Does integrated cognitive and balance (dual-task) training improve balance and reduce falls risk in individuals with cerebellar ataxia?

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ABSTRACT
Frequent falls in people with cerebellar ataxia (CA) is a significant problem. Therefore, an intervention that could improve balance and reduce the number of falls is of paramount importance from the patients’ perspective. Combining cognitive training with physical training to improve balance is a new approach for reducing the risk of falls in patient populations who are at risk for falls. To determine if adding structured cognitive demands to conventional balance and coordination training we designed the Cognitive-coupled Intensive Balance Training (CIBT) program. We found that the more intensive and focused CIBT intervention reduced dual-task cost, improved balance, and reduced the number of falls in a sample of individuals with CA. We hypothesize that (1) CIBT will improve balance and reduce falls; and (2) CIBT will be a cost-effective treatment option for improving balance and reduce falls. To test these hypotheses, we propose conducting a randomized controlled trial (RCT) with economic evaluation. This paper reports the findings of our study testing the feasibility of the CIBT program, rationale for testing our hypothesis and an overview of our future study design to test the effectiveness and cost-effectiveness of the CIBT program.

Background
Cerebellar ataxia (CA) includes health conditions affecting the cerebellum or its connections resulting in postural instability, gait disturbance, incoordination and cognitive impairment [1,2]. The prevalence of health conditions resulting in CA is estimated as 8.22/100,000 [3]. Spinocerebellar ataxia, a genetic disorder resulting in CA has a prevalence of 0.9–3.0/100,000 [4]. Poor balance and walking difficulties are hallmarks of diseases associated with CA [2,5]. Nearly 93% of people with CA report at least one fall over the past 12-month period [6]. Falls are very common in spinocerebellar ataxia type 3 [7]. An estimate of the annual excess cost of medical expenses per person with CA is € 18776 [8]. However, the cost of falls and falls related consequences are not well understood.

Therapeutic exercises are regarded as the first line intervention for individuals with CA [9]. Evidence-based guidelines in this population is limited [2]. Intact cerebellum, plays a key role in motor adaptation and regulation of balance [10]. However, people with CA show limited motor re-learning [11]. In contrast, some studies show evidence for motor re-learning with repeated practice [12,13]. Therefore, understanding the potential for motor re-learning is critical for designing therapeutic intervention in this population.

Dual task paradigm
A recent systematic review reported that dual tasking, that is, simultaneous performance of two tasks involving physical and cognitive tasks [14], predicts falls in people with cognitive impairment [15]. A recent study involving healthy adults found additional activation of the cerebellum during dual tasking and reported that the cerebellum is likely to control the neural networks responsible for such activities [16]. Dual tasking is found to deteriorate the performance of either or both tasks in people with neurological disorders [17,18]. This deficiency in dual-task performance relative to single-task performance is referred to as dual-task cost [19]. Training balance using dual-task is found to improve the ability to perform dual-task, that is, reduce the...
dual-task cost among people with stroke [20], Parkinson’s disease [21] and traumatic brain injury [22]. In individuals with CA, dual tasking is associated increased risk for falls [23] and gait disturbance [24]. Clinical studies on individuals with CA found that adding cognitive demand to a physical task increases the dual-task cost [23,25,26]. Difficulty in performing dual-tasks is due to the increase in demands in motor and cognitive resources.

Intensive balance and coordination training are found to be effective in reducing the symptoms of in-coordination, motor performance [27] and a short-term reduction in the number of falls [28]. However, the available interventions do not address the deficiency during cognitive-motor interaction or dual-task cost in this population. Dual-task training has been found to improve this interaction in people with neurological disorders [21,22,29,30]. Dual-task training is highly relevant to people with CA due to the presence of poor motor-cognitive interaction and the associated cognitive deficits [24]. Theory-driven claims are available for the use of dual-task training in CA [23,24]. However, to date, there is no study evaluating the effectiveness of dual-task training in people with CA [24].

**Studies in context**

Previously, we evaluated the effect of Tai-Chi training on improving balance and reducing the number of falls in people with neurological disorders [31]. Tai-Chi requires attention in order to engage in the correct sequence of movement and memory to remember the correct moves while practising [32]. This combination of physical activity with cognition (attention and memory) makes Tai-Chi a dual tasking exercise [32].

The systematic review with meta-analysis we conducted found no studies testing the effect of Tai-Chi for improving balance in CA [31]. Therefore, we conducted a feasibility study to evaluate the preliminary effects of Tai-Chi for improving balance and functional independence in CA; and test the feasibility and safety of the intervention for a future randomized controlled trial (RCT) [33]. The feasibility study [33] found beneficial effects of Tai-Chi for improving balance in people with CA.

We then conducted an RCT to compare the effectiveness of Tai-Chi compared with usual care control (no Tai-Chi) for improving balance and falls in people with CA. A trained Tai-Chi Master delivered the 8-form Tai Chi as group therapy for 60 min, once in 2 weeks for 12 weeks. Participants then complete unsupervised Tai Chi exercise for 60 min, twice a week for 6 months. After analysing 6-month follow-up data, we found significant improvement in balance measured with the Berg Balance Scale (BBS) and balance sub-component of the Scale for the Assessment and Rating of Ataxia (SARAbal) scale. However, balance measured with objective laboratory-based assessments (Limits of Stability-LOS and Sensory Organization Test- SOT) did not improve significantly relative to no treatment. In addition, the Tai-Chi did not reduce the number of falls at 6 months post-intervention, relative to no treatment [34].

**Feasibility study findings**

Given the lack of improvement in the number of falls in the clinical trial, we developed the Cognitive-coupled Balance Training (CIBT) for balance and falls prevention for people with CA to address the potential reasons for the null findings with respect to falls in the RCT we recently completed. We conducted a single group pre-post design (ethnic reference ID: HSEARS201808070002) to test the feasibility and safety of the intervention with 5 participants with CA. Dual-task cost of balance performance was measured using the Timed up and go test with the formula: (d-TUG - Standard TUG)/Standard-TUG) × 100 [35]. Two objective laboratory-based assessments of balance were done using the composite score of the Sensory Organization Test (SOT) and maximal excursion of Limits of stability test, BBS- Berg Balance Scale, SARA- Scale for the assessment and rating of ataxia, EQ-5D-5L- EuroQol 5 dimension 5 level.

**Hypothesis 1**: Poor attention allocation to balance during dual tasking is a strong predictor of subsequent falls [36]. Improvements in balance and gait facilitate gait automaticity, which in turn allows more attention allocation to the cognitive task resulting in the reduction of risk [36] and fear of falls [37] among the elderly. Therefore, we hypothesise a greater reduction in the number of falls following dual-task in comparison to single-task training.

**Hypothesis 2**: Results of our pilot study demonstrate that the dual-task training (CIBT) program has the potential to reduce the number of falls (d = 0.91) in people with CA. Therefore we hypothesise a reduction in the number of falls will result in the reduction in healthcare utility making the intervention (dual-task training) cost-effective for falls prevention.

**Study protocol**

An assessor and statistician blinded two-arm parallel group, RCT comparing dual-task (CIBT) to single-task (conventional balance, coordination and cognitive) training will be conducted with 44 participants with CA. Eligible participants will be randomized to study groups and allocation will be concealed. Participants will be randomized to one
<table>
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<th>Outcome measures</th>
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<td>Baseline characteristics</td>
<td>Age, age at disease onset, gender, employment status, disease diagnosis, disease duration, signs of cerebellar dysfunction (gait ataxia, dysmetria, speech disturbance and nystagmus), use of walking aid (users, non-users) and medication history</td>
<td>✓✓§</td>
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<tr>
<td><strong>Primary outcome measures</strong></td>
<td>Reports the deficiency of balance and cognition in dual-task performance relative to single-task performance will be reported in percentage. Lower the percentage obtained better the dual tasking performance of balance and cognition.</td>
<td>✓✓✓</td>
</tr>
<tr>
<td>Dual-task cost of balance and cognitive performance</td>
<td>Will be assessed using the Bertec * system. Ability to stand unsupported in conditions challenging the visual, vestibular and somato-sensory inputs will be assessed [42,43]. We will assess (1) equilibrium score using the center of gravity (COG) sway of each condition, (2) composite equilibrium score and (3) sensory analysis ratio.</td>
<td>✓✓✓</td>
</tr>
<tr>
<td>Secondary outcome measures</td>
<td>The SOT variables will be repeated adding a cognitive task to assess static balance during dual tasking. Participants will be instructed to count backwards for a random number. Lower score indicating poor performance of sensory interaction during dual-task.</td>
<td>✓✓✓</td>
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<tr>
<td>SOT</td>
<td>Will be assessed using the Bertec * system. The LOS assesses the ability to shift weight in 8 different directions. We will assess Reaction time (RT) and Maximal Excursion (MxE)</td>
<td>✓✓✓</td>
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<tr>
<td>Dual-task SOT (d-SOT)</td>
<td>Number of falls will be obtained used digital diary. We operationally define a fall as an event when the person ends up on the ground or other surfaces due to a trip or any other unintentional activity, and a near fall as an unexpected loss of balance that did not result in complete loss of upright standing.</td>
<td>✓✓✓</td>
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<td>Limits of stability (LOS)</td>
<td>Montreal Cognitive Assessment (MoCA), MoCA estimates memory, executive function, attention, language, abstraction, naming, delayed recall and orientation [38]. This brief tool scores cognitive function out of 30, with a higher score equating to better function [38].</td>
<td>✓✓✓</td>
</tr>
<tr>
<td>Number of falls</td>
<td>Scale for the Assessment &amp; Rating of Ataxia (SARA) is a measure for rating severity of ataxia [44]. SARA has eight sub-components with a total score of 40, higher scores indicating greater severity of symptoms due to ataxia. It is reported to have good reliability, validity and responsiveness in CA. [40,41,44]</td>
<td>✓✓✓</td>
</tr>
<tr>
<td>Balance sub-components of SARA (SARAbal)</td>
<td>Gait, walking and standing sub-components of the SARA are relevant to balance assessment and is called the SARA-bal. [40,41] SARAbal is scored out of 18 with higher the score obtained greater the severity of balance impairment.</td>
<td>✓✓✓</td>
</tr>
<tr>
<td>Berg Balance Scale (BBS)</td>
<td>EuroQol-5-dimension-5-level (EQ-5D-5L). Health status will be assessed using the EuroQol-5-dimension-5-level (EQ-5D-5L). It is a standardised measure of health status used for economic appraisal. [45]</td>
<td>✓✓✓</td>
</tr>
<tr>
<td>Medical expense</td>
<td>Is an ongoing assessment from the onset of intervention.</td>
<td>✓✓✓</td>
</tr>
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</table>

SOT – Sensory Organization Test, d-SOT – dual-task Sensory Organization test.
of the two groups: Group 1: Dual-task (CIBT) training; and Group 2: Single-task active control (conventional balance, coordination and cognition) training.

**Sample size calculation**

We will enrol 44 participants (22 in each group), allowing 10% attrition rate. Using the data from our pilot study, for using dual-task cost of balance performance as a primary outcome measure, assuming 90% power, 5% type I error and allowing 10% dropout, the required sample size is 44 (22 in each group).

**Participants**

Study inclusion criteria include: (1) men and women in the age group of 18–60 years; (2) with a confirmed diagnosis of CA (of any type); (3) able to walk independently with or without walking assistive aids. Study exclusion criteria will be: (1) previous history of other neurological diseases (such as Parkinson’s disease, stroke, or polyneuropathies) or musculoskeletal problems severely impairing balance, gait or motor performance; (2) able to walk only with handheld support (3) severe visual impairment preventing from exercise participation and (4) severe cognitive impairment with scores < 16 on the Montreal Cognitive Assessment (MoCA) scale [38].

**Randomization and blinding**

A person not involved in the study will randomize participants to study groups in permuted blocks through computer-generated random numbers list. One HK registered physiotherapist (RA1) will be recruited to provide intervention to participants. Assessments will be performed blinded to the treatment conditions. Statistical analysis will be performed blinded to the treatment condition by the statistician.

**Procedure**

First baseline assessment (T1) will be completed after written informed consent. Participants will then be requested to return after 6 weeks for a second baseline assessment (T2). Study intervention will not be provided during this six-week period. Consistent with a previous study [27], in order to allow a prospective number of falls assessment and progress in disease severity, we plan to conduct two baseline assessments at a 6-week interval. Post-intervention assessment will be performed after 4 weeks of intervention (T3) and a follow-up assessment will be performed after 6 months (T4).

**Intervention**

Treatment will be initiated for both the groups after the second baseline assessment. The exercise intervention will continue for 7 months, beginning with supervised training at PolyU for 1-month. Intervention for both groups will be for 60 min, 3 times a week for 4 weeks. At the end of the training phase at PolyU, participants will be asked to complete an unsupervised home exercise programme over the next 6 months, based on the trial intervention.

Group 1: Dual-task (CIBT- experimental) group participants will receive 10 min of warm-up, 40 min of CIBT training and 10 min of cool down exercises. CIBT program includes performing four types of cognitive tasks during sit to stand, standing with feet apart, one leg, tandem standing, multidirectional reaching, stair climbing and walking (10 m) tasks. The four cognitive tasks will include: counting backwards by subtracting 4 numbers (for mental tracking), naming fruits, vegetables, or animals (for working memory), auditory cues for performing activities, example, perform heel raise when you hear the alphabet H (for improving attention and auditory discrimination), short story telling (for verbal fluency). In addition, falls prevention strategies will be taught. These exercises are consistent with previous studies on dual-task training for people with mild cognitive impairment [39].

Group 2: Single-task (conventional balance, coordination and cognitive training- active control) group participants will receive 10 min of warm-up, 20 min of conventional balance and coordination exercises that are in accordance to previously published literature [27], 20 min of cognitive training as single-task (same 4 tasks provided for the CIBT) and 10 min of cool down. In addition, falls prevention strategies will also be taught.

**Outcome measure**

Table 2 reports the summary of the proposed outcome measures, domains tested, interpretation and the assessment timeline.

Participants will be instructed to complete the digital diary once every week. A printed version of the cost and falls diary will be provided to participants who do not have regular access to the internet. Postage-paid envelopes will be added to each printed cost diary to obtain a better response rate and participants will be instructed to post the completed forms once a month.

**Statistical analyses**

**Hypothesis 1:** Changes in primary and secondary outcome measure between mean baseline (T2), post-intervention (T3) and follow-up (T4) across the intervention groups will be evaluated using an Analysis of covariance (ANCOVA) at 95% confidence interval. The baseline score will be adjusted for disease duration, ataxia severity and assistive walking device usage (co-variates). Time points 2 and 3 will be compared to establish immediate treatment effects and T2 and T4 will report retention of treatment effect.

**Hypothesis 2:** The EQ-5D-5L response will be converted into utility scores which will be used to estimate the quality-adjusted life-year (QALY) gain or loss over the follow-up period. The mean QALY gain or loss will be calculated for each group at six months. In addition, the mean incremental QALY gain will be estimated for the intervention groups. The incremental cost-effectiveness ratio (ICER) will be calculated using the mean incremental cost and mean incremental effect by substituting with the formula: ICER = ΔC/ΔE, where E is the gain in QALY and C is the cost. The cost-effectiveness of the intervention groups will be geographically represented using the cost-effectiveness plane (CE). The threshold (λ) for cost-effectiveness or the amount of money the country is willing to pay to gain one unit of effect (QALY) will be calculated.

**Consequences of hypotheses**

If the hypotheses we made were found true, the findings of this cutting-edge research are important to the clinicians, researchers, policy-makers and people with CA. This study finding will have important clinical implications by clarifying if adding a cognitive demand to routine balance and coordination training will result in additional benefits on improving balance and reducing falls in comparison with usual care in people with CA.

**Conclusion**

People with CA also present with varying degrees of cognitive impairments making it difficult for them to perform dual-tasks in daily activities. Dual tasking has been found to deteriorate the performance of either or both tasks in people with CA. The use of dual-task training to reduce dual-task cost has been found to be effective in stroke, Parkinson’s disease and the elderly population. The use of dual-task training to improve balance and reduce the number of falls for people with CA is novel and worthwhile testing.

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Conflict of interest
The team of authors report no conflict of interest.

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