Long-Term Effects of Coordinative Training in Degenerative Cerebellar Disease

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Abstract: Few clinical studies have evaluated physiotherapeutic interventions for patients with degenerative cerebellar disease. In particular, evidence for long-term effects and transfer to activities of daily life is rare. We have recently shown that coordinative training leads to short-term improvements in motor performance. To evaluate long-term benefits and translation to real world function, we here assessed motor performance and achievements in activities of daily life 1 year after a 4 week intensive coordinative training, which was followed by a home training program. Effects were assessed by clinical rating scales, a goal attainment score and quantitative movement analysis. Despite gradual decline of motor performance and gradual increase of ataxia symptoms due to progression of disease after 1 year, improvements in motor performance and achievements in activities of daily life persisted. Thus, also in patients with degenerative cerebellar disease, continuous coordinative training leads to long-term improvements, which translate to real world function.

Key words: cerebellum; cerebellar ataxia; neurorehabilitation; motor control; dynamic balance

Degenerative ataxias lead to progressive unsteadiness of gait with a high risk of falling and severe impairments in daily life.1–3 As no pharmacologic treatments are available, physiotherapeutic training currently presents the only therapy to improve ataxia dysfunctions. Its benefit, however, remains controversial as the cerebellum functions as a primary site for adaptation of limb movements and dynamic regulation of balance, and as cerebellar patients are known to have deficits in motor learning.4–9 So far, effects of physiotherapeutic interventions in ataxia patients have been assessed only rarely10–17 and most studies failed to report any data about long-term effects and transfer to daily life activities.18 Such data, however, are needed to show that improvements in clinical and laboratory tests are not just transient short-term effects but indeed translate to sustained improvements in real world function.19

We have recently shown that a 4-week intensive coordinative training leads to short-term improvements in motor performance.20 Here, we present analyses concerning long-term effects 1 year after intervention with accompanying training according to a homework protocol.

PATIENTS AND METHODS

Patients

We examined 14 patients suffering from degenerative cerebellar disease including 8 patients (C1–C8) with predominant affection of the cerebellum and 6 patients (A1–A6) with predominant afferent ataxia (Table 1). From the short-term study,20 two patients of the cerebellar group had to be excluded as they developed additional signs of orthostatic and urinary dysfunction, parkinsonism, and pyramidal dysfunction, thus fulfilling the criteria of probable multiple system atrophy of cerebellar type (MSA-C).21

All patients were able to walk a distance of 10 m with or without walking aid. All experimental procedures were approved by the local ethics committee. Patients gave written informed consent.

Study Design

We assessed the long-term effectiveness of a 4-week course of intensive coordinative training, followed by
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Age of onset</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Home training</th>
<th>SARA</th>
<th>GAS-Individually selected goals</th>
<th>GAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intensity</td>
<td>Demand</td>
<td>BT</td>
<td>AT</td>
</tr>
<tr>
<td>C1 55</td>
<td>52</td>
<td>F</td>
<td>IDCA</td>
<td>5/5</td>
<td>4/5</td>
<td>17</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>C2 79</td>
<td>76</td>
<td>F</td>
<td>SCA 6</td>
<td>3/5</td>
<td>3/5</td>
<td>13.5</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>C3 66</td>
<td>56</td>
<td>M</td>
<td>ADCA</td>
<td>5/5</td>
<td>3/5</td>
<td>15</td>
<td>9</td>
<td>10.5</td>
</tr>
<tr>
<td>C4 71</td>
<td>67</td>
<td>M</td>
<td>IDCA</td>
<td>5/5</td>
<td>5/5</td>
<td>13.5</td>
<td>9.5</td>
<td>10</td>
</tr>
<tr>
<td>C5 71</td>
<td>51</td>
<td>F</td>
<td>SCA 6</td>
<td>4/5</td>
<td>2/5</td>
<td>17</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>C6 47</td>
<td>31</td>
<td>M</td>
<td>IDCA</td>
<td>5/5</td>
<td>3/5</td>
<td>14</td>
<td>8.5</td>
<td>13</td>
</tr>
<tr>
<td>C7 67</td>
<td>43</td>
<td>M</td>
<td>IDCA</td>
<td>3/5</td>
<td>5/5</td>
<td>24.5</td>
<td>19</td>
<td>17.5</td>
</tr>
<tr>
<td>C8 69</td>
<td>57</td>
<td>M</td>
<td>SCA 2</td>
<td>5/5</td>
<td>4/5</td>
<td>11.5</td>
<td>8.5</td>
<td>10.5</td>
</tr>
<tr>
<td>ØC 65.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.7</td>
<td>10.8</td>
<td>12.6</td>
</tr>
<tr>
<td>A1 44</td>
<td>34</td>
<td>F</td>
<td>SANDO</td>
<td>3/5</td>
<td>3/5</td>
<td>14</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>A2 69</td>
<td>56</td>
<td>M</td>
<td>IDCA with SA</td>
<td>4/5</td>
<td>1/5</td>
<td>23</td>
<td>16.5</td>
<td>22.5</td>
</tr>
<tr>
<td>A3 40</td>
<td>22</td>
<td>F</td>
<td>SANDO</td>
<td>2/5</td>
<td>4/5</td>
<td>12.5</td>
<td>8</td>
<td>14.5</td>
</tr>
<tr>
<td>A4 51</td>
<td>31</td>
<td>M</td>
<td>FA</td>
<td>2/5</td>
<td>5/5</td>
<td>19</td>
<td>16</td>
<td>21.5</td>
</tr>
<tr>
<td>A5 69</td>
<td>44</td>
<td>M</td>
<td>FA</td>
<td>5/5</td>
<td>3/5</td>
<td>20</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>A6 64</td>
<td>44</td>
<td>F</td>
<td>FA</td>
<td>1/5</td>
<td>1/5</td>
<td>17</td>
<td>14</td>
<td>20.5</td>
</tr>
<tr>
<td>ØA 56.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17.5</td>
<td>13.9</td>
<td>18.8</td>
</tr>
<tr>
<td>ØAll 61.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.5</td>
<td>12.1</td>
<td>15.1</td>
</tr>
</tbody>
</table>

Ataxia was clinically assessed using the scale for the assessment and rating of ataxia (SARA) as primary outcome measure at the three time points: BT: Before training, AT: after training and LT: at long-term examination after one year.

In the patient column, “C” indicates individuals with predominantly cerebellar ataxia while “A” indicates patients with afferent ataxia, Ø denotes average, IDCA, idiopathic cerebellar ataxia; SA, sensory neuropathy; ADCA: autosomal dominant cerebellar ataxia; SCA 6, spinocerebellar ataxia type 6; SCA 2, spinocerebellar ataxia type 2; SANDO, Sensory ataxic neuropathy with dysarthria and ophthalmoparesis caused by mutations in the polymerase gamma gene (POLG); FA, Friedreich’s ataxia.

Home training: categorization based on interview data, assessing the intensity and the composition of exercises; maximal score is 5, higher scores mean more demanding exercises or higher intensity respectively (see Appendix B). Goal attainment score (GAS): Personally selected goals of the goal attainment score and the scores obtained after the intervention period (AT) and after one year (LT). Described goals correspond to score 2. Scores range from −1 to 4 (−1 is worse than baseline, 0 is baseline, 1 is less than expected outcome, 2 is expected outcome, 3 is greater than expected outcome, 4 is much greater than expected outcome).
1 year during which the patients were asked to continue exercises at home. To evaluate the long-term effects, we compare the results of three examinations: before training (BT), after 4-week training (AT), and at long-term assessment (LT) after 1 year.

**Coordinative Physiotherapy**

The physiotherapy program consisted of a 4-week intensive training with three sessions of 1 hour per week. Exercises included the following categories: (1) static balance e.g. standing on one leg; (2) dynamic balance e.g. sidesteps, climbing stairs; (3) whole-body movements to train trunk-limb coordination; (4) steps to prevent falling and falling strategies; (5) movements to treat or prevent contracture (Appendix A).

After the 4-week intervention period, all patients received an individual training schedule and were asked to perform exercises at home for 1 hour each day. All exercises were part of the preceding coordinative training program, but patients were instructed to perform only exercises at home that were safe depending on their respective individual motor skills. Home training was categorized on the basis of interview data, assessing the intensity and the composition of exercises (Table1, Appendix B).

**Clinical Scales and Individual Goal Attainment**

Primary outcome measure was the scale for the assessment and rating of ataxia (SARA), which has been approved as a valid measure of disease severity in spinocerebellar and idiopathic ataxias as well as in Friedreich’s Ataxia. SARA was assessed by a neurologist experienced in ataxia (M.S.). A physiotherapist (S.B.) rated balance-control capacities using the Berg balance score (BBS). In addition, each patient selected a personal goal reflecting an individually important activity of daily life. These goals were determined before training and achievements were rated within a goal attainment score (GAS). A score of “0” reflects function at baseline, “−1” means worse than baseline and “+1” to “+4” indicates different degrees of improvement (Table1, Appendix C).

**Quantitative Movement Analysis**

Motor performance was evaluated by quantitative movement analysis using a motion capture system (see Ref. 20 for details). We examined gait and a dynamic balance task. For gait, patients were instructed to walk at a self-determined pace. We examined standard gait parameters and a specific measure for temporal variability of intra-limb coordination. This measure $v_b$ has been shown to detect temporal abnormalities in intra-limb coordination that are specific for patients with cerebellar dysfunctions.

In the dynamic balance task, subjects stood in an upright position with both legs on a treadmill and were warned that the treadmill would be activated in the next few seconds. The treadmill was programmed to run for one second with an acceleration of 6 m/s² and a maximal velocity of 0.4 m/s in posterior direction. Subjects were protected from falling by a safety harness and were instructed to compensate the perturbation by anteriorly directed steps (see Ref. 20 for details).

**Statistical Analysis**

Correlations between training intensity and course of ataxia symptoms (SARA scores) were computed using Spearman rank correlation. Group differences between assessments BT, AT, and LT were confirmed by using a Wilcoxon signed-rank test for pair-wise comparisons. For the latter we report two significance levels: uncorrected ($P < 0.05$*) and Bonferroni-corrected for multiple comparisons ($P < 0.05/3 = 0.016**$).

**RESULTS**

The SARA score decreased significantly ($−4.4$ points on average) when comparing pre/post intervention (BT/AT, Wilcoxon signed-rank test: $Z = −3.3, P = 0.001**$). After 1 year, ataxia deteriorated again (AT/LT; $Z = −2.9, P = 0.003**$). However, SARA scores were still significantly better than at baseline for the cerebellar group (BT/LT; $Z = −2.1, P = 0.03$*) whereas the afferent group was stable compared to baseline (Fig. 1A,B). Importantly, long-term benefit seems to depend on training: training intensity in coordination exercises (Table1) correlated significantly with differences in SARA scores after 1 year (BT/LT; $P = 0.01$).

Assessments of balance capacities using the BBS showed significantly improved performance for all patients after intervention (BT/AT; $Z = −3.1, P = 0.003**$). Although long-term assessment revealed a significant decrease of capacities (AT/LT; $Z = −2.9, P = 0.003**$), average BBS scores were slightly - not significantly - higher after 1 year compared to baseline ($Z = −1.1, P = 0.24, BT: 44.4 ± 8.5; LT: 45.9 ± 8.6$).

The goal attainment scores show a substantial retention of training effects for activities of daily life (Table 1): for all patients, the average rating was 2.57 ($2 = $expected outcome, $3 = $greater than expected outcome).
outcome) after training (AT) and 2.07 after 1 year (LT). For example, patient A3 who was unable to walk 10 m unattended before training (baseline score, 0) had initially indicated the goal to walk a distance of 30 m with a full cup without spilling something (=expected outcome, +2), as this has been a major problem to her in daily life. At long-term assessment, she was able to walk 30 m and more without spilling something.

Movement analysis revealed partly different results for the two patient subgroups. Only for the cerebellar group, gait velocity was significantly increased after intervention (BT/AT: $Z = -2.7, P = 0.007^{**}$), which was not preserved at long-term assessment.

Quantifying the joint coordination variability using the measure $v_{bh}$ (see Methods) revealed a reduced temporal variability in intra-limb coordination after training ($Z = -2.29, P = 0.022^*$) and at long-term assess-
ment ($Z = -1.98, P = 0.047^*)$ for the group of cerebellar patients (Fig. 1E). For the dynamic balance task on the treadmill, cerebellar patients showed decreased body sway after intervention (BT/AT; $Z = 2.29, P = 0.02^*$). This implies an improvement in dynamic balance control and the capability to compensate for perturbations, which has strong everyday relevance. However, long-term assessment revealed an increase of body sway (AT/LT, $Z = -1.96, P = 0.05$), indicating that improvements did - although still better by trend than baseline - not fully persist after intensive intervention.

**DISCUSSION**

This study focused on long-term effects of coordinative training for patients with degenerative ataxias. The results revealed a significant reduction of ataxia symptoms measured by the clinical scale SARA for the cerebellar group, which persisted after 1 year. Thus, despite of a gradual decline of motor performance and gradual increase of ataxia symptoms due to progression of underlying neurodegeneration (and the lower intensity of home training), patient benefits did persist over a long-term period.

The natural disease progression of degenerative cerebellar ataxias is 0.6–2.5 points per year on the SARA scale depending on genotypes (data of the EUROSCA natural history study; Thomas Klockgether, personal communication). This implies that the average improvement achieved by training ($−4.9$ SARA points after intervention and $−3.1$ SARA points after 1 year for the cerebellar group) is equivalent to gaining back functional performance of two or more years of disease progression.

The results of the goal attainment score demonstrate that these training effects translate into an improvement in personally important functions of daily life.

For the afferent group, the improvement in ataxia symptoms were less pronounced than in the cerebellar group and did not persist for long-term assessment.

Specific improvements in balance and coordination tasks as well as the differential results for patient subgroups make it unlikely that the observed effects have been mediated predominantly by nonspecific mechanisms such as improved cardiovascular endurance.

Importantly, long-term outcome seems to be influenced by training intensity at home. Thus, continuous training of whole body coordination exercises seems crucial for stabilizing improvements in patients with ataxia. We therefore recommend professionally administered physiotherapy, which focuses on whole body coordination exercises and is complemented by home training as standard of care in patients with degenerative ataxia.

In conclusion, this study delivers evidence for long-term benefits of coordinative training for such patients. Future studies are required to examine in more detail e.g. necessary training intensities and durations, training strategies for different levels of severity of ataxia and a comparison with other types of interventions.

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**Author Roles:** Winfried Ilg was involved in conception, organization, and execution of research project, design and execution of statistical analysis, and writing of the first draft of manuscript. Doris Brötz was involved in conception and execution of research project, review and critique of statistical analysis, and review and critique of manuscript. Susanne Burkard was involved in execution of research project, review and critique of statistical analysis, and review and critique of manuscript. Martin A. Giese was involved in review and critique of statistical analysis, and review and critique of manuscript. Ludger Schöls was involved in conception of research project, design of statistical analysis, and review and critique of manuscript. Dr. Martin A. Giese served as an editorial board member of Cognitive Neurodynamics. He received research fundings from the Deutsche Forschungsgemeinschaft [SFB 555 (Co-PI) and GI305/2(PI)], the EU [Cobol FP6-NEST-2005-Path-IMP-043403(Co-PI)], [SEARISE FP7-ICT-215866(Co-PI)], Volkswagen Foundation [I/765567-1(PI)], and HSP-Grant [RGP54/2004 (Co-PI)]. Dr. Matthias Synofzik received speakers honoraria from Fresenius Kabi and Actelion Pharmaceuticals and research support from the Volkswagen Foundation (European platform). Doris Brötz served as a member of the editorial board of Physioscience.

**APPENDIX A**

**Details of Physiotherapeutic Exercises**

The physiotherapy program consisted of a 4-week course of intensive training with three sessions of 1
APPENDIX A1. Details of physiotherapeutic exercises during the intervention period

<table>
<thead>
<tr>
<th>Static balance</th>
<th>Quadruped standing with therapist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standing on one leg</td>
<td>Stabilize the trunk – lift one arm</td>
</tr>
<tr>
<td>Quadruped standing</td>
<td>Stabilize the trunk – lift arm</td>
</tr>
<tr>
<td>Quadruped standing</td>
<td>Lift one arm and the leg of the other side</td>
</tr>
</tbody>
</table>

Dynamic balance

- Kneeling – put one foot in front and back alternately
- Kneeling – put one foot to the side and back alternately
- Kneeling – put one foot in front – stand up – put one leg back – kneel alternately
- Standing – step to the side
- Standing – step back
- Climbing stairs
- Walking over uneven ground

Whole body movements to train the trunk-limb coordination

- Quadruped standing: lift one arm and the leg of the other side – flex arm, leg and trunk – extend arm, leg and trunk alternately
- "morning prayer" (Moshe Feldenkrais): kneeling – bend legs, arms and trunk (*package sitting) – extend legs, arms and trunk alternately
- Kneeling – sit besides the heel on the right side – kneel alternately
- Kneeling – sit besides the heel on the left side alternately

Steps to prevent falling and falling strategies in order to prevent trauma

- Standing – step to the side, step in front, step back
- Standing – crossover step in a dynamic alteration*
- Standing – the therapist pushes the patient in altered directions – the patient has to react quickly with fall preventing steps*
- Standing – bend the trunk and the knees to touch the floor – erect the body alternately*
- Standing – bend the trunk and the knees, touch the floor and go down to quadruped standing*
- Standing – the therapist pushes the patient – the patient has to react quickly – bend and go to the floor in a controlled manner*
- Walking – the therapist pushes the patient – the patient has to react quickly – bend and go to the floor in a controlled manner*

Movements to treat or prevent contracture especially movements of shoulders and spine

- Extension of the spine: prone lying, push up the shoulder girdle from prone lying; prone lying on a wedge
- Rotation of the spine: supine lying – knees bended – rotate the knees to the right and left side
- Flexion of the shoulder: supine lying – lift the arms in the direction of the head

APPENDIX B. Categorization of home training

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Composition/Demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = only with therapist 2×/week</td>
<td>1 = 0–20%</td>
</tr>
<tr>
<td>2 = only with therapist, 2×/week, &gt;30 min p. session</td>
<td>2 = 21–40%</td>
</tr>
<tr>
<td>3 = 3×/week, &gt;30 min. p. session</td>
<td>3 = 41–60%</td>
</tr>
<tr>
<td>4 = 5–7×/week, &lt; 20 min. p. session</td>
<td>4 = 61–80%</td>
</tr>
<tr>
<td>5 = 7×/week, &gt; 20 min. p. session</td>
<td>5 = 81–100%</td>
</tr>
</tbody>
</table>

Higher scores mean more demanding exercises or higher intensity respectively. The demand of the exercises was categorized based on the degree of exercises requiring dynamic regulation of balance and whole body coordination.

APPENDIX C

Goal Attainment Scaling

Goal Attainment Scaling (GAS)25 is a method for setting personal goals and measuring the degree of

APPENDIX C1. Personally selected goal of the goal attainment score exemplarily shown for patient C4

<table>
<thead>
<tr>
<th>Individual goal patient C4: Walking around a table with small distance without swaying</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>The patient walks around the table mainly by touching the table</td>
<td>0</td>
</tr>
<tr>
<td>The patient can walk around the table without touching the table most of the time</td>
<td>1</td>
</tr>
<tr>
<td>The patient can walk around the table without touching the table</td>
<td>2</td>
</tr>
<tr>
<td>The patient can walk around the table without touching the table and he is able to look around sometimes</td>
<td>3</td>
</tr>
<tr>
<td>The patient can walk around the table without touching the table and he is able to look around the whole time</td>
<td>4</td>
</tr>
</tbody>
</table>

Five levels of goal attainment were defined before the intervention started. After Intervention (AT) and at long-term assessment, the goal attainment is rated. Scores range from −1 to 4 (−1: worse than baseline, 0: baseline, 1: less than expected outcome, 2: expected outcome, 3: greater than expected outcome, 4: much greater than expected outcome).
APPENDIX C2. Personally selected goal of the goal attainment score for patient C2

<table>
<thead>
<tr>
<th>Individual goal patient C2: Walking up a staircase without using a stairrail</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient can walk up 10 steps of a staircase with an alternating foot pattern; without support; with one hand on rail most of the time; patient feels safe</td>
<td>0</td>
</tr>
<tr>
<td>Patient can walk up 10 steps of a staircase with an alternating foot pattern; patient walks free without one hand on rail most of the time; 50 cm max. distance to the handrail; patient feels rather unsafe</td>
<td>1</td>
</tr>
<tr>
<td>Patient can walk up 10 steps of a staircase with an alternating foot pattern; patient walks free without one hand on rail most of the time; 50 cm max. distance to the handrail; patient feels safe</td>
<td>2</td>
</tr>
<tr>
<td>Patient can walk up 10 steps of a staircase with an alternating foot pattern; patient walks free in the middle of the staircase with distance &gt; 1 m to the handrail; patient feels unsafe</td>
<td>3</td>
</tr>
<tr>
<td>Patient can walk up 10 steps of a staircase with an alternating foot pattern; patient walks free in the middle of the staircase with distance &gt; 1 m to the handrail; patient feels safe</td>
<td>4</td>
</tr>
</tbody>
</table>

goal achievement by creating an individualized point scale (=1, 0, 1, 2, 3, 4) of potential outcomes for each activity undertaken. Each scale is created de novo starting from the individual skills of the patient at baseline (= score 0) and the expected level of achievement (= score +2) of a particular individual goal. Above and below this level, indicators of underachievement and over-achievement (i.e., getting not as far as, or farther than expected) were created in order to evaluate the degree of success in achieving the goal. Tables C1 and C2 show individual examples.

REFERENCES