Case Report

Vibration assisted rehabilitation in patients with Pompe disease: A case series

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Abstract

The results of three cases with infantile-onset Pompe disease participating in a rehabilitation program with home-based vibration training will be presented. In this retrospective observational case study, the cases participated in the neuromuscular training program “Auf die Beine”, which combines two blocks of intensive, goal directed training with 6 months of home-based whole body vibration (WBV). Assessments by the means of a dual-energy X-ray absorptiometry and grip strength were applied at multiple points throughout the program. Two cases showed an increase in lean mass index of +0.319 kg/m², +0.721 kg/m² and bone mineral content of +0.028 kg/m², +0.031 kg/m² over one year. Additionally physiotherapeutic therapy goals could be achieved. In the remaining child lean mass index did not change, bone mineral content decreased by -0.03 kg. The neuromuscular rehabilitation program “Auf die Beine” has shown to be safe and effective in two of three cases for muscle and bone mass gain as well as in achievement of physiotherapeutic goals. To summarize, WBV is an innovative therapy in a rehabilitation concept, which might be helpful in Pompe disease, but further studies with larger cohorts are needed.

Keywords: Bone Density, Physiotherapy, Pompe Disease, Rehabilitation, Whole Body Vibration

Introduction

Pompe disease is rare, as only 1 of 40,000 children are affected. It is caused by a genetic alpha-acid glucosidase deficiency, which leads to an accumulation of glycogen in tissues, most prominently in muscle. Symptoms are progressive myopathy, a loss of pulmonary function and cardiomyopathy, followed by arrhythmia. Pompe disease is a progressive disease, hence worsening of symptoms is to be expected.

Patients have difficulties while walking or cannot walk at all. Additionally, fine and gross motor function can be restricted. Pompe disease can be categorized by late-onset and infantile-onset, characterized by the appearance of symptoms. An onset before the age of 12 months is classified as infantile-onset Pompe disease and is often accompanied by more severe symptoms than in the late-onset forms.

State of the art treatment is an enzyme replacement therapy (ERT). ERT prolongs survival as well as the time until ventilation is needed. On average, patients start ventilation at the age of 7.5 years. Since classic infantile-onset patients die at a median age of 6-8 months, in this report we describe the non-classic infantile-onset Pompe disease.

Non-pharmacological treatment of children with Pompe disease includes physiotherapy to preserve muscle strength, and prevention of secondary impairments such as contractures, deformity and osteopenia. Due to weakness...
in the respiratory muscles and severe motor dysfunction in Pompe disease, training may be restricted, significantly narrowing down the training modalities.

Nevertheless, it is known that a more active use of muscle should not only lead to a better mobility in all day living, but also to an osteoanabolic effect, as described in the functional-muscle bone unit. On contrary, lack of muscle movement due to immobility would lead to muscle weakness and degradation of bone mass.

Recently whole body vibration (WBV) has moved into focus in pediatric rehabilitation. Compared to other exercise modalities, WBV can be applied independent of the subjects’ motility and health. Previous reports have shown promising results on children with neuromuscular diseases. Vibrations are applied through an oscillating surface that induces reflex-based muscle contractions to the patient including involuntary muscle stimulation. The effects of WBV have been described in late-onset Pompe disease cases before. These studies see great potential in WBV.

The aim of this retrospective analysis was to assess the safety and possible benefits to enable future controlled studies on WBV for patients with infantile-onset Pompe disease.

### Materials and Methods

The present study is a retrospective data analysis of three cases, with infantile-onset Pompe disease, receiving the standard ERT and participating in the rehabilitation program “Auf die Beine” at the Centre of Prevention and Rehabilitation (University of Cologne, Germany) (Figures 1, 2). Data was collected in a secure data base and retrospectively analyzed. The analysis was approved by the Ethics Committee of the University of Cologne (16-269) and the register has been registered at http://www.germanctr.de (DRKS00011331). Written consent was obtained from the legal guardians of all children.

### Participants

Inclusion criteria were the diagnosis non-classical infantile-onset Pompe disease and at least completion of one of the outcome assessments at two consecutive visits. Exclusion criteria were all other diagnoses influencing motor function and surgery during the participation. Patients were excluded from analysis for the following reasons: If data was not plausible after comparison with source data and patient file if the child had planned surgery during participation at

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**Figure 1.** "Auf die Beine": Interval-Rehabilitation with home based vibration assisted training. WBV = whole body vibration. MO = Start; M6 = six months since start; M12 = 12 months since start.
the concept. As a result, three cases could be identified, searching the patients registered from 2006 to 2020. Case characteristics are depicted in Table 1.

Rehabilitation protocol

The rehabilitation program “Auf die Beine” has been previously described10-16 and is part of the healthcare available in Germany. “Auf die Beine” combines intensive, goal directed training during in-patient stays (Figure 2) with WBV as a home training program for six months (Figure 1). For the WBV training, a side-alternating platform (System Galileo®, Novotec Medical, Pforzheim, Germany) was used and provided by the centre. The specific training interventions for each case are shown in Table 2.

Assessments

During the first year, assessments are applied at baseline (M0), after 6 months (M6) of home training and intensive stays, and after 12 months (M12), in a six-month follow-up. The program can be repeated after initial participation for a second year (Figure 1). At each measuring time point an osteodensitometry...
Table 1. Case data.

|                        | Case 1 | Case 2 | Case 3 |
|------------------------|--------|--------|--------|
| Age (years) at M0/M6/M12| 8 / - / 9 | 7 / 8 / 8 | 5 / 6 / 7 |
| Sex (male/female)      | f      | m      | m      |
| Height (m) at M0/M6/M12| 1.29 / n.i. / 1.38 | 1.13 / 1.17 / 1.20 | 1.11 / 1.16 / 1.18 |
| Weight (kg) at M0/M6/M12| 33.5 / n.i. / 34.5 | 19.2 / 20.9 / 23.1 | 17.3 / 19.2 / 21.0 |
| Ability to sit         | yes    | yes    | yes    |
| Ability to stand       | Difficult with assistance | With assistance | With assistance |
| High protein diet      | n.i.   | Nutritional supplements | n.i.   |
| Use of respiratory therapy | yes  | yes  | no     |
| Auf die Beine year 1   | - / - / - | x / x / x | x / x / x |
| Auf die Beine year 2   | x / - / x | x / x / - | - / - / - |
| n.i. = no information. |        |        |        |

Table 2. Training interventions.

| Intervention          | Case 1 | Case 2 | Case 3 |
|-----------------------|--------|--------|--------|
| PT                    | Bobath | x      | x      |
|                       | Vojta  | x      | x      |
|                       | (since 2013) | | |
| WBV                   | x      | x      | x      |
| Gait training         | x      | x      | (1-minute walking test, crawling) |
| Resistance training   | x (since 2013) | x      | x (with motomed®) |
| Pool                  | x      | x      | |
| PT = physiotherapy.   |        |        |        |

Table 3. Measurements osteodensitometry.

|                        | Case 1 | Case 2 | Case 3 |
|------------------------|--------|--------|--------|
| LBM/height² (LMI) in kg/m² |        |        |        |
| M0                     | 7.085  | 9.020  | 9.408  |
| M6                     | n.i.   | 9.404  | 9.527  |
| M12                    | 7.101  | 9.339  | 10.129 |
| BMC in kg              |        |        |        |
| M0                     | 0.4256 | 0.3335 | 0.1947 |
| M6                     | n.i.   | 0.3569 | 0.2243 |
| M12                    | 0.3997 | 0.4146 | 0.264  |
| BMD in kg              |        |        |        |
| M0                     | 0.426  | 0.334  | 0.195  |
| M6                     | n.i.   | 0.357  | 0.224  |
| M12                    | 0.400  | 0.415  | 0.264  |
| BMD Z-Score in SD      |        |        |        |
| M0                     | -3.30  | -2.40  | -2.80  |
| M6                     | n.i.   | -2.20  | -2.70  |
| M12                    | -3.80  | -2.20  | -2.70  |
| n.i. = no information. |        |        |        |
| SD = standard deviation. |        |        |        |
by means of a dual-energy X-ray absorptiometry (iDXA with Encore©, software version 14.1, GE Healthcare, Buckinghamshire, UK) was performed, measuring the lean body mass (LBM), bone mineral content (BMC) and the bone mineral density (BMD). Additionally, for case 2 the grip strength was measured by a hand dynamometer (Jamar® hand dynamometer, Patterson Medical, former Sammons Preston) in the first and second year. For easier comparison from this point on LBM is related to height² and referred to as lean mass index (LMI) in kg/m².

Outcome measures have not always been available from clinical routine data (M0, M6/M4, and M12); therefore, the different cases present with different outcome measures. Additionally, the cases differed in the attendance of the program (Table 1).

Statistical analysis

Descriptive methods were used due to the small sample size. The Data was analyzed via Microsoft® Excel® for Microsoft 365 MSO (16.0.14326.20164) 64-Bit.

Results

Case 1

Data is only available for the second year at M0 and M12 as depicted in Table 1. Case 1 grew, scaling 1.29 m in M6 and 1.38 m in M12. The LMI just slightly improved by 0.016 kg/m². BMC and BMD did decrease, which is reflected in the BMD Z-Score. (Table 3).

In terms of relevant achievements, case 1 could only partly achieve her therapy goals. Central aims were the improvement of muscle strength, strengthening of the trunk and preservation of the current abilities. Latter was achieved until M4, after which the arm and the leg strength deteriorated; however, the remaining gross motor skills were stable. The parents did not observe a change for trunk control.

Case 2

There were no DXA-measurements made in the second rehabilitation program. Data is depicted in Table 3. The case's height measured 1.13 m at the start of the intensive training (M0), 1.17 m at the 6-month examination (M6) and 1.20 m at the end of the first program (M12).

An improvement of the LMI after the intensive training period at M6 could be observed with a slight drop after M6 until M12. Overall, the LMI-increase scaled 0.028 kg/m².

Similar results could be observed in BMC and BMD. The BMD Z-Score did improve by 0.2 (Table 3).

Most noticeable is the improvement in grip strength. It increased during the training by ~230% (Figure 3).

Overall therapeutic goals for case 2 where trunk and pelvic strengthening and stabilisation, improvement of respiration and mobilisation of the lower extremities. Most of these goals where achieved. Trunk control had significantly increased, as well as muscle strength in the pelvis and shoulder region. Standing at the bench was briefly possible after training. Respiration improved in terms of deeper and calmer breathing after M6. Overall, gross motor skills improved.

Case 3

During the program, he grew seven cm, starting at 1.11m, 1.16 m at M6 and 1.18 m at M12. LMI did increase relevantly by 0.721 kg/m². Similar to case 2 the BMC and BMD improved. The BMD Z-Score increased by 0.1 (Table 3).
Analysing the achievement of the therapy goals, which were improvement in trunk control, muscle strengthening and a more diverse locomotion, a positive trend is visible. By the end of the program, he could raise his trunk more easily and hold this position for longer periods of time. Additionally, general planning and implementation of movement was increasingly noticeable. The only negative trend was the progressing knee contracture.

Side effects

Case 1 suffered a deterioration in arm movement, as she had increasing difficulties raising her left arm four months after the first out-patient follow-up examination. Finally it is not possible to exclude that this is due to WBV, but more likely an effect of the advancing myopathy, common for the progressive Pompe disease. For the time being case 1 was advised by her attending doctor to pause WBV until a magnetic resonance imaging could be conducted. Due to metal braces, this check-up was delayed. Four months of home training would have remained until the 12-month follow-up examination, which she could not accomplish. Additionally, it was already before the deterioration difficult for the family to perform the home exercises as recommended. At M12 the family stated that they would begin the WBV once again, having the approval of their attending doctor.

Discussion

We presented a series of non-classical infantile-onset Pompe disease patients, which participated in the rehabilitation program “Auf die Beine”. As to be expected by the positive results of cases with different neuromuscular diseases, participating in “Auf die Beine”10-16,26 two of the three Pompe disease cases showed promising results after the WBV-program. Pompe disease is a progressive condition. That means, even a stabilisation of symptoms displays a positive impact of the therapy.

Therapy goals

The case’s therapy goals, excluding case 1, could be fulfilled even suggesting walking independently with aids as a future long-term goal for case 2. As most goals included muscle strengthening, these positive results are apparent in the LMI. Therapy goals were selected for each child individually in cooperation with the parents and the attending physiotherapist.

Lean Mass Index (LMI)

Over the course of the program an increase of LMI was noticeable for all cases. In case 1 the LMI increased just slightly, still ranking 3.738 kg/m² below average (10.839 kg/m²) at M12 when compared to healthy peers27. However even the perpetuation of the LMI is a good result, acknowledging the progressive myopathy. Case 2 presented with a positive progression of lean body mass, the LMI still stating 2.422 kg/m² below average at M12, but with a relevant gain during this one year program. The increase in muscle and muscle strength is demonstrated by the grip strength measures. The slight decrease in LMI between M6 and M12 could probably be explained by less conscientious training when at home. Case 3 did show very promising results in LMI with a relevant increase. A comparison to the average was not possible in case 3, since he was under eight years old, at which reference data are available.

Comparison to other studies

One study in late-onset cases also hints to a positive influence of WBV on muscle strength. The response to the therapy differed between the patients as well. The authors suggested that the different severity of the disease has an influence24. The same was seen for our case 1, who suffered a deterioration in arm movement despite the WBV. However, movement-limiting contractures could be reduced. Comparing our outcome to another study, analysing WBV in a late-onset Pompe disease case, who did not receive ERT, similar results occurred25. For this case, the peak lower extremity power improved by 64%. Similar to our cases, when excluding case 1’s deterioration in arm movement, no functional declines where seen. Furthermore, our case 2 did show an increase in grip strength, an assessment, also used for the case in Khan et al.’s study25. In this study on contrary, there was no change in grip strength.

Bone mineral content (BMC), Bone mineral density (BMD)

When observing the bone mineral content for case 2 and 3 an improvement is noticeable, following the theory of the functional muscle bone unit7. Case 1 had a slight decrease in BMC, by 0.0259 kg, which aligns with the deterioration in arm movement and the discontinuation of the training 4 months before the last follow-up examination (M12). Analogical to BMC, BMD improved through the WBV.

BMD Z-Score

When comparing the age adjusted BMD Z-Scores of our three cases, all cases have, as expected, a reduced Z-Score at -3.3 (1), -2.4 (2) and -2.8 (3). Over the therapy year for two cases an increase was noticeable. Case 1 showed a worsening score. Overall, the greatest improvement had case 2 (+0.2 SD), resulting in a gain in bone mineral density.

ERT and WBV

Chien et al. 2015 reported a positive effect of ERT on survival and motor development; even though, muscle weaknesses did occur28. However, all cases in the study on ERT could walk independently, which was not the case for our cases. Similar results were found in Chen et al. ‘s Chocran review on ERT in 2017 for infantile-onset Pompe disease3. The therapy improved cardiomyopathy and extended the overall and ventilation free survival. However, these findings were graded as low quality evidence, since no numerical
results were available. The Cochrane Review stated that more research with standardized measurements would be needed. Even though, this raises the question to what extent these promising outcomes in our study are the result of WBV or of ERT.

**Effect of physiotherapy**

The effect of general physiotherapy in late-onset Pompe disease cases has been reported before\(^5,6\). The first study by Fayjee et. al. suggests a positive influence. 64% of the physiotherapists evaluate the treatment goals as fulfilled. 72% of the patients perceived the therapy as beneficial\(^5\). This aligns with our results, emphasizing a positive effect of physiotherapy. The guideline of physical therapy management even stresses, that strenuous strengthening and excessive muscle contractions are to be avoided, since this further contributes to muscle degeneration\(^7\). Therefore, WBV, which can be adapted to the patient’s abilities and stimulates the muscle without the need of overly strenuous exercises, may be a useful addition to the physiotherapy treatment. In addition, our results show, that WBV combined with intensive training did not show serious side effects apart from natural progression in the cases reported. The results in our study promote this combination of therapy methods as well.

**Limitations**

Limitations of this study are the small sample size. Since it is just a report of three cases, it is not possible to make general assumptions. Furthermore, it is discussable, whether the improvements are due to the program “Auf die Beine” or an effect of the ERT. This study is also limited by the description of a multi-modular rehabilitation program. It is not possible to assess which intervention was the most efficient. Future research should further investigate the encouraging trends shown in the results reported. Specifically, the combination of the drug treatment ERT combined with physical therapy concepts. Timing of treatment and intensity of muscle activation (depending on duration of medical treatment) must be analyzed in controlled trials. The treatment regimens differed between the cases, particularly case 1. Therefore, standardization and comparison between the cases is difficult.

**Conclusion**

To summarize, if executed properly, the WBV in the rehabilitation program “Auf die Beine” shows promising results. The training was very well tolerated, with no mobility losses or other side effects. For our cases, depletion of muscle mass could be prevented, partly even achieving significant gains. It does require great compliance of children and parents, to manage the extensive exercises. A general prediction of the impact of the WBV on patients with infantile-onset Pompe disease is not possible. More studies, with larger cohorts, are needed to further analyse the impact of the WBV on patients with infantile-onset Pompe disease.

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