawa H, Hanakawa T. Impaired Adaptive Motor Learning Is Correlated With Cerebellar Hemispheric Gray Matter Atrophy in Spinocerebellar Ataxia Patients: A Voxel-Based Morphometry Study. Front Neurol. 2019;10:1183. DOI:10.3389/fneur.2019.01183

[50] Miterko LN, Baker KB, Beckinghausen J, Bradnam LV, Cheng MY, Cooperrider J, et al. Consensus Paper: Experimental Neurostimulation of the Cerebellum. Cerebellum. 2019;18(6):1064-1097. DOI:10.1007/s12311-019-01041-5

[51] Thach WT, Bastian AJ. Role of the cerebellum in the control and adaptation of gait in health and disease. Prog Brain Res. 2004;143:353-366. DOI:10.1016/s0079-6123(03)43034-3

[52] Miyai I. Challenge of neurorehabilitation for cerebellar degenerative diseases. Cerebellum. 2012;11(2):436-437. DOI:10.1007/s12311-011-0327-5

[53] Schmitz-Hubsch T, Tezenas du Montcel S, Baliko L, Boesch S, Bonato S, Fancellu R, et al. Reliability and validity of the International Cooperative Ataxia Rating Scale: a study in 156 spinocerebellar ataxia patients. Mov Disord. 2006;21(5):699-704. DOI:10.1002/mds.20781

[54] Schmitz-Hubsch T, Fimmers R, Rakowicz M, Rola R, Zdzienicka E, Fancellu R, et al. Responsiveness of different rating instruments in spinocerebellar ataxia patients. Neurology. 2010;74(8):678-684. DOI:10.1212/WNL.0b013e3181d1a6c9

[55] Schmahmann JD, Gardner R, MacMore J, Vangel MG. Development of a brief ataxia rating scale (BARS) based on a modified form of the ICARS. Mov Disord. 2009;24(12):1820-1828. DOI:10.1002/mds.22681

[56] Sullivan R, Yau WY, O'Connor E, Houlden H. Spinocerebellar ataxia: an update. J Neurol. 2019;266(2):533-544. DOI:10.1007/s00415-018-9076-4

[57] Honda T, Mitoma H, Yoshida H, Bando K, Terashi H, Taguchi T, et al. Assessment and Rating of Motor Cerebellar Ataxias With the Kinect v2 Depth Sensor: Extending Our Appraisal.

Front Neurol. 2020;11:179. DOI:10.3389/fneur.2020.00179

[58] Schniepp R, Schlick C, Pradhan C, Dieterich M, Brandt T, Jahn K, et al. The interrelationship between disease severity, dynamic stability, and falls in cerebellar ataxia. J Neurol. 2016;263(7):1409-1417. DOI:10.1007/s00415-016-8142-z

[59] Winser SJ, Smith C, Hale LA, Claydon LS, Whitney SL. Balance outcome measures in cerebellar ataxia: a Delphi survey. Disabil Rehabil. 2015;37(2):165-170. DOI:10.3109/09638288.2014.913709

[60] Kondo Y, Bando K, Ariake Y, Katsuta W, Todoroki K, Nishida D, et al. Test-retest reliability and minimal detectable change of the Balance Evaluation Systems Test and its two abbreviated versions in persons with mild to moderate spinocerebellar ataxia: A pilot study. NeuroRehabilitation. 2020. DOI:10.3233/NRE-203154

[61] Horak FB, Wrisley DM, Frank J. The Balance Evaluation Systems Test (BESTest) to differentiate balance deficits. Phys Ther. 2009;89(5):484-498. DOI:10.2522/ptj.20080071

[62] Miyai I, Ito M, Hattori N, Mihara M, Hatakenaka M, Yagura H, et al. Cerebellar ataxia rehabilitation trial in degenerative cerebellar diseases. Neurorehabil Neural Repair. 2012;26(5):515-522. DOI:10.1177/1545968311425918

[63] Ilg W, Synofzik M, Brotz D, Burkard S, Giese MA, Schols L. Intensive coordinative training improves motor performance in degenerative cerebellar disease. Neurology. 2009;73(22):1823-1830. DOI:10.1212/WNL.0b013e3181c33adf

[64] Ilg W, Seemann J, Giese M, Traschutz A, Schols L, Timmann D, et al. Real-life gait assessment in degenerative cerebellar ataxia: Toward ecologically valid biomarkers. Neurology. 2020;95(9):e1199-ee210. DOI:10.1212/WNL.0000000000010176

[65] Gouelle A, Megrot F, Presedo A, Husson I, Yelnik A, Pennecot GF. The gait variability index: a new way to quantify fluctuation magnitude of spatiotemporal parameters during gait. Gait Posture. 2013;38(3):461-465. DOI:10.1016/j.gaitpost.2013.01.013

[66] Fuca E, Guglielmotto M, Boda E, Rossi F, Leto K, Buffo A. Preventive motor training but not progenitor grafting ameliorates cerebellar ataxia and deregulated autophagy in tambaleante mice. Neurobiol Dis. 2017;102:49-59. DOI:10.1016/j.nbd.2017.02.005

[67] Fryer JD, Yu P, Kang H, Mandel-Brehm C, Carter AN, Crespo-Barreto J, et al. Exercise and genetic rescue of SCA1 via the transcriptional repressor Capicua. Science. 2011;334(6056):690-693. DOI:10.1126/science.1212673

[68] Kawato M, Ohmae S, Hoang H, Sanger T. 50 Years Since the Marr, Ito, and Albus Models of the Cerebellum. Neuroscience. 2020. DOI:10.1016/j.neuroscience.2020.06.019

[69] Fernandez-Ruiz J, Velasquez-Perez L, Diaz R, Drucker-Colin R, Perez-Gonzalez R, Canales N, et al. Prism adaptation in spinocerebellar ataxia type 2. Neuropsychologia. 2007;45(12):2692-2698. DOI:10.1016/j.neuropsychologia.2007.04.006

[70] Hashimoto Y, Honda T, Matsumura K, Nakao M, Soga K, Katano K, et al. Quantitative evaluation of human cerebellum-dependent motor learning through prism adaptation of hand-reaching movement. PLoS One. 2015;10(3):e0119376. DOI:10.1371/journal.pone.0119376

[71] Kuper M, Wunnemann MJ, ThurlingM,StefanescuRM,MaderwaldS, Elles HG, et al. Activation of the cerebellar cortex and the dentate nucleus in a prism adaptation fMRI study. Hum Brain Mapp. 2014;35(4):1574-1586. DOI:10.1002/hbm.22274

[72] Kitazawa S, Kimura T, Yin PB. Cerebellar complex spikes encode both destinations and errors in arm movements. Nature. 1998;392(6675):494-497. DOI:10.1038/33141

[73] Morton SM, Bastian AJ. Prism adaptation during walking generalizes to reaching and requires the cerebellum. J Neurophysiol. 2004;92(4):2497-2509. DOI:10.1152/jn.00129.2004

[74] Martin TA, Keating JG, Goodkin HP, Bastian AJ, Thach WT. Throwing while looking through prisms. II. Specificity and storage of multiple gaze-throw calibrations. Brain. 1996;119 (Pt 4):1199-1211. DOI:10.1093/brain/119.4.1199

[75] Matsugi A. Physical Therapy for Cerebellar Ataxia. In: Suzuki T, editor. Neurological Physical Therapy: IntechOpen; 2017. p. 158-173.

[76] Zesiewicz TA, Wilmot G, Kuo SH, Perlman S, Greenstein PE, Ying SH, et al. Comprehensive systematic review summary: Treatment of cerebellar motor dysfunction and ataxia: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018;90(10):464-471. DOI:10.1212/WNL.0000000000005055

[77] Fonteyn EM, Keus SH, Verstappen CC, Schöls L, de Groot IJ, van de Warrenburg BP. The effectiveness of allied health care in patients with ataxia: a systematic review. J Neurol. 2014;261(2):251-258. DOI:10.1007/s00415-013-6910-6

[78] Synofzik M, Ilg W. Motor training in degenerative spinocerebellar disease: ataxia-specific improvements by intensive physiotherapy and exergames. Biomed Res Int. 2014;2014:583507. DOI:10.1155/2014/583507

[79] Marquer A, Barbieri G, Pérennou D. The assessment and treatment of postural disorders in cerebellar ataxia: a systematic review. Ann Phys Rehabil Med. 2014;57(2):67-78. DOI:10.1016/j.rehab.2014.01.002

[80] Maring JR, Croarkin E. Presentation and progression of Friedreich ataxia and implications for physical therapist examination. Phys Ther. 2007;87(12):1687-1696. DOI:10.2522/ptj.20060232

[81] Lanza G, Casabona JA, Bellomo M, Cantone M, Fisicaro F, Bella R, et al. Update on intensive motor training in spinocerebellar ataxia: time to move a step forward? J Int Med Res. 2020;48(2):300060519854626. DOI:10.1177/0300060519854626

[82] Milne SC, Corben LA, Roberts M, Murphy A, Tai G, Georgiou-Karistianis N, et al. Can rehabilitation improve the health and well-being in Friedreich's ataxia: a randomized controlled trial? Clin Rehabil. 2018;32(5):630-643. DOI:10.1177/0269215517736903

[83] Keller JL, Bastian AJ. A home balance exercise program improves walking in people with cerebellar ataxia. Neurorehabil Neural Repair. 2014;28(8):770-778. DOI:10.1177/1545968314522350

[84] Dias JF, Oliveira VC, Borges PRT, Dutra F, Mancini MC, Kirkwood RN, et al. Effectiveness of exercises by telerehabilitation on pain, physical function and quality of life in people with physical disabilities: a systematic review of randomised controlled trials with GRADE recommendations.

Br J Sports Med. 2020. DOI:10.1136/bjsports-2019-101375

[85] Vaz DV, Schettino ReC, Rolla de Castro TR, Teixeira VR, Cavalcanti Furtado SR, de Mello Figueiredo E. Treadmill training for ataxic patients: a single-subject experimental design. Clin Rehabil. 2008;22(3):234-241. DOI:10.1177/0269215507081578

[86] Freund JE, Stetts DM. Use of trunk stabilization and locomotor training in an adult with cerebellar ataxia: a single system design. Physiother Theory Pract. 2010;26(7):447-458. DOI:10.3109/09593980903532234

[87] Im SJ, Kim YH, Kim KH, Han JW, Yoon SJ, Park JH. The effect of a task-specific locomotor training strategy on gait stability in patients with cerebellar disease: a feasibility study. Disabil Rehabil. 2017;39(10):1002-1008. DOI:10.1080/09638288.2016.1177124

[88] Fonteyn EM, Heeren A, Engels JJ, Boer JJ, van de Warrenburg BP, Weerdesteyn V. Gait adaptability training improves obstacle avoidance and dynamic stability in patients with cerebellar degeneration. Gait Posture. 2014;40(1):247-251. DOI:10.1016/j.gaitpost.2014.04.190

[89] Van de Warrenburg BP, Bakker M, Kremer BP, Bloem BR, Allum JH. Trunk sway in patients with spinocerebellar ataxia. Mov Disord. 2005;20(8):1006-1013. DOI:10.1002/mds.20486

[90] Globas C, du Montcel ST, Baliko L, Boesch S, Depondt C, DiDonato S, et al. Early symptoms in spinocerebellar ataxia type 1, 2, 3, and 6. Mov Disord. 2008;23(15):2232-2238. DOI:10.1002/mds.22288

[91] Rochester L, Galna B, Lord S, Mhiripiri D, Eglon G, Chinnery PF. Gait impairment precedes clinical symptoms in spinocerebellar ataxia type 6. Mov Disord. 2014;29(2):252-255. DOI:10.1002/mds.25706

[92] Choudhury S, Chatterjee S, Chatterjee K, Banerjee R, Humby J, Mondal B, et al. Clinical Characterization of Genetically Diagnosed Cases of Spinocerebellar Ataxia Type 12 from India. Mov Disord Clin Pract. 2018;5(1):39-46. DOI:10.1002/mdc3.12551

[93] Morton SM, Bastian AJ. Cerebellar control of balance and locomotion. Neuroscientist. 2004;10(3):247-259. DOI:10.1177/1073858404263517

[94] Buckley E, Mazzà C, McNeill A. A systematic review of the gait characteristics associated with Cerebellar Ataxia. Gait Posture. 2018;60:154-163. DOI:10.1016/j.gaitpost.2017.11.024

[95] Ilg W, Golla H, Thier P, Giese MA. Specific influences of cerebellar dysfunctions on gait. Brain. 2007;130(Pt 3):786-798. DOI:10.1093/brain/awl376

[96] Higuchi T. Visuomotor control of human adaptive locomotion: understanding the anticipatory nature. Front Psychol. 2013;4:277. DOI:10.3389/fpsyg.2013.00277

[97] McFadyen BJ, Fiset F, Charette C. Substituting anticipatory locomotor adjustments online is time constrained. Exp Brain Res. 2018;236(7):1985-1996. DOI:10.1007/s00221-018-5277-4

[98] Staab JP, Balaban CD, Furman JM. Threat assessment and locomotion: clinical applications of an integrated model of anxiety and postural control. Semin Neurol. 2013;33(3):297-306. DOI:10.1055/s-0033-1356462

[99] Pohl M, Rockstroh G, Rückriem S, Mrass G, Mehrholz J. Immediate effects of speed-dependent treadmill training on gait parameters in early Parkinson's

disease. Arch Phys Med Rehabil. 2003;84(12):1760-1766. DOI:10.1016/s0003-9993(03)00433-7

[100] Herman T, Giladi N, Hausdorff JM. Treadmill training for the treatment of gait disturbances in people with Parkinson's disease: a mini-review. J Neural Transm (Vienna). 2009;116(3):307-318. DOI:10.1007/s00702-008-0139-z

[101] Schniepp R, Wuehr M, Neuhaeusser M, Kamenova M, Dimitriadis K, Klopstock T, et al. Locomotion speed determines gait variability in cerebellar ataxia and vestibular failure. Mov Disord. 2012;27(1):125-131. DOI:10.1002/mds.23978

[102] Ilg W, Brötz D, Burkard S, Giese MA, Schöls L, Synofzik M. Long-term effects of coordinative training in degenerative cerebellar disease. Mov Disord. 2010;25(13):2239-2246. DOI:10.1002/mds.23222

[103] Paulson HL. The spinocerebellar ataxias. J Neuroophthalmol. 2009;29(3):227-237. DOI:10.1097/WNO0b013e3181b416de

[104] Winser S, Pang MYC, Rauszen JS, Chan AYY, Chen CH, Whitney SL. Does integrated cognitive and balance (dual-task) training improve balance and reduce falls risk in individuals with cerebellar ataxia? Med Hypotheses. 2019;126:149-153. DOI:10.1016/j.mehy.2019.03.001

[105] Ilg W, Schatton C, Schicks J, Giese MA, Schöls L, Synofzik M. Video game-based coordinative training improves ataxia in children with degenerative ataxia. Neurology. 2012;79(20):2056-2060. DOI:10.1212/WNL.0b013e3182749e67

[106] Winser SJ, Kannan P, Pang M, Smith C, Tsang WW. Potential Benefits and Safety of. J Altern Complement Med. 2018;24(12):1221-1223. DOI:10.1089/acm.2017.0396

[107] Schatton C, Synofzik M, Fleszar Z, Giese MA, Schöls L, Ilg W. Individualized exergame training improves postural control in advanced degenerative spinocerebellar ataxia: A rater-blinded, intra-individually controlled trial. Parkinsonism Relat Disord. 2017;39:80-84. DOI:10.1016/j.parkreldis.2017.03.016

[108] Tsukahara A, Yoshida K, Matsushima A, Ajima K, Kuroda C, Mizukami N, et al. Evaluation of walking smoothness using wearable robotic system curara(R) for spinocerebellar degeneration patients. IEEE Int Conf Rehabil Robot. 2017;2017:1494-1499. DOI:10.1109/ICORR.2017.8009459

[109] Tsukahara A, Yoshida K, Matsushima A, Ajima K, Kuroda C, Mizukami N, et al. Effects of gait support in patients with spinocerebellar degeneration by a wearable robot based on synchronization control. J Neuroeng Rehabil. 2018;15(1):84. DOI:10.1186/s12984-018-0425-4

[110] Portaro S, Russo M, Bramanti A, Leo A, Billeri L, Manuli A, et al. The role of robotic gait training and tDCS in Friedrich ataxia rehabilitation: A case report. Medicine (Baltimore). 2019;98(8):e14447. DOI:10.1097/MD.0000000000014447

[111] Bateni H, Maki BE. Assistive devices for balance and mobility: benefits, demands, and adverse consequences. Arch Phys Med Rehabil. 2005;86(1):134-145. DOI:10.1016/j.apmr.2004.04.023

[112] Lam R. Practice tips: choosing the correct walking aid for patients. Can Fam Physician. 2007;53(12):2115-2116

[113] Martins M, Santos C, Frizera A, Ceres R. Real time control of the ASBGo walker through a physical human–robot interface. Measurement. 2014;48:77-86. DOI:10.1016/j.measurement.2013.10.031

[114] Moreira R, Alves J, Matias A, Santos C. Smart and Assistive Walker - ASBGo: Rehabilitation Robotics: A Smart-Walker to Assist Ataxic Patients. Adv Exp Med Biol. 2019;1170:37-68. DOI:10.1007/978-3-030-24230-5_2

[115] Abbud G, Janelle C, Vocos M. The use of a trained dog as a gait aid for clients with ataxia: a case report. Physiother Can. 2014;66(1):33-35. DOI:10.3138/ptc.2013-17

[116] Nagumo K, Kunimi Y, Nomura S, Beppu M, Hirayama K. The handkerchief guide: a simple and practical method to improve ataxic gait in cerebellar subjects. Rinsho Shinkeigaku. 2015;55(5):311-319. DOI:10.5692/clinicalneurol.cn-000630

[117] Kashyap B, Phan D, Pathirana PN, Horne M, Power L, Szmulewicz D. Objective Assessment of Cerebellar Ataxia: A Comprehensive and Refined Approach. Scientific reports. 2020;10(1):9493. DOI:10.1038/s41598-020-65303-7

[118] Summa S, Schirinzi T, Bernava GM, Romano A, Favetta M, Valente EM, et al. Development of SaraHome: A novel, well-accepted, technology-based assessment tool for patients with ataxia. Comput Methods Programs Biomed. 2020;188:105257. DOI:10.1016/j.cmpb.2019.105257

[119] Nguyen KD, Corben LA, Pathirana PN, Horne MK, Delatycki MB, Szmulewicz DJ. An Instrumented Measurement Scheme for the Assessment of Upper Limb Function in Individuals with Friedreich Ataxia. Annu Int Conf IEEE Eng Med Biol Soc. 2019;2019:317-320. DOI:10.1109/EMBC.2019.8857107

[120] Nguyen KD, Corben LA, Pathirana PN, Horne MK, Delatycki MB, Szmulewicz DJ. The Assessment of Upper Limb Functionality in Friedreich Ataxia via Self-Feeding Activity. IEEE Trans Neural Syst Rehabil Eng. 2020;28(4):924-933. DOI:10.1109/TNSRE.2020.2977354

[121] Nguyen KD, Corben LA, Pathirana PN, Horne MK, Delatycki MB, Szmulewicz DJ. Assessment of Disease Progression in Friedreich Ataxia using an Instrumented Self Feeding Activity. Annu Int Conf IEEE Eng Med Biol Soc. 2020;2020:3827-3830. DOI:10.1109/EMBC44109.2020.9175980

[122] Okahara Y, Takano K, Komori T, Nagao M, Iwadate Y, Kansaku K. Operation of a P300-based brain-computer interface by patients with spinocerebellar ataxia. Clin Neurophysiol Pract. 2017;2:147-153. DOI:10.1016/j.cnp.2017.06.004

[123] Newman GI, Ying SH, Choi Y-S, Kim H-N, Presacco A, Kothare MV, et al., editors. Brain Computer Interface in Cerebellar Ataxia2010; Berlin, Heidelberg: Springer Berlin Heidelberg.

[124] Benussi A, Pascual-Leone A, Borroni B. Non-Invasive Cerebellar Stimulation in Neurodegenerative Ataxia: A Literature Review. Int J Mol Sci. 2020;21(6). DOI:10.3390/ijms21061948

[125] Franca C, de Andrade DC, Teixeira MJ, Galhardoni R, Silva V, Barbosa ER, et al. Effects of cerebellar neuromodulation in movement disorders: A systematic review. Brain Stimul. 2018;11(2):249-260. DOI:10.1016/j.brs.2017.11.015

[126] Matsugi A, Douchi S, Hasada R, Mori N, Okada Y, Yoshida N, et al. Cerebellar Repetitive Transcranial Magnetic Stimulation and Noisy Galvanic Vestibular Stimulation

Change Vestibulospinal Function. Front Neurosci. 2020;14:388. DOI:10.3389/fnins.2020.00388

[127] Benussi A, Koch G, Cotelli M, Padovani A, Borroni B. Cerebellar transcranial direct current stimulation in patients with ataxia: A double-blind, randomized, sham-controlled study. Mov Disord. 2015;30(12):1701-1705. DOI:10.1002/mds.26356

[128] Benussi A, Dell'Era V, Cantoni V, Bonetta E, Grasso R, Manenti R, et al. Cerebello-spinal tDCS in ataxia: A randomized, double-blind, sham-controlled, crossover trial. Neurology. 2018;91(12):e1090-ee101. DOI:10.1212/WNL.0000000000006210

[129] Matsugi A. Reader response: Cerebello-spinal tDCS in ataxia: A randomized, double-blind, sham-controlled, crossover trial. Neurology. 2019;92(23):1121. DOI:10.1212/WNL.0000000000007623