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Original Article

Motor improvement in children with PMM2-CDG syndrome following a six-month rehabilitation treatment utilising whole-body vibration; a retrospective study

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Abstract

Objective: The aim of this study was to assess the effect of a six-month interval rehabilitation treatment on motor function of children with PMM2-CDG syndrome (#212065 Congenital disorder of glycosylation, Type Ia; CDG1A, OMIM catalogue number). **Methods**: The concept 'Auf die Beine' (Center for Prevention and Rehabilitation of the University of Cologne, Germany) combines two short inpatient stays (1 to 2 weeks) with a six-month whole-body vibration (WBV) home-training program. 13 patients with PMM2-CDG syndrome participated in this concept from 2006 until 2015. Assessments at start, six months and 12 months (follow-up): Gross Motor Function Measure (GMFM-66), One-Minute Walk Test (1MWT) and instrumented gait analyses. **Results**: The GMFM-66 (9 of 13 children) improved by 5.3 (mean) points (SD 3.2) at 12 months (p=0.0039). The 1MWT (6 of 13 children) improved by 19.17 meter (SD 16.51) after 12 months (p=0.0313). Gait analysis (9 of 13 children) measured by pathlength/distance ratio improved by -0.8 (SD 1.9) at 12 months (p=0.0195). **Conclusion**: Patients with PMM2-CDG syndrome benefit from the interval rehabilitation program 'Auf die Beine' including WBV.

Keywords: Children, Rehabilitation, Physiotherapy, PMM2-CDG Syndrome, Whole-body Vibration

Introduction

"Congenital Disorders of Glycosylation" (CDG) are a group of diseases that are caused by genetic defects of the glycoprotein, glycolipid or glycosylphosphatidylinositol (GPI) biosynthesis, that lead to multi-organ diseases, which include neurological symptoms[1,2]. To date, some 130 different types are known[3]. According to the localization in the synthesis pathway, CDG syndromes can be divided into four different groups. 1) protein N-glycosylation defects; 2) protein O-glycosylation defects; 3) glycolipid and GPI-anchor synthesis defects and 4) multiple glycosylation pathways and other pathway defects[4]. The group of protein N-glycosylation defects occurs most frequently[4]. Approximately 80% of all known CDG-patients belong to subtype 1a, referred to in the more recent nomenclature as type PMM2-CDG, which is related to the affected gene PMM2[5]. This gene encodes the enzyme phosphomannomutase[2], which converts Man-6-P to Man-1-P in the cytoplasm[4,6].

PMM2-CDG patients often show dysmorphisms, including inverted nipples, subcutaneous fat pads and lipodystrophies of the buttocks, strabismus, retinitis pigmentosa[7], a mild hepatopathy, a history of thrombosis[8], pericarditis and increased levels of insulin[9] and growth hormone. Neurological symptoms include cerebellar hypoplasia with ataxia, muscular hypotension and psychomotor retardation[2,10].

The disease course of PMM2-CDG syndrome has been

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Table 1. Study demographics.

Children with CDG subtype PMM2 (n)	13
Gender	9 female / 4 male
Mean age at recruitment [years] (range)	8.3 (3.2 – 17.3)
Mean height at recruitment [cm] (range)	118 (88.5 – 167.5)
Mean Z-scores (height) ±SD	-1.97 ±1.9
Mean weight at recruitment [kg] (range)	26.4 (12.4 – 58.6)
Mean BMI at recruitment [kg/m^2] (range)	17.0 (13.9 – 25.6)
Mean Z-scores (BMI) ±SD	-0,36 ±0,89

divided into an infantile multisystemic stage, late-infancy atactic with cognitive disability stage, and the adult stage with non-progressive disability[11]. The course is not uniform[12]. Children affected by the multisystemic type show two different forms of progression. A non-fatal neurological form, in which children develop developmental delay, muscular hypotonia, internal squint, and hyporeflexia. Furthermore, there is a failure to thrive and subcutaneous fat pads. These children develop neuropathy with retinitis pigmentosa in the first or second decade of life. In addition, in the fatal form a mortality of up to 20% in the first year of life[13].

Symptoms of the late infantile form occur at the age of three to ten years. In addition to muscular hypotension, these children also show ataxia, global developmental delay with a loss of walking ability, and mild to moderate mental retardation. Seizures, stroke-like episodes, retinitis pigmentosa, joint contractures and skeletal deformities are also common[5,11]. The life expectancy is limited, although reaching the age of 67 has been described in the literature[14].

An effective therapy of neurological symptoms is not yet available[15]. Drug therapy options are limited and under development. *In vitro* and *in vivo* therapeutic trials by administration of mannose were performed[16]. Unfortunately, no significant clinical or biochemical success was achieved[17-19]. However, some parents observed improvements in their children's psychomotor abilities[20]. Recent pharmacological developments include the production of Man-1-P and the use of liposomes as delivery vehicles[21], as well as the development of pharmacological chaperones capable of inhibiting the misfolded enzyme PMM2[22,23].

Physiotherapy is an important part of the interdisciplinary treatment of patients with PMM2-CDG. But there are not enough controlled trials yet to give recommendations about frequency, intensity or timing. Whole body vibration (WBV) has been used frequently in adults and children with and without disabling conditions to reach positive results on muscle and bone[24-26].

There are acute effects like increased oxygen consumption and muscle temperature. Furthermore also long term effects like less muscle and bone loss in case of immobilization[27].

Home programs with WBV in combination with physiotherapy are feasible and potentially effective[25,26,28-31].

WBV might have a potential benefit for patients with PMM2-CDG because it is activating muscle spindles and stimulating alpha motor neurons through 1a afferent fibers[32-34]; therefore it might have a neuroprotective effect. Based on this rational we have established a neuromuscular rehabilitation program including WBV 'Auf die Beine'. The program consists of a combination of two short, intensive in-patient stays (interval rehabilitation) combined with six months home-based WBV training.

In this retrospective analysis we present the results for motor function after participation at the program 'Auf die Beine' (routine procedure of the German health care system) for patients with PMM2-CDG at baseline, after 6 months of home-based WBV training combined with intensive functional training and additional 6 months follow-up. The aim of this study was to assess the effect of a six-month interval rehabilitation treatment on motor function of children with PMM2-CDG syndrome.

Method

We performed a retrospective analysis of the data of children with CDG syndrome, who participated in the rehabilitation program 'Auf die Beine' of the Center for Prevention and Rehabilitation of the University of Cologne in the period 2006 to 2015. We collected the data from the prospective registry of the center http://www.germanctr.de (DRKS00011331). The study was approved by the Ethics Committee of the Medical Faculty of the University of Cologne (16-269). An agreement of the patients to the data collection was provided upon recruitment.

Study population

In total, 13 children, 9 girls and 4 boys, with CDG syndrome, aged from 3.2 to 17.3 years, were recruited in the rehabilitation program 'Auf die Beine' from 2006 to 2015. The population demographics are depicted in Table 1.

The rehabilitation program 'Auf die Beine'

The program 'Auf die Beine' was developed at the University of Cologne as a rehabilitation program for children with motor disorders, caused by various underlying conditions. The timeline of the program is depicted in Figure 1. The program includes intervals of inpatient stays combined with home-training.

It starts with a thirteen-day inpatient stay in the rehabilitation clinic, where patients receive different therapies for four hours per day, including multiple sessions of WBV training. Further, the children receive physiotherapy according to Bobath or Vojta, medical training therapy

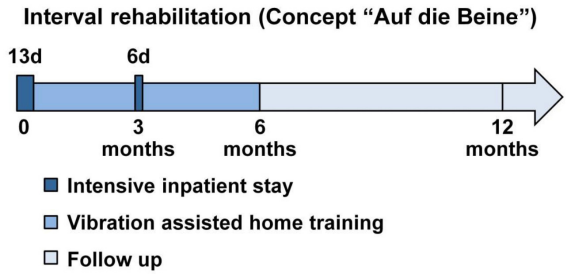

Figure 1. Interval rehabilitation concept 'Auf die Beine'.

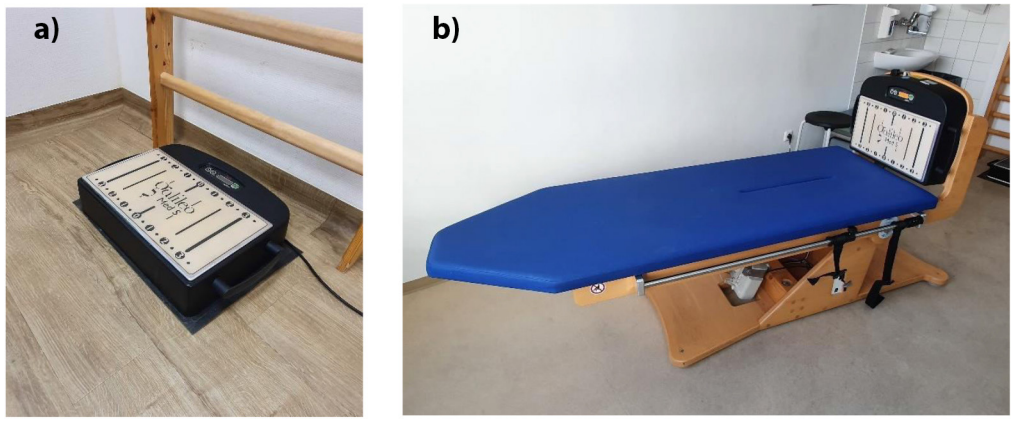

Figure 2. a) Standing vibration platform b) Vibration platform attached to a tilting table.

(MTT), treadmill, robot-assisted exercise, swimming and, if applicable, group therapy. During the first week of the stay, six different exercises on the whole body vibration system are individually chosen and practiced for each child, depending on the individual motor development skills and the goals of each child. The treating physician and physiotherapists in cooperation with the children and their caregivers set individual goals correspond to the WHO-ICF (International Classification of Functioning, Disability and Health). Often the goal is part of the chapter Mobility or Self-care of the Activities and Participation component. A goal must be specific, measurable, accepted, realistic and terminable[35]. The goals have a high relevance to everyday life.

In the second week, the children's caregivers are instructed in performing a WBV home-training with their child, consisting of these six exercises. At the end of the inpatient stay, each patient receives a WBV device and an individual training log, in which the individual WBV exercises are illustrated.

Home-training consists of 10 training units per week. Each unit consists of three of the six individual WBV exercises. An exercise of WBV lasts 3 minutes. The sessions can be carried out over the course of the week as suits the family. The caregivers shall report the daily home-training in the training log.

Three months later, in a six-day inpatient stay, the children receive a rehabilitation program, similar to one of the first stay. This stay further serves to monitor and improve the quality of home-training and to appropriately adjust the WBV exercises. The stay is also followed by a three-month WBV home-training.

In two outpatient visits at six (M6) and twelve months (M12) the staff of the center assesses motor changes using standardized tools further described at 'Assessments'.

WBV training

WBV training was performed on a Galileo® Med S standing vibration platform (Novotec Medical GmbH, Pforzheim, Germany), which has been described elsewhere (https://

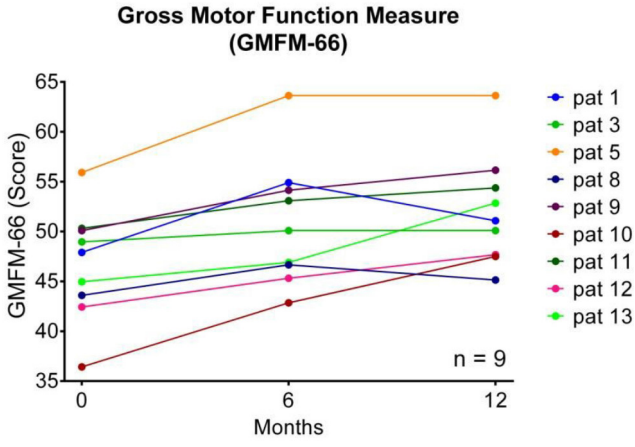

Figure 3. Gross Motor Function Measure (GMFM-66).

Table 2. Results GMFM-66 Score.

Pat - ID	sex	Age (years) M 0	Height (cm) M 0	Weight (kg) M 0	BMI (kg/cm²) M 0	GMFM-66 Score M 0	GMFM-66 Score M 6	GMFM-66 Score M 12	GMFM-66 Score M 6-0	GMFM-66 Score M 12-6	GMFM-66 Score M 12-0
Pat 1	w	5.0	96.5	13.3	14.3	47.9	54.9	51.1	7.0	-3.8	3.2
Pat 3	w	17.3	140.0	41.6	21.2	49.0	50.1	50.1	1.1	0.0	1.1
Pat 5	m	10.8	152.0	39.0	16.9	55.9	63.6	63.6	7.7	0.0	7.7
Pat 8	w	4.1	101.0	16.0	15.7	43.6	46.7	45.1	3.1	-1.5	1.5
Pat 9	m	6.2	117.0	21.3	15.6	50.1	54.2	56.2	4.1	2.0	6.1
Pat 10	w	3.2	94.0	12.6	14.3	36.4	42.9	47.5	6.4	4.7	11.1
Pat 11	w	3.4	88.5	12.6	16.1	50.3	53.1	54.4	2.8	1.3	4.1
Pat 12	w	3.7	96.5	12.9	13.9	42.4	45.3	47.7	2.9	2.4	5.2
Pat 13	m	3.4	90.0	12.4	15.3	45.0	46.9	52.9	1.9	5.9	7.9

www.galileo-training.com). Briefly, the device is 616 x 405 x 120 mm large and has 31 kg mass. The device can produce side-alternating vibrations with peak-to-peak displacement up to 7,8 mm within a frequency range of 5–27 Hz, Peak acceleration 11,4g (Figure 2a). The vibration parameters are manufacturer's data and have not been checked in practice.

The side-alternating movement of the device triggers spinal reflexes, leading to an improvement of the neuromuscular functions[28]. Different vibration frequencies are used to promote muscle strength (20-27Hz) or balance and coordination (5-12Hz)[36].

The vibration platform was placed on the ground. When it was necessary, the children used a wall bars or handholds to facilitate balance control.

Children who cannot stand, or be completely verticalized, are training on a WBV system attached to a tilting table, which can be raised up to 90° (Figure 2b). Frequencies were set individually, magnitude was constant. Each child performed individually determined exercises in different positioning, static as well as partly dynamic. The position of the feet on the platform during the vibration was on midfoot or on forefoot. The exercises were performed with flexed joints, especially knee and elbow joints. Predominantly the feet were most subjected to vibration. The exercises were performed with orthoses, shoes or barefoot. To prevent fidding of the feet, some children used an anti-slip mat. Preparatory exercises or warm-up prior to the vibration was not necessary. Some children had previous experience with WBV. The description was made in accordance with the Reporting Guidelines for Whole-Body Vibration[37].

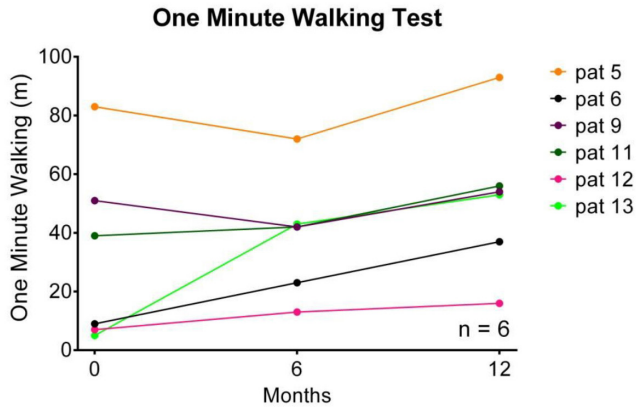

Figure 4. One Minute Walking Test.

Table 3. Results One Minute Walking Test.

Pat - ID	sex	Age (years) M 0	Height (cm) M 0	Weight (kg) M 0	BMI (kg/cm²) M 0	1MWT (m) M 0	1MWT (m) M 6	1MWT (m) M 12	1MWT (m) M 6-0	1MWT (m) M 12-6	1MWT (m) M 12-0
Pat 5	m	10.8	152.0	39.0	16.9	83	72	93	-11	21	10
Pat 6	m	16.6	167.5	58.6	20.9	9	23	37	14	14	28
Pat 9	m	6.2	117.0	21.3	15.6	51	42	54	-9	12	3
Pat 11	w	3.4	88.5	12.6	16.1	39	42	56	3	14	17
Pat 12	w	3.7	96.5	12.9	13.9	7	13	16	6	3	9
Pat 13	m	3.4	90.0	12.4	15.3	5	43	53	38	10	48

Assessments

Assessments were performed at start (during the first inpatient stay), at 6 months after training and after 12 months (follow-up). Following assessments were used: 1. The Gross Motor Function Measure (GMFM-66), a five-dimension tool assessing lying, turning, running, jumping and crowling validated for children with cerebral palsy[3839]. 2. The One minute walking test (1MWT), a test assessing walking capacity, as well as a gait analysis by measuring ground reaction forces, to assess the patients' motor skills and their changes[40]. 3. The mechanographic gait analysis is carried out on a six-meter-long gangway (Leonardo Mechanography Gangway, Novotec Medical GmbH, Baden-Württemberg, Germany) using an automatic, software-based motion analysis (Leonardo Mechanography GW RES Software Version 4.2.b06.01e, Novotec Medical GmbH, Baden-Württemberg, Germany) and collecting a variety of functional parameters, such as pace length, speed, weight transfer on the legs and the pathlength/distance ratio[41]. The last parameter measures the deviation of the center of gravity from the target direction when walking, and can depict changes in the coordination, steadibility and gear efficiency. The expected ratio in healthy individuals is 1.0 - 1.1.

Statistical analysis

We applied an intra-individual control design in which individual patients formed their own control group. The various test parameters were collected at the beginning of the therapy (M0), at the end of the six-month training (M6) and in a six-month follow-up (M12). We used the Wilcoxon matched-pairs signed rank test was used to calculate the significance of changes ($p < 0.05$).

Results

Thirteen children with PMM2-CDG completed the baseline visit (M0) since 2006.

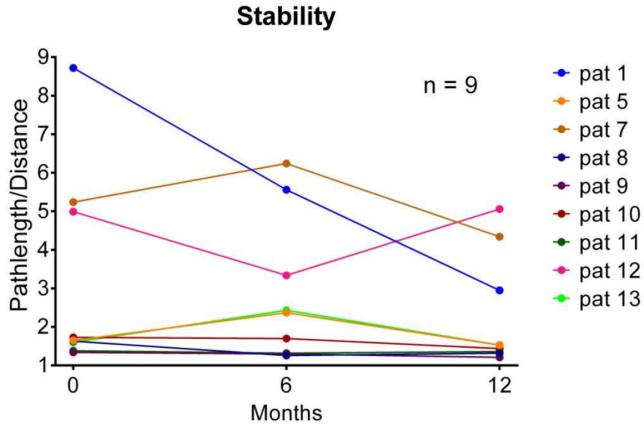

Figure 5. Stability.

Table 4. Results Gangway (Pathlength/Distance).

Pat - ID	sex	Age (years) M 0	Height (cm) M 0	Weight (kg) M 0	BMI (kg/cm²) M 0	Path. Length/ Distance M 0	Path. Length/ Distance M 6	Path. Length/ Distance M 12	Path. Length/ Distance M 6-0	Path. Length/ Distance M 12-6	Path. Length/ Distance M 12-0
Pat 1	w	5.0	96.5	13.3	14.3	8.72	5.56	2.95	-3.16	-2.61	-5.77
Pat 5	m	10.8	152.0	39.0	16.9	1.65	2.37	1.53	0.72	-0.84	-0.12
Pat 7	w	14.8	125.0	26.3	16.8	5.24	6.24	4.34	1.00	-1.90	-0.90
Pat 8	w	4.1	101.0	16.0	15.7	1.63	1.26	1.32	-0.37	0.06	-0.31
Pat 9	m	6.2	117.0	21.3	15.6	1.34	1.30	1.21	-0.04	-0.09	-0.13
Pat 10	w	3.2	94.0	12.6	14.3	1.73	1.70	1.44	-0.03	-0.26	-0.29
Pat 11	w	3.4	88.5	12.6	16.1	1.38	1.32	1.36	-0.06	0.04	-0.02
Pat 12	w	3.7	96.5	12.9	13.9	4.99	3.34	5.06	-1.65	1.72	0.07
Pat 13	m	3.4	90.0	12.4	15.3	1.60	2.43	1.53	0.83	-0.90	-0.07

Among these 13 patients, GMFM-66 was performed thrice in 9 patients (MO, M6, M12). The children showed a mean improvement of 4.1 points (SD 2.3) at six months (p=0.0039). At M12, 7 of the 9 children showed a further improvement (mean difference M12-MO 5.3 points, SD 3.2, p=0.0039) (Table 2, Figure 3).

The 1MWT was performed in six children (MO, M6, M12). Among them, four showed an improvement at six months and two showed a decrease (mean improvement 6.83m, SD 17.9, p=0.56), but all of them could improve at 12 months (mean difference M12-MO 19.18m, SD 16.5, p=0.0313) (Table 3, Figure 4).

The gait analysis was performed on all 13 children. We evaluated the parameters steplength thrice (MO, M6, M12) on all 13 children, speed on eight children and pathlength/distance on nine children. In M12 compared to MO, we found a statistically significant mean improvement in pathlength/distance of 0.8 (p=0.0195) (Table 4, Figure 5).

Discussion

The GMFM-66 showed an improvement in all 9 patients with PMM2-CDG syndrome measured after 6 months and the improvement could be further increased during the following six-month period without WBV (M12). At the time of the 12 months follow-up six children of this group showed further improvement. The remaining three children stayed stable or showed a little decrease to M6 but increase to MO. One

girl (patient 8 in Figure 3) showed very little cooperation in M12, so that her performance probably does not reflect her maximum abilities at the time. The GMFM-66 has been developed and validated for children with cerebral palsy[38,39]. This well-proven test is equally well-suited to children with CDG syndrome, because even these children may have motor limitations in all five categories of the test procedure similar to children suffering from cerebral palsy.

Four out of six children showed an increase in the walking capacity at M6, assessed by the 1MWT. Noteworthy is a further increase during the follow-up without additional WBV training, which was found at M12 in all six children, including patients 5 and 9 (Figure 4).This can be argued as a further improvement of the acquired motor ability after the first six months by using the new skill in all day living situations. For instance, learning to walk or walking safely is the primary goal in the majority of children with PMM2-CDG. The long-term improvement of walking capacity in the M12 showed that after six months of intensive home training, the children had formed a basis that enables them to build on it continuously in everyday life by applying the newly achieved skills in the follow-up period. These observations were also reflected in the results of the gangway analysis.

Patients with PMM2-CDG are affected to varying degrees of severity in terms of their motor impairment and therefore also differ in their development over time. The course is not uniform[12]. Overall, PMM2-CDG can be classified as a progressive disease with regard to motor skills up to around the age of 16.

Individual patients have shown stable results in some assessments after 12 months in our therapy concept. Whether this can already be seen as a positive therapy effect cannot be assessed with certainty due to the lack of a control group.

Overall, we consider our rehabilitation program to be an effective therapy, especially given the progressive course of the disease.

WBV training uses the monosynaptic reflex through muscle stimulation and has a positive effect on muscle strength and coordination[42]. A vibration plate transmits the vibrations to the person who trains on it. The vibrations trigger reflex-based muscle contractions[32,33]. A typical WBV session takes 3x3 minutes (3 exercises à 3 minutes) at a frequency of 20 Hz. This creates 10.800 mechanical impulses to the involved muscles (similar to three hours of walking)[27]. So, it comes to faster gain of muscle function. WBV seems to increase the bone mineral density in children and adults, who have compromised bone mass, while postmenopausal women only have small or none benefit[43].

So far, the efficacy of WBV has been demonstrated in children with cerebral palsy[44], osteogenesis imperfecta[45], spina bifida[46], Down syndrome[42] and spinal muscle atrophy[31].

Another study of our working group has depicted the positive effect of the Cologne rehabilitation program “Auf die Beine” in a cohort of 46 children with progressive and non-progressive ataxia[47]. Significant improvement of motor skills and walking capacity was seen in both groups at M6[47]. Stark et al. (2018) described a positive effect of the Cologne rehabilitation program on children with spinal muscle atrophy type II and III. The Gross Motor Function Measure showed an increase of 1.7 (3.7) points (P=0.124) and the Hammersmith Functional Mobility Scale a significant increase of 2.73 ± 1.79 points (P=0.007) after 12 months[31]. Hoyer-Kuhn et al. depicted children with osteogenesis imperfecta, who improved their motor functions (GMFM-66, walking capacity). In addition they showed an increase of the bone mineral density[45].

Regardless of the difference of etiologies, all those children show a limited ability to use their muscles intensively. This muscle inactivity is counteracted by using our treatment that includes intensive WBV.

There are no studies reporting the effect of physiotherapy in children with PMM2-CDG.

The patients with PMM2-CDG syndrome also suffer from ataxia, caused by cerebellar hypoplasia, muscular hypotension and psychomotor retardation. These symptoms are also typical for children suffering from progressive and non-progressive ataxia respectively M. Down and even for cerebral palsy. Therefore, it does not seem surprising that we could observe the positive results, we described above.

Limitations

The number of patients is small and there was no control group.

Some assessments could not be always performed on all patients in clinical practice. Some reasons include lack of cooperation of the child, lack of time, missing walking splints, since the 1MWT and the gait analysis should always be conducted using the same aids, etc. The assessments were not validated for patients with CDG syndrome. There is a Score ICARS as a quantitative assessment for children with ataxia that also is valid for children with CDG-syndrome[48]. So far we do not use it in our clinic, because the majority of our patients suffer from cerebral palsy. So the physiotherapists have most experiences with carrying out the GMFM66. In our opinion, a great routine of therapists in carrying out the test procedure is of particular importance for maximum comparability. However, we will soon incorporate the ICARS in our test routine. Apart from WBV, other physiotherapeutic means were used during the three-week inpatient stay. Further, the standard care, including for instance outpatient speech therapy or physiotherapy, were performed continuously and were not paused during the intensive rehabilitation treatment.

Conclusion

The Cologne rehabilitation program “Auf die Beine” effectively improved motor skills, walking capacity and stability in children with PMM2-CDG syndrome. This is very remarkable, considering the natural progressive course of the disease, with expected loss of motor skills. Since causal treatment is not an option, this supportive treatment

presents a serious offer to improve patients' motor skills. Future studies should confirm if repetition of such a treatment may achieve further motor improvement and thus, if the progressive course of the condition could be slowed down.

Ethics approval

The study was approved by the Ethics Committee of the Medical Faculty of the University of Cologne (16-269).

Consent to participate

An agreement of the patients to the data collection was provided upon recruitment.

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