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Title page

Can pre-screening vestibulocerebellar involvement followed by targeted training improve the outcomes of balance in cerebellar ataxia?

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Can pre-screening vestibulocerebellar involvement followed by targeted training improve the outcomes of balance in cerebellar ataxia?

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Abstract

Balance problems and frequent falls are common among clients with Cerebellar Ataxia (CA). CA is not a disease by itself but a collection of symptoms due to the involvement of cerebellum or its pathways. Presently the treatment for balance problems for CA is not standardized. Interventions available to improve balance are not specific to symptoms presentation. Functionally the cerebellum is divided into the spinocerebellum, vestibulocerebellum and corticocerebellum. Each functional zone has a distinct role in maintaining balance. Therefore, the presentation of symptoms will vary according to the functional zone involved. Pre-screening clients with CA for identifying the part of cerebellum involved will facilitate clinicians to provide tailor-made interventions for targeting specific symptoms for better outcomes. Pre-screening clients with CA according to the part of cerebellum involved is not in practice and our study will introduce this concept. We hypothesize pre-screening participants with spinocerebellar ataxia (SCA) for the involvement vestibulocerebellum followed by prescribing vestibulocerebellum targeted exercises will have better outcomes when compared to conventional balance training. We plan to conduct two related studies. In study 1 we will screen participants with CA for the involvement of vestibulocerebellum. In study 2, the effects of vestibulocerebellum targeted balance exercises on balance will be studied. We will assess the Subjective Visual Vertical (SVV) deviation and postural sway pattern to screen participants into people with and without vestibulocerebellar involvement. SVV deviation will be estimated using a computerized Subjective Visual Vertical (cSVV) device and postural sway pattern will be assessed using the limits of stability program of the Bertec© Balance system. The obtained SVV deviation scores will be used to derive at cut-off scores to discriminate clients with and without vestibulocerebellar involvement. The second study will test the treatment effects of conventional exercises plus vestibulocerebellum targeted exercises to improve balance by correcting SVV deviation in SCA with vestibulocerebellar involvement. The intervention is planned as 12 one-to-one sessions over three months period. Participants will be reassessed after the intervention and 3 months post-intervention. The findings of this cutting-edge research are extremely important to the clinicians, researchers and clients with SCA.

Key words: Spinocerebellar ataxia, balance, vestibulocerebellum, subjective visual vertical

Introduction:

The concept of personalized medicine (categorizing patients, to prescribe tailor-made intervention to enhance outcomes) is gaining popularity in healthcare. Better outcomes are achieved through early detection, improvement in diagnosis, and efficient intervention delivery. Personalized medicine for managing balance dysfunction in clients with cerebellar ataxia (CA) is worthwhile exploring. Cerebellar ataxia (CA) is an umbrella term that includes health conditions with genetic or non-genetic inheritance resulting in postural instability, in-coordination of gait, speech, limb, and eyeball movements. Though the incidence of CA is low,[1] the burden of CA on quality of life[2] 2 and global economy[3] is significant. Poor balance and walking difficulties are hallmarks of health conditions associated with CA.[4] Among the genetic disorders that result in CA, the spinocerebellar ataxias (SCA) is common having a prevalence of between 0.9 and 3.0 per 100 000 depending on the exact type. SCA is an autosomal dominant hereditary disease resulting in ataxia.[5] There are over 40 types of SCA and the most common type is the SCA 6.[5 6] Frequent falls are common among clients with SCA.[7] Implementing a screening protocol to identify the target group and delivering tailor-made training is the most acceptable treatment strategy in modern medicine.[8] However, such screening protocols or standardized guidelines for intervention are not available for treating balance problems in SCA.[9] This is due primarily to the limited number of high-quality studies in this field as well as the heterogeneity of the health conditions resulting in CA.[10] In addition, the effects of physiotherapy and exercises for improving symptoms of CA including balance deficits are largely unknown.[11] This justifies the need for conducting a study to explore a pathway that improves the efficiency of interventions targeted for this population.

Importance of localizing the involvement of functional zones of the cerebellum:

Functionally the cerebellum is divided into vestibulocerebellum, spinocerebellum, and corticocerebellum or neocerebellum.[12] Each functional zone has a distinct role in maintaining balance and equilibrium. The vestibulocerebellum has its primary connections with the vestibular nucleus. It has a significant role in the control of balance, gait, locomotion, and eye movements.[6 13] The vestibulocerebellum controls the axial muscles responsible for equilibrium and is also responsible for the compensatory postural adjustments to counteract falls during perturbations.[14] The exact role of the spinocerebellum on balance is not clearly understood[15]; it is thought to control and refine execution of on-going movement by comparing and correcting the actual movement happening against the intended movement.[13] The extensive inputs from the anterior and posterior spinocerebellar tracts enable spinocerebellum to control movement execution.[15] The corticocerebellum is involved in higher level functions such as planning or preparation of movement and evaluation of sensory information for action as a part of motor learning process.[15 16] Since the presentation of balance dysfunction is distinct between the functional zones involvement, we hypothesize that targeted tailor-made exercises based on the presentation will provide better outcomes for balance in clients with SCA. For instance, emphasis could be placed on training gait and equilibrium in clients with the vestibulocerebellar lesion,[6] proprioceptive training could be administered for clients with spinocerebellar lesions and complex balance activities such as dual tasks training may be administered for clients with the corticocerebellar lesion.[17] This paper will focus on pre-screening participants for vestibulocerebellar involvement followed by prescribing vestibulocerebellum targeted exercises to improve balance in participants with SCA.

The vestibulocerebellum modulates balance through its connections with vestibular system.[18] The vestibular system is responsible for visual stabilization and postural stability during head movements and provides information on one's spatial orientation to the immediate environment. Visual stabilization is achieved through the vestibulo-ocular reflex.[19] Anatomically the vestibular system is classified into peripheral and central.[20] The semicircular canals and the paired otolith organs comprise the peripheral vestibular system. The peripheral vestibular organs communicate with the vestibular nuclei which have an extensive connection with the brainstem, reticular formation, thalamus and cerebellum. These connections are collectively called the central vestibular pathway. The cerebellum controls and modulates the vestibular system through the vestibulocerebellum.[18 20]

Despite evidence that the clinical presentation of balance and postural control in clients with SCA may vary with the location of insult to the cerebellum,[15] it is unclear how well current balance measures accurately identify the involved functional zone of the cerebellum. A previous Delphi survey and a systematic review conducted by our team identified a wide range of outcome measures for the assessment of balance in participants with CA.[21 22] Over half of these measures were either not standardized or were not psychometrically tested for eligibility in clients with CA. Subsequently, a psychometric analysis was conducted to identify a standardized set of balance outcome measures for people with CA. The psychometric analysis found Berg Balance Scale (BBS) and the balance sub-components of the Scale for the assessment and Rating of Ataxia (SARAbal) as most appropriate measures for balance assessment in CA.[23 24] However, these tools do not localize the functional zone involved. The recently developed cerebellar-specific measures such as Scale for the Assessment and Rating of Ataxia (SARA) and International Co-operative Ataxia Rating Scale (ICARS)[25 26] have not gained popularity among health-care practitioners for the assessment of balance in CA[9] The available cerebellar-specific measures are largely disease severity rating tools with balance assessment as a sub-component rather than a standalone balance quantifying tool.[17 25] It is therefore evident that current clinical practice utilizes inappropriate measures or use measures that do not have a focus on localizing the functional zone of cerebellum.

Assessing the integrity of vestibulocerebellum:

Force platform: Presently there are no standardized methods available for identifying the involvement of functional zones of the cerebellum. The pattern of postural sway could be considered to differentiate functional zones involved using force plate.[17 27] Mauritz et al.(1979), demonstrated that studying the pattern of postural sway and sway amplitude using force plate enabled identification of lesions of different functional zones of the cerebellum.[28] Based on the findings they suggested that clients with spinocerebellar lesion may have a postural tremor in an anteroposterior direction with a specific frequency of 3 Hz. [28] Lesions of corticocerebellum show limited postural instability without directional preference and lesions of the vestibulocerebellum may result in severely affected multidirectional postural sways.[28] The amplitude of postural sway along different directions in relation to the line of gravity ranged between 4mm and 12mm.

Sensory Organization Test (SOT): a laboratory-based assessment for testing sensory interaction for maintaining balance [29] could be considered for determining the integrity of the vestibular system that might be related to vestibulocerebellar involvement. However, a previous study by our team found SOT unsuitable for this population.[30] The SOT was found to have significant floor effects.[31] Among ten included participants, 4 (40%) were ineligible for SOT because they were unable to stand unsupported for 10 seconds. Although SOT might predict the integrity of vestibulocerebellum, it might not be suitable for all clients with SCA. A tool that allows assessment of balance in seated position might be best for clients with SCA.

Subjective Visual Vertical (SVV) test: To study the integrity of central vestibular pathway in participants with CA, the current research team recently conducted an observation study on 20 participants with CA secondary to multiple sclerosis.[32] The integrity of central vestibular pathway was assessed using a computerized Subjective Visual Vertical (cSVV) device. This spatial orientation testing device studies the ability of the client to accurately perceive verticality and tests the function of utricle and superior vestibular nerve of the vestibular system.[33 34] The severity of vestibular dysfunction can be correlated to the magnitude of deviation of the SVV, which is a reflection of the difference between the actual vertical and perceived vertical of the client. Though this test has been extensively used in clients with peripheral vestibular disorders such as unilateral otholith dysfunction,[35 36] studies have found that findings of cSVV could identify central vestibular pathway dysfunctions in clients with multiple sclerosis,[37] stroke,[38] Parkinson's disease[39] and CA.[40] In our study we found a statistically significant moderate correlation (Spearman's rho correlation) between SVV deviation and measures of balance [Berg Balance scale (r= -0.59), Timed Up and Go test (r= -0.58)], ataxia severity [ICARS (r=0.56), SARA (r=0.62) and functional independence [Barthel index (r=-0.47).[32] These findings imply a positive correlation between SVV deviation and vestibulocerebellar integrity. Similarly, Serra et al (2003), found significant correlation between SVV deviation and Kurtzke Functional Systems Score (FSS) for cerebellar function providing evidence for the use of SVV deviation for screening central vestibular pathway in clients with CA.[40] To our knowledge no studies have evaluated the difference between SVV deviation between participants with different functional cerebellar zone involvement in isolated cerebellar lesions such as SCA. We hypothesize that there will be a difference in the pattern of SVV deviation between participants with and without vestibulocerebellar involvement in SCA.

Lesson learnt with balance training not specific to functional zone involvement:

Previously, this research team studied the effects of a 12-week Tai Chi training programme for balance in participants with CA (not restricted to SCA).[30] The outcome measures used in that trial for balance assessment were not specific to identification of functional zones. In addition, the intervention tested (Tai Chi) was delivered as group therapy and was not tailor-made according to the presentation of the participant. The results of that study were inconclusive; significant improvement was identified following Tai Chi in clinical measures of balance using BBS and SARAbal however, objective laboratory-based assessments of balance (Limits of Stability-LOS and SOT) did not improve. This lack of improvement could be because the intervention lacked targeted training. We, therefore, hypothesize that tailor-made rehabilitation approach with regard to the location of the lesion and presentation of symptoms will have a positive influence on balance in participants with CA.

There are two main implications from the previous study done by our team of participants with CA secondary to multiple sclerosis.[32] Firstly, the moderate correlation between SVV deviation, balance scores and disease severity is an indication that not all participants with CA have involvement of the vestibulocerebellum. Secondly, multiple sclerosis is a disease that affects multiple regions of the brain that includes spinal cord, visual pathway, cerebral cortex, cerebellum and basal ganglia.[41 42] It is acknowledged that the identified balance limitations may have contributions from muscle weakness, sensory impairment, vertigo, and lesions to the basal ganglia. Therefore, there is a compelling need to conduct a study in participants with SCA where the disease and presentation are directly related to the lesion of the cerebellum or its connections.

Hypotheses

We hypothesize SCA participants presenting with multi-directional sway on a force platform in standing will exhibit greater SVV deviation. Secondly, a greater deviation of the SVV is suggestive of vestibulocerebellar involvement in people with SCA. Thirdly, participants with greater balance problems will have a moderate to strong correlation between SVV deviation and balance assessed using clinical outcome measures (BBS and SARA- balance sub-components). Lastly, vestibulocerebellum targeted balance training will be most beneficial among SCA participants presenting with vestibulocerebellar involvement. Figure 1 illustrates our proposed hypothesis on the significance of vestibulo-cerebellar screening followed by targeted training.

Insert figure 1 about here

Evaluation of hypotheses

We aim to explore if pre-screening participants with SCA for the involvement vestibulocerebellum followed by prescribing vestibulocerebellum targeted exercises have better outcomes when compared to conventional balance training. To answer this aim, we have the following objectives:

Objective 1: Determine if the SVV deviation using cSVV is a predictor of vestibulocerebellar involvement in participants with SCA.

Objective 2: Determine the correlation between the SVV deviation and balance (assessed using a battery of clinical and laboratory-based assessment tools), functional independence, disease severity and duration; and predict the cut-off scores for the SVV deviation to discriminate between participants with and without vestibulocerebellar involvement.

Objective 3: Explore the benefits of vestibulocerebellum targeted training in improving balance in SCA with vestibulocerebellar involvement.

Overview: We plan to conduct two related studies to answer three objectives. Study 1will evaluate the pattern of postural sway in standing using a force platform. Based on the study by Mauritz et al, (1979)[28] using force platform, we will categorize participants with and without the involvement of vestibulocerebellum. Figure 2 illustrates the postural sway pattern of two participants with and without vestibulocerebellar involvement. After categorizing, the participants' SVV will be assessed using the cSVV device. The difference between the SVV deviation of participants with and without vestibulocerebellar involvement will then be evaluated. Based on these findings, cut-off scores for discriminating participants with and without vestibulocerebellar involvement using SVV deviation will be estimated. Study 2 (intervention study) will be conducted to explore the preliminary benefits and feasibility of using vestibulocerebellum targeted balance exercises in SCA participants with vestibulocerebellar involvement. This will be a non-randomized experimental design where participants with vestibulocerebellar involvement will be categorized into experimental and control groups. Participants of experimental group will undergo conventional exercises plus vestibulocerebellum targeted balance exercises. Control group will undergo usual care. The intervention will be given for 12 weeks and assessment will be done pre-intervention, post-intervention and followed up at

3 months post-intervention. Details of intervention is provided under the section “Intervention for study 3”.

Insert Figure 2 about here.

Ethics, registration, recruitment criteria and logistics: Ethics approval will be obtained from PolyU ethics committee (‘Human Subjects Ethics application review System’), the Institutional Review Board (IRB) of University of Pittsburgh and Hospital Authority, Hong Kong. For study 1 we will include participants (1) in the age group of 18-65 years with SCA (of any type), (2) who can stand unsupported for at least 10 seconds (to facilitate assessment of postural sway on force platform), and (3) who give consent to access medical record. Volunteers with the previous history of stroke or any other neurological disorders not directly associated with ataxia and severe cognitive and visual impairments will be excluded. For study 2 participants who do not stand unsupported (cSVV device does not require the participant to stand) will also be included in addition to the above-mentioned inclusion criteria. Enrolled participants will be assessed using the following primary and secondary outcome measures.

Outcome measures: Subjective Visual Vertical (SVV) will be assessed using The SYNAPSYS, (a computer-based assessment- cSVV) and postural sway will be assessed using LOS test of Bertec© system. Secondary outcome measures include balance assessment using the SOT,[43] Berg Balance Scale,[44] balance sub-component of the Scale for the Assessment and Rating of Ataxia (SARAbal)[26] and falls rate. Functional independence will be assessed using the Barthel Index.[45]

Intervention for study 2: All participants will receive conventional balance training exercises.[46] The experimental group will receive conventional exercises plus vestibulocerebellum targeted balance exercises. Both groups will receive 12 sessions over 3-months and each session lasting for 60 minutes. Vestibulocerebellum targeted exercises will include both vestibular adaptation and vestibular substitution exercises.[47] They include exercises to challenge the visual and somatosensory systems, vestibular adaptation, exercises to improve gaze stability, substitution exercises and advice on safety awareness techniques such as the use of the assistive device for falls prevention.[47 48] The dosage of intervention item will be tailor-made depending on the severity of balance problems.

Sample size estimation: G-power software was used for this estimation.[49] Assuming 80% power, an alpha level of 0.05 and a correlation of 0.70 between the SVV deviation and BBS from our previous observation,[32] the sample size estimated for study 1 is 37. For study 2, assuming the same power and level of significance and an effect size of 0.8 for BBS from our previous study,[30] the sample size required is 42 (21 in each group). Anticipating 20% attrition we will target at collecting 50 (25 each group) samples.

Statistical analysis: For study 1, two assessors will independently examine the pattern of the sway of all participants to predict the involvement of vestibulocerebellum. The findings will be checked for consistency. Included participants will then be grouped based on vestibulocerebellar involvement. Group differences of cSVV scores between participants with and without vestibulocerebellar involvement will be determined using Mann-Whitney U Test (Objective 1). Spearman correlation coefficient (ρS), bivariate analysis of a non-parametric sample will be used to establish the correlation between the SVV scores and measures of balance, disease severity and functional status. Further, a receiver operating characteristics (ROC) curve will be constructed to determine cut off scores, sensitivity, and specificity of SVV deviation to predict the involvement of vestibulocerebellum (Objective 2). For study 2, Analysis of co-variance

(ANCOVA) will be conducted to explore the effect of intervention between groups post-intervention and at 3 months post-intervention (Objective 4). ANCOVA using baseline scores as the covariate is the preferred statistical test in group comparisons as it yields unbiased estimates of treatment effect.[50]

Consequences of hypotheses

If the hypotheses we made is found true, the findings of the two proposed studies will provide an insight on the need to pre-screen functional zone of cerebellum involved in clients with SCA; so that intervention for improving balance could be tailor-made according to the presentation. We hypothesize screening followed by tailored exercises is likely to show better improvement in balance when compared to conventional balance exercises among clients with SCA. Our project will inform researchers and clinicians on the cut-off scores of SVV deviation for discriminating between participants with and without vestibulocerebellar involvement in SCA.

Conclusion

Although the incidence of CA is not as high as other neurological disorders, the disability and its limitations to the quality of life are significant for those suffering from CA. Frequent falls in this population are a significant problem as they increase the burden of disease both on the individual and healthcare system. The current framework for improving balance in clients with SCA is not standardized. Through this experiment, we sort to standardize the treatment strategy for improving balance among clients with SCA. The convenience of undergoing SVV deviation examination in a seated position using the cSVV enhances the appropriateness of this test in clients having difficulty in standing. Our proposed model suggesting pre-screening clients for vestibulocerebellar involvement using the SVV deviation is novel and worthwhile testing.

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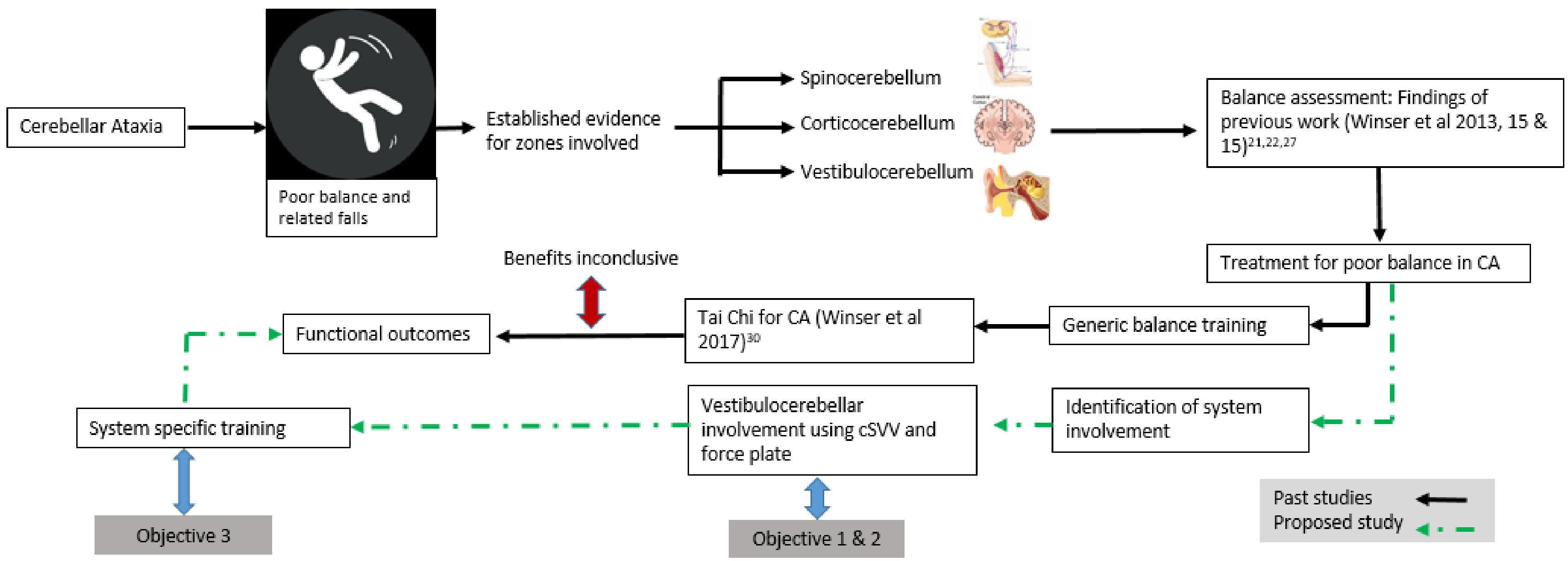
Figure 1: Hypothesis of the proposed study



CA- Cerebellar ataxia

Figure 2: Postural sway pattern using force platform

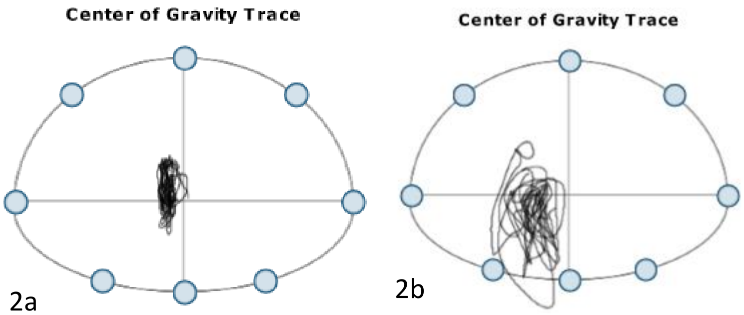


Figure 2a: Postural sway trace of participant diagnosed SCA type 3. Sway is unidirectional, in anteroposterior direction of the Limits of Stability (LOS) grid indicating either spinocerebellar or corticocerebellar involvement. Figure 2b: Sway trace of participant diagnosed SCA type 6. The sway pattern is multidirectional and sway is even in all directions. Indicative of the involvement of vestibulocerebellar.