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Research Article

Preliminary Recommendations for a Literature-Based Physiotherapeutic Concept for Children and Adolescents with Chemotherapy-Induced Peripheral Neuropathy

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Article Information

Received date: Jul 03, 2018
Accepted date: Aug 16, 2018
Published date: Aug 20, 2018

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Keywords Chemotherapy; Children; CIPN; Physical therapy

Abbreviations ALL: Acute Lymphoblastic Leukemia; CIPN: Chemotherapy-Induces Peripheral Neuropathy; CTCAE: Common Terminology Criteria for Adverse Events; Ped-mTNS: Pediatric-modified Total Neuropathy Scale; ROM: Range of Motion; WBV: Whole Body Vibration

Abstract

Chemotherapy-Induced Peripheral Neuropathy (CIPN) is one of the most concerning side-effect of chemotherapeutic agents and is known to cause loss of sensation, muscle weakness, deficits in balance, neuropathic pain as well as autonomic symptoms. It can lead to a reduced participation in activities of everyday life and a decreased quality of life. Physical therapy offers one possibility to approach these problems. The overall purpose of this paper was the development of a literature-based physiotherapeutic strategy for the treatment of CIPN in children and adolescents.

Methods: For concept construction a literature search in the medical databases MEDLINE, the Cochrane library, PEDro, CINAHL and Embasewas performed. Results have been reviewed and assessed according to their applicability to pediatric CIPN patients.

Results: Most studies found in the literature were conducted with adults or childhood cancer patients with no specifically diagnosed CIPN. No study could be found explicitly examining physical therapy options for CIPN in children and adolescents. The concept consists of twelve age- and severity-adapted therapy settings and is designed for children and adolescents between the ages of 2-17 years.

Conclusion: The proposed physiotherapeutic strategies are the first step towards an evidence-based approach in the treatment of CIPN symptoms in children and adolescents. According to literature, sensorimotor training seems to have the highest potential to improve CIPN symptoms. Further, some studies support evidence for foot bathing, exercises for strengthening and stretching as well as vibration therapy.

Introduction

Chemotherapy can influence the human organism in many ways. Cytostatic agents destroy cancer cells and have numerous negative side-effects at the same time. One of most clinically relevant side-effects associated with therapy is Chemotherapy-Induced Peripheral Neuropathy (CIPN). Considering the increasing number of longtime survivors [1], the rehabilitation of CIPN gets more and more important. Making a full recovery is especially important for children because symptoms of neuropathy constitute a high risk for developmental disorders and secondary diseases. The use of chemotherapeutic agents such as platinum derivatives, vinca alkaloids, taxanes or newer antibody-based forms can lead to neuronal damages on cell bodies as well as on axons. Particularly Vincristine and its wide-spread application in pediatric oncology is known for its cytotoxic effect on nerves with the consequence of an abnormal axonal transport [2]. Symptoms can range from positive symptoms including allodynia, hypersensitivity, paresthesia and pain to negative symptoms such as the loss of vibration sense, reduced proprioception, ataxic gait, muscle weakness as well as the loss of coordination and declining reflexes [2]. Moreover, survivors of Acute Lymphoblastic Leukemia (ALL) show higher inactivity levels than comparable groups, which can lead to an increased risk of cardiovascular diseases even as a long-term effect [3]. An early physiotherapeutic intervention is therefore indicated to facilitate age-appropriate development, improve the quality of life as well as minimize long-term damages. In fact, a published physiotherapeutic concept for the treatment of pediatric CIPN does not exist yet [4]. Therefore, the overall objective of this paper was the development of a literature-based concept for the treatment of children and adolescents with CIPN.

Methods

The concept developed is based on a literature search in the electronic databases MEDLINE via PubMed and Livivo, The Cochrane Library, PEDro, CINAHL and Embaseusing the terms

Table 1: Inclusion criteria.

Types of studies	Randomized Controlled Trials (RCT), Clinical Controlled Trials (CCT), Controlled Trials (CT), Journal articles, Reviews
Date of publication	2000 to January 2018
Languages	English, German
Patients	Children, adults
Intervention	Physiotherapeutic interventions for the treatment of neuropathy symptoms

Chemotherapy induced peripheral neuropathy and all its synonyms, children, pediatric * exercise and physical therapy which were combined (AND) in various ways. In addition, a hand search of reference lists was performed. MeSH-Terms applied were Leukemia, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Neurotoxicity Syndromes/therapy, Child*, Infant, Adolescent, Exercise*, Physical Therapy Modalities and Exercise Therapy.

As an initial step, titles and abstracts of the resulted studies were screened using the criteria mentioned below. Further, a full text screening of potentially relevant studies was performed to identify the final number of studies used for this work. Tables 1 and 2 show an overview of the eligibility criteria applied. Adults were intentionally included to broaden the spectrum of the study. For a quality review of the papers PEDro Scale, a rating tool for clinical trials from the Centre of Evidence-Based Physiotherapy, was applied. Hereby, a maximum Score of 11 can be reached while a higher score implicates a higher evidence level (Tables 1 and 2).

Results

In total, the literature search yielded 801 results, whereof 16 studies were identified as relevant. Eight of these 16 studies analyzed pediatric patients. Two publications [14,15] conducted studies on children with ALL and physical deficits caused by CIPN, five [19-23] examined the potential of exercise programs regarding the reduction of symptoms in patients with ALL or other forms of childhood cancer but not specifically CIPN and one [11] examined the effect of Whole Body Vibration (WBV) on bone mineral density among childhood cancer survivors. The focus was not intentionally set on ALL but is explained by the high and clinically relevant number of ALL in pediatric cancer patients. Other studies did not differ between the diagnosis but can also potentially contain patients with other common types of childhood cancer. None of these have examined physiotherapeutic interventions specifically for the treatment of CIPN in children and adolescents. Because of lacking pediatric studies, examinations with adult CIPN patients were also included in this work. Hereby, all reviewed studies that concentrated on adults [5,6,9-10,12,16-18] described physiotherapeutic treatment options for CIPN (massage, foot bathing/massage, sensor motor and exercise training, WBV). An overview of the included studies sorted by children and adults shows table 3.

Study evaluation

Different authors have been investigating the effect of massage, foot bathing/massage, vibration therapy, exercise programs, sensor motor training on CIPN or assumed CIPN-related physical deficits caused by chemotherapy.

Massage

So far, there is only a single case study conducted by Cunningham et al. [5] which examined the effects of massage in a 45-year old patient who had been treated with Docetaxel and Cisplatin and developed CIPN (Grade 2 of the Common Terminology Criteria for Adverse Events). The patient received massage treatments three times a week over a period of six weeks. Each massage lasted about 45 minutes while two therapists worked on the patient simultaneously. The main part consisted of initial Effleurages, followed by Petrissages. At the end of the evaluation period, the symptoms had been reduced from grade 2 to grade 1, the patient was pain-free and formication and numbness had decreased while the temperature in fingers and toes had increased. Total change in pre-treatment temperature (after 10-15 minutes of acclimatization just before the treatment began) from baseline to the last treatment was +8.5°C and 8.7°C in the hands and +2.1°C and 2.4°C in the feet. The patient stated to feel warmth in his limbs for the first time since the beginning of chemotherapy. Even three months after therapy, the symptoms remained unchanged, except for a little pain returning. The author assumes that massage is the reason for the improved blood circulation. This allows for a more efficient nutrient communication and, consequentially, a faster removal of neurotoxic substances as well as a faster regeneration of nerve damage. But to confirm these findings more well-designed studies with bigger sample sizes are needed.

Foot massage and bathing

Likewise, only little study material exists on foot massage and bathing and its effect on CIPN symptoms. A quasi-experimental study from Park & Park [6] tried to find out whether foot massage or foot bathing is more effective. For this, 48 patients were assigned to one of two groups and received over a period of two weeks eight treatments of 30 minutes of either foot bathing or foot massage. The authors' conclusion was that foot baths show better results than foot massages regarding increasing skin temperature, grade of neurotoxicity and quality of life. While in the foot bathing group

Table 2: Exclusion criteria.

General	Not fulfilling the inclusion criteria
Intervention	Main treatment with drugs, non-physiotherapeutic interventions, electrotherapy, other forms of neuropathy (e.g. diabetic neuropathy)
Publication	Non-scientific forms of publications
Quality	Insufficient replicability because of poor methodological quality

the foot skin temperature was increased significantly by 0.80°C during the first session and by 1.00°C during the eighth session, it was increased in the foot massage group only by 0.09°C during the first session and by 0.14°C during the eighth session. Further, 25% of the patients of the foot bathing group reported an improvement in symptoms, while in the foot massage group only 8.3% stated that symptoms improved. General quality of life, assessed by the Functional Assessment of Cancer Therapy-General (FACT-G), also tended to increase in the foot bathing group from 62.75 (±11.29) to 65.33 (±12.96), while it significantly decreased in the foot massage group ($p<0.001$). However, the study did not compare the results to a control group due to lacking CIPN cases, but which is an important limitation of this investigation.

Whole body vibration (WBV)

Another proposed way of reducing symptoms of CIPN is vibration therapy. The oscillating force effect elongates the muscle-tendon complex through stretch reflexes. Thus, the muscle-tendon complex of the gastrocnemius muscle elongated by about 1% when exposed to a vibration of 6Hz [7]. Streckmann et al. recommend for adult's frequencies between 10 and 15 Hz for muscle relaxation and frequencies over 18 Hz for training purposes [8]. Whether these data are also valid for children and adolescents is unclear. Moreover, the authors assume in their review that vibration training affected gait, pain and atrophied muscles positively and improved the isometric force and postural control. In addition, Rittweger also emphasis potential benefits of WBV and recommend it even for pediatric patients with CIPN but could not provide results from studies with children [7]. Schonsteiner et al. [9] show similar results with adult patients and recommend WBV as part of an integrated program. In their study with 131 CIPN patients WBV took place next to massage, mobilization and physical exercises and was significantly associated with a higher reduction of time needed for the Chair Rising Test (CRT) ($p=0.02$) which implicates an improved physical fitness and coordination. Additionally, the warm detection-threshold has also improved significantly ($p=0.02$).However, the results of the review from Verhulst et al.[10] which focused the influence of WBV on the parameters strength, balance and pain in adult patients with CIPN suggest an insufficient amount of evidence as the overall methodological quality was low. Four out of five reviewed studies scored 0-4 on the PEDro scale and one scoring 7. No consistent effect of WBV on pain was found. Nevertheless, positive effects regarding an improvement of strength and balance performance could be described. Because of lacking studies with pediatric patients,

Table 3: Summary table of the included studies.

Authors (PEDro-Score)	n	Study type	Outcome	Disease	Intervention
CHILDREN					
Hartmann et al. (2008) (5/11) [14]	247	Case-Control-Study	Muscle strength, ROM, motor performance	ALL, Wilms tumor, B-non-Hodgkin lymphoma, malignant mesenchymal tumors	No intervention
Moyer-Mileur et al. (2009) (7/11) [21]	13	Randomized controlled Trial	Anthropometrics, dietary intake, cardiovascular fitness, physical activity	ALL	Training program consisting of aerobic, muscular, flexibility, recreational sports and lifestyle activity
Marchese et al. (2004) (10/11) [19]	28	Randomized Controlled Trial	Knee extension and ankle dorsiflexion strength, ROM, endurance capacity, quality of life	ALL	5 therapy sessions + home program (stretching, strength training, aerobic fitness)
Hartmann et al. (2009) (10/11) [20]	51	Randomized Trial	Bone mineral density, ROM, motor performance	ALL	exercises for hand and leg function + stretching and jumping exercises
Wright et al. (2005) (5/11) [15]	188	Cross-sectional study	Balance, physical activity, health-related quality of life	ALL	No intervention
Mogil et al. (2016) (10/11) [11]	65	Double-blind randomized clinical trial	Bone mineral density	Child-hood Cancer	WBV
Rustler et al. (2017) [22]	204	Review	Effects of inpatient exercises	Child-hood Cancer	Exercise interventions (aerobic, strength, balance training, stretching)
Beulertz et al. (2015) (6/11) [23]	33	Explorative study	Motor Performance, Level of Activity, Quality of Life	Child-hood Cancer	Endurance, strength and coordination exercises
ADULTS					
Cunningham et al. (2011) [5]	1	Single case study	Pain, temperature in hands/feet, formication, numbness	CIPN	Massage therapy
Park &Park (2015) (7/11) [6]	48	Quasi-experimental study	Skin temperature, grade of neurotoxicity, calcium and magnesium plasma, quality of life	CIPN	Foot massage and bathing
Streckmann et al. (2014) (8/11) [12]	61	Randomized Controlled Trial	Quality of life, peripheral neuropathy, activity level, balance control	CIPN	Sensorimotor/ endurance/ strength training
Verhulst et al. (2015) [10]		Review	Strength, balance, pain	CIPN	WBV
Schönsteiner et al. (2017) (7/11) [9]	131	Exploratory phase-2 study	Physical fitness, coordination	CIPN	WBV + massage, mobilization, physical exercises
Kleckner et al. (2018) (8/11) [17]	355	Randomized controlled trial	Hot/coldness in hands/feet, numbness, tingling	CIPN	EXCAP (Exercise for Cancer Patients: progressive walking and resistance exercise program)
Zimmer et al. (2018) (10/11) [18]	30	Randomized controlled trial	Strength and balance function	CIPN	Endurance, resistance, balance training
Tofthagen et al. (2012) (4/11) [16]	3	Interventional study	Strength, balance, TUG, mCTSIB, DGI, neuropathic symptoms	CIPN	Balance and strength training

the scientific support for WBV as additional treatment option for children with neuropathy symptoms is weak; anyhow one can assume that WBV contains some positive effects at least for balance and strength parameters. Further, as a positive side effect an increasing Bone Mineral Density (BMD) can be seen in young childhood cancer survivors [11].

Sensorimotor training

Sensorimotor Training (SMT) seems to be one of the most promising therapy options for the treatment of CIPN symptoms [8,12,13]. A trial from Streckmann et al. of moderate methodological quality (scoring 8 on the PEDro scale) examined 30 adult Lymphoma-patients completing a 36-week training program. Each training session lasted one hour and was performed twice a week. The program consisted of four strengthening exercises with a Thera-Band®, an aerobic activity for 10-30 minutes and SMT with exercises for balance with an increasing level of difficulty and unsteady ground. Positions were held for 20 seconds, repeated three times with breaks of at least 20 seconds between the different exercises. At the end of the evaluation period, the quality of life ($p=0.03$) and balance performance of the Intervention Group (IG) significantly improved accompanied by an increased activity level, whereby 87.5% of the intervention group showed less symptoms of polyneuropathy ($p<0.001$). The data of the Control Group (CG) remained stable over a longer period and even decreased. Moreover, the level of aerobic performance ($p=0.05$) as well as the additional amount of exercises that were carried out at home ($p=0.02$) differed significantly between the two groups in favor for the IG. The authors assume that neuroplasticity plays an important role in explaining the positive results of SMT. Through this, the receptor density increases, while inactive neurons are activated, and the excitability threshold decreases. Furthermore, the results are especially linked to the SMT and cannot be reached solely through aerobic or strengthening training [12].

Exercise programs

Children suffering from chemotherapy-related side-effects show compared to healthy peers several physical deficits in form of a decreased peripheral muscle strength and ankle dorsiflexion, reduced wrist dorsiflexors on the non-dominant side and pinch grip on both sides [14]. Moreover, deficits in balance are detectable which are furthermore associated with a lower physical activity and a reduced health related quality of life [15]. Exercise programs may address these problems and consist of various strengthening, mobilization and stretching exercises. As a study conducted by Tofthagen et al. [16] shows, exercise programs seem to have high potential regarding improvements of CIPN-associated symptoms. Three adult participants who underwent a 12-week lasting therapy program mainly consisting of a bi-weekly 35 to 50-minute balance and strength training gained improvements in strength, balance and neuropathy after four weeks and continuing improvements over time. Kleckner et al. [17] investigated 355 adult cancer patients receiving taxane, platinum, or vinca alkaloid-based chemotherapy and were randomized either to a control group just receiving chemotherapy or chemotherapy plus EXAP (Exercise for Cancer Patients), a six week-lasting home-based exercise program. All patients reported worse CIPN-symptoms after six weeks of chemotherapy, however, the exercise group showed significant smaller increases in CIPN severity. For the numbness and tingling the change for controls was greater ($p=0.003$) than for exercisers ($p=0.027$). The same is true for hot/coldness (exercise group: $p=0.022$; controls: $p<0.0001$). Supporting effects of exercise training on CIPN have been also reported by Zimmer et al. [18] where 17 adults with metastasized colorectal cancer underwent an eight-week supervised exercise program, including endurance, resistance and balance training (CG: n=13 received written standard recommendations for physical fitness). While neuropathic symptoms remained stable in the IG it significantly worsened in the CG. Further, the IG improved their strength and balance function, no significant differences were found regarding endurance capacity.

In children with ALL (aged 4-18 years), induced by CIPN, Marchese et al. [19] diagnosed a reduced active ROM of the ankle dorsiflexors and a decreased knee extension force. To address these problems, the patients completed five therapy sessions, each lasting 20 to 60 minutes, and an exercise program at home containing functional exercises. In addition, they had to perform exercises such as bilateral stretching of the ankle dorsiflexors five days a week, held for 30 seconds, as well as three sets of ten repetitions of strengthening exercises for the lower limbs three times a week, and aerobic fitness (walking, biking or swimming) every day for four months. At the end of the therapy, the intervention group showed significant improvement regarding the active ROM of the dorsiflexors as well as an increased force of the knee extensors ($p<0.01$), whereas the values of the control group remained stable.

Hartmann et al. [20] had 25 children with ALL complete a physiotherapeutic program at home over a period of two years, accompanied by therapy sessions every six weeks in which motor abilities were assessed and the exercises adapted. The program consisted of daily exercises for hand and leg function, stretching exercises for ankle mobility as well as short-burst high-intensity exercises every day, e.g. jumps, twice a day. In contrast, the control group received a standard care without additional therapy sessions. Both groups reached motor improvements ($p=0.055$), although the intervention group did not achieve as good a result. Both groups stayed below the level of healthy peers and their passive ankle mobility decreased significantly ($p=0.001$). Another study from Moyer-Mileur et al. [21] investigated 13 children with ALL, aged four to ten years, completing a one-year lasting training program. In comparison to the control group, the activity level of the intervention group increased significantly ($p=0.05$) and they showed an improved cardiovascular fitness ($p=0.06$).Comparable positive influence on motor performance, level of activity and Quality of Live (QL) of childhood cancer patients found Beulertz et al. [22] in their investigation of a 6-month group-based therapeutic exercise program. Here, 20 out of 33 childhood cancer patients (CG1: 13) underwent a supervised exercise program including endurance, strength training and coordination exercises while each session took place once a week and lasted 60 minutes. The results show improvements in terms of motor performance, emotional well-being and overall level of activity in favor for the IG. Additionally, a review from Rustler et al.[23] confirms these findings and comes to the conclusion that exercise programs can safely and effective be implemented in inpatient acute care of pediatric cancer patients and shows no intervention-related adverse events.

Table 4: Table for defining the right therapy setting.

	Degree of severity I	Degree of severity II	Degree of severity III
Age Group A(2-5)	Therapy Setting AI	Therapy Setting AII	Therapy Setting AIII
Age Group B(6-9)	Therapy Setting BI	Therapy Setting BII	Therapy Setting BIII
Age Group C(10-13)	Therapy Setting CI	Therapy Setting CII	Therapy Setting CIII
Age Group D(14-17)	Therapy Setting DI	Therapy Setting DII	Therapy Setting DIII

Concept

Summarizing findings of the literature

Physical therapy does not only consist of one kind of therapy. Moreover, within its wider definition it contains various methods which facilitate physical wellbeing. Thus, in this context vibration therapy as well as exercise and sensorimotor training next to massage or manual therapy as well-known applications also belongs to physical therapy and were therefore investigated. Most promising therapy option seems to be sensorimotor training even though no study with pediatric CIPN patients was conducted until now. Furthermore, several exercise programs have been tested, which mostly consist of a mix of endurance, strength training and stretching exercises. Studies show a higher reduction of symptoms for the intervention group than controls why these results can be interpreted as beneficial for pediatric cancer patients. In addition, WBV can be assumed to bring some positive effects with it, e.g. optimized bone mineral density, improved functional fitness, coordination, strength and balance. However, the level of evidence is inconsistent and weak and only valid for adults. As physical deficits are complex, a multidimensional approach is required. Therefore, the following proposed strategy not only focus on one special therapy type but tries to combine the applications found in the literature and transfer it to pediatric patients.

Transfer and concept development

Because none of the above-mentioned studies examined physical therapy in pediatric CIPN and therefore could provide a definite answer, the concept is based on the transfer of interventions that have already been tested with adults. Transfer in this context means that the described therapy options aren't identically with the methods tested with adults but modified for children and adolescents. To meet pediatric patients' needs, the concept also takes into consideration what children with physical deficits suffering from CIPN are subjected to, e.g. strength and balance deficits. Therefore, the therapy strategy also contains own ideas which were not tested yet with children or adolescents with CIPN. Moreover, CIPN can cause various individual and age-related needs and the motor and cognitive performances of children affected can vary strongly. Therefore, a differentiated approach is required. To meet the requirements, the concept is divided into twelve therapy settings. Table 4 (containing the variables age and degree of severity) shows which therapy setting is most suitable. In this context, degree of severity tries to rate how severe the patients' clinical symptoms are (Table 4).

For six- to seventeen-year-olds, the degree of severity can be measured via the Pediatric-modified Total Neuropathy Scale (Ped-mTNS) [24] or optionally with the help of the Common Terminology Criteria for Adverse Events (CTCAE). In the Ped-mTNS, a maximum score of 32 can be reached, while a higher value implicates a more severe status. For a better differentiation, children are assigned to one of three gradations of severity depending on their individual score. Hereby, a division into three equal-sized grades of severity appears reasonable because of the continuously increasing severity among higher scores. Thus, the first and lowest degree is defined by a score from 0-10, the second from 11-21 and the third from 22-32. The CTCAE allow a faster assessment and the grades are analogue to the degrees of severity while grade 3 and 4 both corresponds to the third degree of severity. In fact, there exist five grades of the CTCAE, however, the last one is clinically irrelevant because it means death and is therefore not measurable. For two to five-year-old one needs to draw on other methods (Table 5), because the Ped-mTNS is only valid for children and adolescents in school age [24] and the CTCAE is no adequate way of assessing children of this age group (Table 5).

Next to clinical symptoms and the Ped-mTNS, patients within a controlled clinical trial at a German hospital which investigates this concept undergo some more assessments that can also be used for follow up measures. These include an electrophysiological testing of small and large nerve endings via a quantitative sensory testing for diagnosing CIPN. In addition, the neurological status can be accessed through a clinical testing and the International Cooperative Ataxia Rating Scale (ICARS). For analyzing genetic disposition for an increased chemotherapy-sensibility blood is taken from the children. Further, handedness can be determined with help of the Edinburgh Handedness Inventory (EHI), and cognition with the Wurzburg

Table 5: Diagnostic options for two to five-year-old.

Outcome	Method of measuring
Sensibility	Pinprick and light touch sensation
Pain	Visual analogue scale (VAS) with faces that reflect the emotional state
Perception of vibrations	128 Hz tuning fork; Application on the big toe, medial malleolus, the distal interphalangeal joint of the second finger, the ulnar styloid and the medial epicondyle
Reflexes	Achilles- and Patella-tendon-Reflex
Joint mobility	Passive and active ROM with special focus on the ankle joint
Strength	Muscle function testing (MFT) according to Janda
Balance and coordination	One leg stand, Tandem gait on a line, finger-finger/finger-nose-coordination

Ultrakurztest (WUEP-KD). Fine-motor skills are tested in form of writing and drawing tasks on a digital writing tablet, coordination and fine-motor skills with the Perdue Pegboard (PP) Test. A hand dynamometer is used for measure strength of both hands. To examine function of the lower extremities Timed Up and Go test (TUG) as well as Timed Floor to Stand test (TFTS) are applied. Endurance capacity is quantified through the 6-Minutes-Walking-Test (6MWT).

The structure of the settings is similar. Each contains interventions for improving sensibility and reducing pain, exercises for strengthening and joint mobility as well as sensorimotor/ balance exercises. Hereby, the concept is more a guideline than a strict therapy program. It is important that the therapist chooses the intervention options based on the individual needs of their patients as this is the case for e.g. patients with pronounced allodynia. Therapists then can choose more slightly and soft methods instead of intensive and painful stimuli such as a spiky ball-massage. This also gives the therapists space for their own ideas and skills because know-how and equipment differ locally. The difference between the three severity levels is that grade I concentrates on less severe symptoms than II and III do. In most cases, thin (sensory) fibers are affected first, and then thicker (motor) ones, with a special emphasis on distal regions in the beginning. Grade III implicates more severe (motor) problems even in proximal regions.

Therapy setting AI-III: This age class includes the youngest patients, in which ALL is most prevalent. In general, the therapeutic interventions are designed like games to motivate the children. To activate the foot muscles for example, the children can shred newspaper or try to grab objects with their feet. Furthermore, it is partly possible to use slight resistance for training purposes, e.g. with a Thera-Band®. To improve sensibility, the children can dabble in water with their feet or hands, possibly with a ball, walk through a barefoot pathway or the therapist can massage the patient's feet or hands with a spiky ball. Moreover, sensorimotor training can be applied throughout all age classes, for two- to five-year-old also in a game setting, e.g. "the jungle-course" or "the ice floe game", during which the children must prove their balance performance. To intensify the therapy in very severe cases, the concept also suggests respiratory therapy, gait training and interventions to prevent pneumonia.

Therapy setting BI-III: The transition to the previous age group is fluent. Only motor and cognitive status developed further so that the exercises require an advanced level. To improve sensibility and balance performance, for instance, the children were tasked to identify objects with their feet, grab them and put them into a box next to them. However, the therapy setting BI-III is still very playful, so therapy is "hiding" within the scope of various games, for example "The one-legged captain", "Flight from hungry crocodiles" or "Snake in the wall bars" -all are part of the sensorimotor training. The strengthening and mobility exercises in therapy setting BI focus especially on the muscles of the foot, while BII and III also involve the upper body. Furthermore, therapy setting BIII differentiates between children with poor motor performance and those with a better one.

Therapy setting CI-III: Children, aged ten to thirteen years are assigned to age group C, where the lucid component disappears progressively. Instead of slipping into the role of the one-legged captain, the one-leg stand can be trained more specifically to improve balance performance. Other contents are a barefoot pathway, exercises with a rope (to balance or form numbers and letters), jumping on a trampoline or exercises on unsteady ground. The strengthening and mobility exercises concentrate on the distal extremities, especially on the muscles of the foot and the mobility of the ankle joint. To intensify therapy in cases of advanced CIPN, it is also possible to add (robot) assisted gait training (e.g. with Lokomat® or a treadmill), vibration therapy, ADL or respiratory training.

Therapy setting DI-III: The last therapy settings are designed for adolescents, aged fourteen to seventeen years. Interventions for improving sensibility (foot bathing or spiky ball massage, barefoot pathway etc.) remained almost unchanged in comparison to the other settings, whereas exercises for strengthening, mobility and balance require an advanced level of motor and cognitive ability. Interventions become more exercise-like and less playful. Therefore, strengthening exercises for the lower limbs such as squats, lunges, exercises with a stepper or Thera-Band® are recommended. Balance and sensorimotor training takes place in form of specific exercises on unsteady ground, one-leg-stand variations, and slack line-training as well as exercises on a trampoline or with a Swiss ball. The parameters mentioned for sensorimotor training are based on the therapy suggestions from Streckmann et al. [9] and contain three 20-second sets with breaks of 20 - 40 seconds in between and a one-minute break afterwards. Nevertheless, the limit of performance of each patient should be considered always. Autogenous training, progressive muscle relaxation, supportive gait training, vibration/ respiratory therapy or measures for the prevention of contractures are also interventions which are described as additional options for immobile patients.

Discussion

Through pharmacological interventions, pain could be reduced, but strength, balance performance and gait did not improve solely by administering drugs [16]. Moreover, drug therapy also has its limits and, additionally, may have numerous negative side effects [25]. Thus, physical therapy is a sensible alternative, particularly in regard to the fact that, so far, no negative side effects have been noticed [19]. Overall, the literature search was not a satisfying basis for the development of an evidence-based concept but a necessary step towards it. Altogether, there is little evidence for physical therapy. Unfortunately, there exist only few studies that investigated the effect of physical therapy in patients with CIPN, and, most of them are of poor evidence level not least because of small samples. Braam et al. [26] reviewed five studies and evaluated the effect of physical exercise on children with cancer (not specifically CIPN) and found positive effects on physical fitness as shown by improved body composition, flexibility and cardio respiratory fitness. However, no evidence was found for muscle strength, endurance, and level of daily activity, health-related quality of life and fatigue. As far as symptoms of neuropathy go, physical therapists only worked with adult CIPN patients. None of the studies found in the literature evaluated physical therapy for children and adolescents with CIPN. However, as previous studies have shown, it seems to be essential to facilitate physical performance of children with CIPN and physical deficits to avoid long-term damages and maintain the patients' quality of life. Moreover, motor development is the center of physical health and further builds the basis for success in school, social integration and acceptance [27]. So far, sensorimotor training seems to have the highest chance of success. For this reason, the concept, which allows for an age-appropriate therapy, contains a range of games to train balance performance. However, a single method is rarely effective. Therefore, physical therapy as well as this concept is an aggregation of methods containing sensorimotor, strength or gait training as well as manual therapy or other forms of therapy on a neurophysiological basis. Furthermore, the fact that know-how and equipment differ from institution to institution was taken into consideration in the development of this concept. It is important that the therapy is orientated as far as possible on evidence-based methods, however, designed individually meeting the special needs of every child. This paper should therefore be considered a guideline rather than a strict therapy plan. That makes it more flexible but less comparable at the same time.

Conclusion

Physical therapy shows high potential regarding the improvement of CIPN symptoms, especially no negative side effects are noticed yet. Therefore, it seems to be a soft but helpful therapy option next to medical therapy. However, evidence for physical therapy methods aren't sufficiently proven yet, so further studies of high methodological quality and bigger sample sizes are needed. For this reason, the described idea of a physiotherapeutic strategy for children suffering from CIPN is a first step in the approach to this problem and will be tested within a controlled clinical trial at the Charite Berlin, Germany, beginning in 2018.

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