Protocol

Early Intensive Leg Training to Enhance Walking in Children With Perinatal Stroke: Protocol for a Randomized Controlled Trial

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Background. Development of motor pathways is modulated by activity in these pathways, when they are maturing (ie, critical period). Perinatal stroke injures motor pathways, including the corticospinal tracts, reducing their activity and impairing motor function. Current intervention for the lower limb emphasizes passive approaches (stretching, braces, botulinum toxin injections). The study hypothesis was that intensive, early, child-initiated activity during the critical period will enhance connectivity of motor pathways to the legs and improve motor function.

Objective. The study objective was to determine whether early intervention with intensive activity is better than standard care, intervention delivered during the proposed critical period is better than after, and the outcomes are different when the intervention is delivered by a physical therapist in an institution vs. a parent at home.

Design. A prospective, delay-group, single-blind, randomized controlled trial (RCT) and a parallel, cohort study of children living beyond commuting distance and receiving an intervention delivered by their parent.

Setting. The RCT intervention was provided in university laboratories, and parent training was provided in the childs home.

Participants. Children 8 months to 3 years old with MRI-confirmed perinatal ischemic stroke and early signs of hemiparesis.

Intervention. Intensive, play-based leg activity with weights for the affected leg and foot, 1 hour/day, 4 days/week for 12 weeks.

Measurements. The primary outcome was the Gross Motor Function Measure-66 score. Secondary outcomes were motion analysis of walking, full-day step counts, motor evoked potentials from transcranial magnetic stimulation, and patellar tendon reflexes.

Limitations. Inter-individual heterogeneity in the severity of the stroke and behavioral differences are substantial but measurable. Differences in intervention delivery and assessment scoring are minimized by standardization and training.

Conclusions. The intervention, contrary to current practice, could change physical therapy interventions for children with perinatal stroke.

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Perinatal stroke is a leading cause of hemiplegic cerebral palsy (CP), which accounts for about 30% of CP.[1] The children typically develop unilateral sensory and motor impairments contralateral to the affected cortex. Their movement problems have been associated with damage to motor pathways from the brain, including the corticospinal tract (CST).[2]

Current treatment to improve upper limb function often includes constraint-induced movement therapy (CIMT), in which the unaffected hand is constrained while intense, structured training is provided to the affected hand.[3–6] These interventions are highly effective.[7,8] In contrast, treatment for the leg is more passive, typically including stretching, an ankle-foot orthosis for the affected leg,[9] and botulinum toxin A injections to reduce the abnormal muscle tone.[10] There has been less focus on targeted, activity-based interventions to improve leg function and minimize gait abnormalities.[11,12] Indeed, gait abnormalities likely contribute to premature, secondary complications such as osteoarthritis,[13,14] leading to reduced mobility with age.[15]

Activity-Dependent Development of Motor Pathways During a Critical Period

One opportunity presented by a brain injury early in life compared to later in adulthood is that the young brain is more malleable. A series of studies in kittens have demonstrated the vital importance of early limb movements in the development of the CST.[16] In mammals, including humans, the CST initially projects extensively to both sides of the spinal cord. Through a competitive, activity-dependent process called refinement, many ipsilateral nerve endings retract, leading to the mature, contralateral pattern of innervation.[17,18] Activity is essential for refinement, as demonstrated by the chemical inactivation of 1 primary motor cortex, between postnatal weeks 3–7 in kittens.[19] In these animals, the silenced side of the motor cortex is at a disadvantage, resulting in a permanent impairment in the use of the contralateral limb, with parallel alterations to the motor circuits.[20,21] Importantly, if these weakened motor pathways are subsequently activated, either by electrical stimulation of the pathways[22] or by motor training[23] while the animal is still young (postnatal weeks 8–10), the histological and behavioral abnormalities are reversed. Identical intervention at an older age (postnatal weeks 20–24) is not as effective.[23] Hence, neuronal activity and limb use are essential during the *critical period* for the normal development of the motor circuits in kittens.

In children with perinatal stroke (stroke between 20 weeks' gestation and 28 days after birth[24]), the lesion reduces the activity of pathways from the affected motor cortex during refinement, putting those pathways at a disadvantage. The resulting innervation of the CST to muscles of the upper limbs becomes dominated by pathways from the unaffected cortex, which includes the normal contralateral projection to the unaffected limb, and an aberrant ipsilateral projection to the affected limb.[25] In contrast, projections from the injured side are weak.[25] The aberrant ipsilateral projection from the intact cortex has been associated with poorer function of the upper extremity.[26,27] Innervation of the CST to the lower limb during development in humans is presumed similar to the upper limb, but remains unknown because it has been difficult to obtain responses in the leg with transcranial magnetic stimulation (TMS) in children under 4 years old.[28]

Estimating the Critical Period for Motor Development in Children

The CST axons reach the lumbar spinal cord around post-gestational week 31,[29,30] and likely penetrate the gray matter to innervate motor neurons that supply the muscles to the leg by post-gestational week 40. Myelination of these CST axons remains immature through 2 years old, when markers for mature myelin become established.[30] Since mature myelin limits plasticity, we predict that the critical period for the refinement of CST to the lower extremities occurs before the age of 2 years.

Early Interventions in Children

Previous attempts at intervening early in children at risk for CP are summarized in systematic reviews.[31–33] The majority of studies have focused on Neurodevelopmental Treatment (NDT), an approach composed largely of handling techniques (ie, passive) and sensory stimulation, with the key ingredient for motor development missing—intensive, child-initiated motor activity.

Reports of child-initiated, activity-based therapy for the lower limb are sparse. Feasibility for intensive therapy of the lower extremity in young children has been demonstrated,[34] in which improvements in gross motor function (Gross Motor Function Measure: GMFM-88), walking speed, and cadence were seen in some. More recently, a single-participant design tested the feasibility and effectiveness of a dynamic, body-weight support system that allowed the children to experience and practice locomotor skills on their own over ground for 6 weeks.[35] Gross motor function (GMFM-66) improved more during the intervention period compared to the 6 weeks before and after the intervention. Another study, using a home program of leg exercises in very young children (<1 year old), showed no differences between the intervention and control groups, but both participation in the exercise and the intervention intensity (8 min/day, 5 days/week) was very low.[36]

Here, the protocol for a randomized controlled trial (RCT) is described. The primary objective is to determine if early, intensive leg training in children with perinatal stroke improves leg function beyond standard care. The secondary objectives are to determine whether: a) the training induces neuroplasticity in the CST and spinal circuitry, b) the age at intervention affects the outcome, and c) the context of the training (therapist in an institution vs. parent at home) affects the outcome. Results from the pilot work prior to this trial are published.[37]

Methods

Study Design

A prospective, delay-group, single-blind, randomized controlled trial (RCT; Figure 1—CONSORT flow diagram—RCT in yellow blocks) is being carried out at two sites: Edmonton and Calgary, Alberta, Canada. After baseline measures, enrolled children are randomly allocated to start intervention immediately—Immediate Group—or delay the treatment—Delay Group (both for a 3-month duration). The Delay Group serves as the control, and will also train for 3 months following the Delay period, in the same way as the Immediate Group. All children are followed for 3 months after training. In addition, all children are assessed when they turn 4 years old, to compare them with another group of 4-year-old children with the same diagnoses receiving standard care only. A biostatistician generated the group allocation sequence using a computer-generated permuted block design (block size 2 to 8), which is concealed in sequentially numbered, sealed envelopes. Clinical and walking outcomes are taken twice at baseline, then monthly for the Delay, Intervention, and Follow-Up Periods. Neurophysiological measures and full-day step counts are taken at baseline, then at the end of each 3-month period, and again at 4 years old, since these measures are not expected to change quickly.

In parallel with the RCT, children whose families live beyond commuting distance can participate (Parent Training; Figure 1—green blocks), in which the child is trained by a parent/guardian, who is coached by our therapists. These children are followed in the same way as the children in the RCT. This group will address the Secondary Objective, context of the training (above), which is especially interesting given the favorable results from home-based CIMT.[6]

Participants and Recruitment

Inclusion criteria were as follows:

1. Hemiplegia with MRI-confirmed perinatal stroke, categorized as neonatal arterial ischemic stroke, arterial presumed perinatal ischemic stroke, or periventricular venous infarct.[38,39]

2. Born at ≥32 weeks' gestation, with current age between 8 months and 3 years old.

3. No other neurological disorders.

4. Written, informed consent from parent/guardian.

5. Parent/guardian able to attend all tests and training.

Exclusion criteria were as follows:

1. Extensive brain injuries beyond the unilateral stroke.

2. Musculoskeletal/cognitive/behavioral impairments that preclude participation in the protocol.

3. Unstable epileptic seizures within the past 6 months or on anti-epileptic medication.

4. Any contraindications to TMS.

5. Botulinum toxin injection or surgery in the legs over the past 6 months.

Participants are identified by our clinical partners. Potentially suitable participants are screened in person by a research physical therapist. Evidence of perinatal stroke is confirmed by a child neurologist (authors AK or JY).

Sample Size Estimate

Pilot data from 3 children suggested that the effect size with the primary outcome measure (GMFM-66) is about 1.0. This is based on a GMFM-66 change of 5.5 points, and the predicted change over 3 months without intervention of approximately 3.5, for children with a GMFCS level of 1 or 2 around 1.5 years old.[40] The standard deviation of the change score is estimated to be 2, resulting in a sample size of approximately 16/group.

Therapist-Directed Intervention

The training is 1 hour/day, 4 days a week for 12 weeks, delivered by a physical therapist at the university. The goal of training is intensive, child-initiated movement from the affected lower extremity. Manual assistance for balance is provided as needed to prevent falls. Activities include ascending and descending stairs and ramps, walking on stable and unstable surfaces, stepping over obstacles, balancing in standing, kicking, and squatting to pick up items. All activities are play based. A session ends after 1 hour or when a child is no longer able or willing to participate in

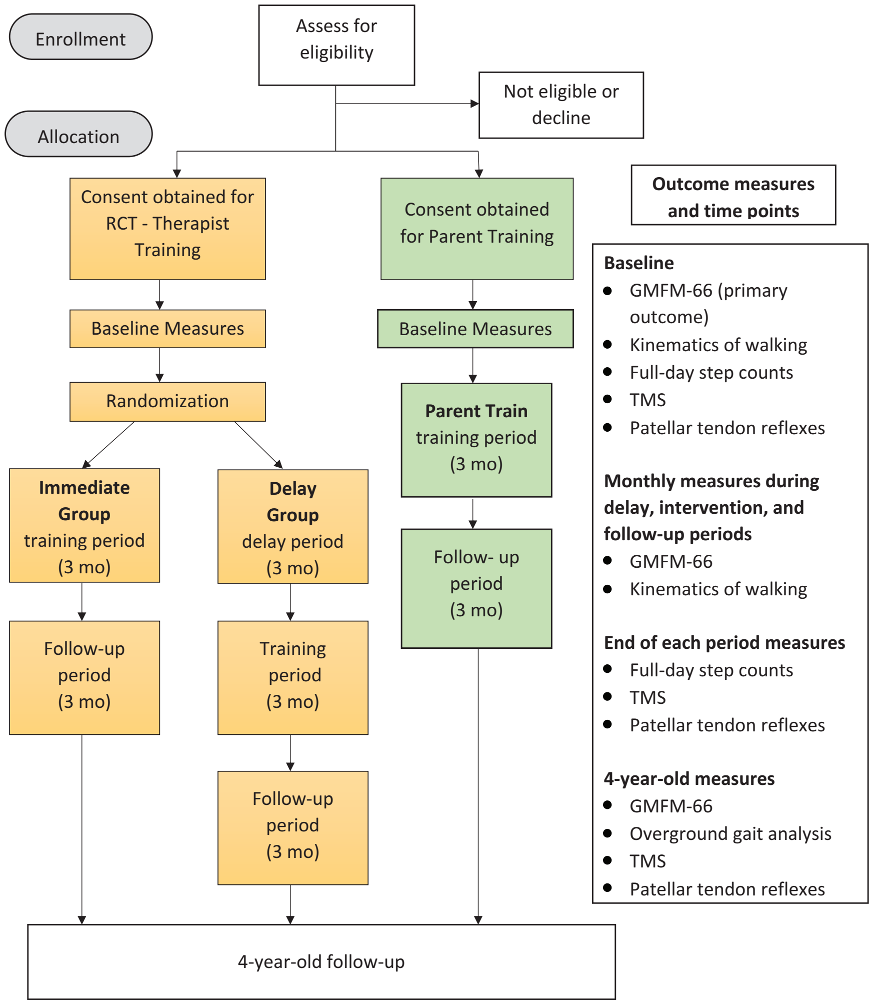

Figure 1.
CONSORT flow diagram. Eligible children enter either the randomized controlled trial (RCT–yellow blocks) if their parents live within commuting distance or the Parent Training trial (green blocks) if they live too far. Children in the RCT are allocated to either train immediately (Immediate Group) or delay training for 3 months (Delay Group). The Delay Group will serve as a control, and they will be trained after the delay period. All children will be followed for 3 months after training and remeasured at 4 years old, when they will be compared with a separate group of 4-year-olds who have not trained. Outcome measures are taken as outlined on the right. GMFM-66 = Gross Motor Function Measure-66, TMS = transcranial magnetic stimulation.

the activities. The aim is for 60 minutes of child-initiated activity.

To increase exercise intensity, weights are placed on the dorsum of the foot and the ankle of the affected limb when the child has sufficient endurance to stay active for 50 to 60 minutes. Ankle weights are commercially available in increments of 110 g, and foot weights are ¼" chain links, ~20 g each, affixed to the foot with elasticized fabric or tape (Figure 2). Children train either in their socks or with soft-soled slippers to enhance active use of the foot and ankle muscles. The weights are chosen to induce slight asymmetry in walking, since movement error induces learning.[41,42] Once walking looks symmetric, the weights are increased. Step counters (StepWatch; Modus Health, Washington, DC) document the total number of steps every session, and volunteers document time spent in each of 3 types of activity: walking (including climbing stairs, ramps), standing (balancing, kicking), and other (which can include jumping, crawling).

Treatment Fidelity

Alignment of the therapist training between the centers is achieved through weekly teleconference meetings, in which the documentation from training is reviewed, and discrepancies addressed. Video recordings of a full training session are compared periodically. Finally, each therapist visits the other center at least once a year to observe and discuss the training.

Parent-Directed Intervention

Parents are coached prior to the training period, in two 1-hour sessions, in which the parent(s) observe and assist the therapist with training of their child. Training goals are explained along with logistics and progression. The parent(s) are provided with a training manual and video that details suggested activities, tailored to the child's age group (eAppendix, available at academic.oup.com/ptj). Ankle and foot weights are provided. The therapist makes weekly phone contact with the family to review training. Training is reviewed by the therapist at monthly visits for testing, and more frequently if parents request. The aim is to make the training as similar as possible with children trained by therapists. Parents document home training using step counters and written logs every session.

Intervention Outcomes

The outcomes were chosen to reflect a) gross motor function, b) kinematics of walking, c) participation in life, d) excitability/connectivity of the CST, and e) excitability of spinal reflexes.

The primary outcome measure was gross motor function, as measured with the GMFM-66. GMFM-66 is a criterion-referenced observational measure to assess change in gross motor function in children with CP. Sixty-six tasks are scored, including the dimensions of: 1) lying and rolling, 2) sitting, 3) crawling and kneeling, 4) standing, and 5) walking/running/jumping.[43] Reliability, validity, and responsiveness to change

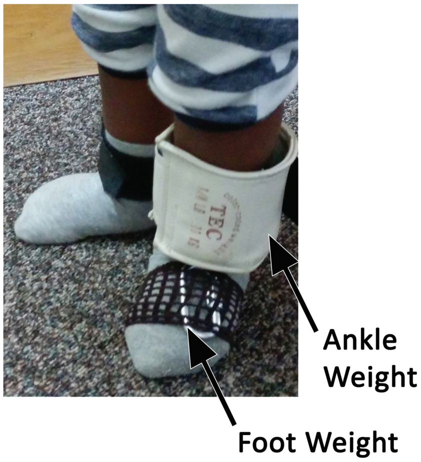

Figure 2.
Weights used in training. Ankle weights are fastened around the lower leg, and ¼" chain links are used on the foot to resist dorsiflexion. Elasticized material holds the chain link in place.

have been established for children 0.5 years old and older.[44,45]

The GMFM-66 is measured by pediatric physical therapists who are not delivering the treatment, and are blinded to the child's group assignment. All assessors participate in initial training and yearly meetings to align assessments. Two initial measures, 1 week apart, are averaged to improve the reliability at baseline. The measure is then repeated monthly throughout the study by the same physical therapist. Blinding is possible because the assessments and training locations are separate. Assessing therapists are further asked to guess the child's study group at each assessment, so that the *guess* scores can be used to determine the success of blinding. The total GMFM-66 score is obtained from the GMFM-66 Ability Estimator, and the dimension scores for standing and walking/running/jumping are estimated using the formula: (total scores obtained in the dimension) × 100/total score possible.

The secondary outcome measures were kinematics of walking, full-day step counts, motor evoked potentials (MEPs), and patellar tendon reflex.

Kinematics of walking. Walking is measured on a treadmill to accommodate children who are not walking independently. A custom-built table for toys in front of the child, and a forearm support for the experimenter supporting the child, are shown in Figure 3. A custom-built split-belt treadmill, with a force plate under each belt, is used in Edmonton. A commercially available treadmill (TR1200B; LifeSpan, Salt Lake City, UT) without force plates is used in Calgary. Walking movements are quantified either with the 3-D Investigator (NDI, Waterloo, Ontario, Canada) in Edmonton or with the Motion Analysis System using 12 Eagle-4 cameras (Santa Rosa, CA) in Calgary. Marker positions are standardized: top of the iliac crest, greater trochanter, knee joint line, lateral malleolus, and head of the 5th metatarsal, bilaterally. Customized MatLab script calculates step length (distance between the ankle markers in the direction of progression), toe clearance (maximum vertical height of the toe marker during the swing phase), and weight support (vertical force during stance phase—available in Edmonton only). Since children with unilateral stroke walk asymmetrically, we quantified the degree of symmetry in each of the above measures using the following formula: |affected leg score – unaffected leg score |(affected leg score + unaffected leg score).

Participation: full-day step counts. Our surrogate measure for participation (as defined by the World Health Organization) is estimated with full-day step counts. Parents place step counters on the child for the waking hours of 6 full days. Step counts are taken at the beginning, middle, and end of each study period (ie, delay, training, and follow-up). Counts are averaged over the 6 days.

Motor-evoked potentials (MEPs). Motor evoked potentials induced by TMS are recorded in leg muscles to determine if there are training-induced changes to the strength of the CST. We have successfully obtained responses in children as young as 8 months old.[46] Surface electromyographic (EMG) electrodes (Kendall Pediatric H59P electrodes; Medtronics, Saint Laurent, Quebec, Canada) are applied to the quadriceps, hamstrings, tibialis anterior, and gastroc-soleus muscle groups, bilaterally. A double-cone coil (outside diameter 125 mm) is positioned over the leg motor cortex, that is, at the vertex in the anteroposterior direction and 2 cm lateral to the midline. The coil is positioned manually for each trial. Two Magstim 200 stimulators connected to a Bistim module (Magstim, Dyfed, United Kingdom) are used to deliver a pair of TMS pulses (interpulse interval of 10 ms, 80% maximum stimulator output). Background contraction is essential to evoke MEPs at this age, so measures are taken with the child standing. Trials are repeated 2–5 times on both the right and left motor cortex. Children play during the testing, and the majority are unconcerned about the TMS. If a child objects to the TMS, the testing is discontinued. The MEPs are analyzed offline to identify the responses, latencies, and magnitudes.

Patellar tendon reflexes. Tendon reflexes are typically asymmetric in children with hemiplegia, with overflow of the reflex to other muscles in the affected limb, thought to reflect persistent, exuberant afferent projections seen in infancy.[47,48] We wondered if our intervention would alter reflex overflow. In the same session as the TMS experiment, stretch reflexes are induced mechanically with a handheld, reflex hammer fabricated from a force transducer. Reflexes are elicited by tapping the patellar tendon of each leg in turn, and recorded with surface EMG from the same muscle groups as above. Reflex overflow (ie, reflexes induced in the untapped muscles) is compared between taps to the affected and unaffected sides, after matching the size of the quadriceps reflex EMG on both sides.

Data Management and Statistical Analysis

Data is stored and managed in Edmonton. Analyses are done by research assistants, trained in Edmonton. Statistical analysis will be assisted by a biostatistician. Change scores over the 3-month study periods will be calculated for each measure. Separate 2-sample,

Figure 3.
Testing and training using a treadmill. The child walks on a treadmill with toys on a table within easy reach and a platform to support the therapist's forearms. The therapist provides support as needed and is in a position to prevent falls.

2-sided *t* tests will be used to compare the Immediate with the Delay Group, and the Immediate and Parent Train groups. For each outcome, multiple linear regression models will be developed to assess the effect of age at time of intervention and type of stroke (ie, venous vs arterial stroke) for the Immediate, Delay, and Parent Train groups separately. Model fit will be examined, and estimates will be provided with 95% CIs.

Trial Monitoring

A monitoring committee is not used because of the small size of the project and the low risk of the experiments. The researchers are responsible for reporting changes to protocol and adverse events to the Research Ethics Board 3, University of Alberta, which approved this study. Yearly renewals of the protocol are monitored by this Board.

Limitations

The severity of the stroke, and the child's willingness to participate in activities, will differ. This can be partly accounted for by baseline scores (severity) and step counts during training (participation in training). Variability in the training and assessments between therapists is minimized through training of therapists and frequent communication (see Treatment Fidelity and Primary Outcome measure).

Discussion

The intervention in this study is based on the neuroscience that activity drives the developing motor system. The focus on early, intensive, child-initiated activity contrasts with current practice, which is typically passive and delivered later (see Introduction). This study runs in parallel with several other studies on early, motor-based intervention for CP, largely for the upper limb.[49–51] Results from these exciting trials could change physical therapy practice for young children at risk of developing CP. Finally, if parents' training at home is equally effective, they could help deliver and/or reinforce training, thereby maximizing intervention outcome.

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Dr Kirton, Dr Watt, Dr Andersen, and Dr Yager are Fellows of the Royal College of Physicians of Canada.
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Ethics Approval

Ethics approval was granted by the University of Alberta, Edmonton, Alberta, Canada, Research Ethics Board 3–Health Research Ethics Board–Health Panel: Pro00032297.

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Disclosures

The authors completed the ICJME Form for Disclosure of Potential Conflicts of Interest. Besides the federal, provincial, and institutional funding that they received, the authors report no conflicts of interest.

Clinical Trial Registration

This study was registered at ClinicalTrials.gov (NCT01773369).

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Training Ideas

Kicking

Balance

Jumping

Riding Toys

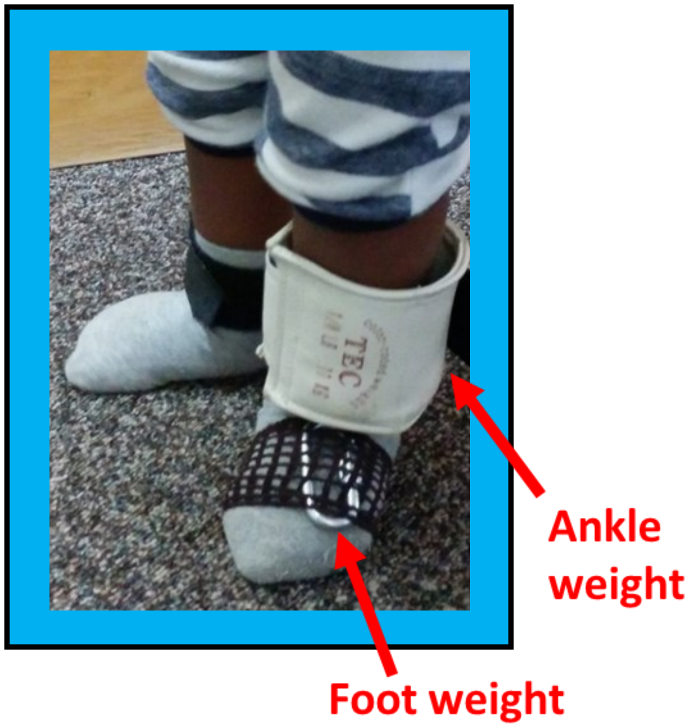
Climbing

Walking

Side Stepping

Stomping Foot

Weighting the Affected Leg



The therapist may give you a small ring weight to place on your child's foot while they train (pictured above). The weight will encourage your child to lift his/her foot. It will also help to strengthen the muscles that lift the foot.

As your child's muscles are strengthened over time, the therapist may increase the weight by adding an additional ring or by wrapping a weight around your child's ankle (pictured above).

Just Learning to Step...
Walking with Support...
Walking with No Help...

Kicking

- Attach a rattle or bell to the affected leg
- Hang toys above your child's feet and encourage kicking
- Tie a helium balloon to the affected leg and watch it bob-ble
- Tape a balloon to the floor for your child to kick
- Sit your child on a bench with feet dangling and place a tippy toy in front to kick
- Have your child kick a ball a short distance then chase it and kick again - a heavy, slow moving ball works best
- Build block towers for your child to knock down
- Place cones or blocks in a row for your child to kick over
- Give your child a cylinder or ball to roll back and forth under her/his foot
- Set up a goal or target to kick the ball towards
- Play "Soccer bowling" by setting up cones to knock over by kicking a ball. Encourage kicking with the affected leg

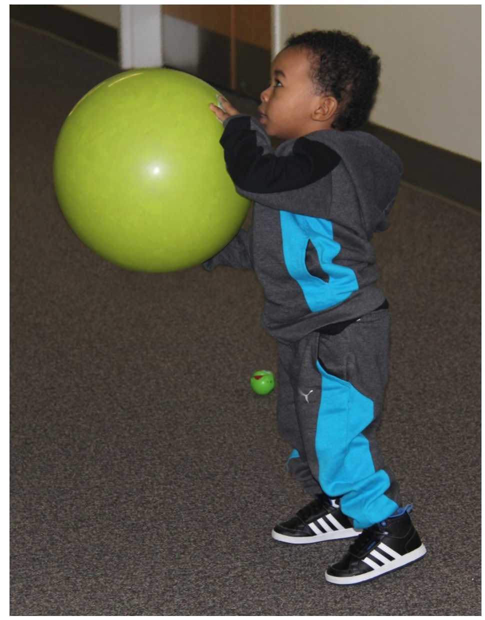
Side stepping

- Place a toy beside your child's foot for them to knock over
- Place toys at the opposite end of furniture to encourage child to cruise towards them
- Play 'Ring around the Rosy' or other circle games
- Put on some music and dance sideways with your child
- Have child do "box step" by making small flat box on floor (eg. tape, piece of cardboard, etc.) and having child step to each corner while always facing the same direction
- Create a narrow space between two pieces of furniture that your child can only get through by walking sideways

Just Learning to Step...
Walking with Support...
Walking with No Help...

Walking

- Help your child to walk over different surfaces like sand, grass, or foam
- Dance to music with your child
- Make an obstacle course with cushions to climb over
- Make a ramp out of a board for your child to walk up and down
- Encourage your child to walk up and down hills or a slide
- Put low toys or other objects on the floor for your child to step over
- Encourage your child to push or pull toys or objects like a doll stroller or laundry basket
- Help your child to walk with as little support as possible



- Hide small toys for your child to search for
- Encourage your child to pull toys while walking backwards
- Have your child opening doors towards them
- Play back and forth games (eg. get a block from a box and bring it across the room to build a tower)
- Give your child a large object to carry with two hands
- Let you child step into and out of a low box or hula hoop
- Put the vacuum cleaner hose out in a snake for your child to step over
- Play games that involve changing directions often and quickly like tag
- Play “Simon says” to reinforce movements learned, or work on movements of difficulty
- Play Red light, Green light

Just Learning to Step...
Walking with Support...
Walking with No Help...

Balance

- Have you child pick up toy from floor while standing and return to standing
- Hold toys up high so your child reaches over-head or out to the side
- Give your child toys to hold so (s)he will let go of other support
- Get your child to swing his/her arms around while standing
- Encourage your child to squat without sitting down and return to stand
- Hold a stick or hula hoop at different heights for your child to step over
- Encourage your child to touch her/his toes to a ‘target’ like a parent’s hand or a sticker on the floor
- ‘Drive’ a toy car under your child’s foot
- Have you child kick with the unaffected leg while standing on the affected leg
- Give your child a large teddy or toy to carry
- Sing “If you’re happy and you know it…” with different activities such as turn around, touch the ground, reach up high
- Pretend to be different animals with your child: flap your arms like bird, walk on hands and feet like bear, bend your knees and swing your arms like a monkey, crab walk
- Make a ‘balance beam’ out of a board on the floor or a curb
- Have your child give you “High fives” with her/his feet in standing

Just Learning to Step...
Walking with Support...
Walking with No Help...

Stomping foot

Things for your child to stomp on:

- Baby mat with ‘activities’, piano mat
- Squeaky toys
- Soap bubbles
- Bubble wrap
- Drum or tub that makes a loud noise
- A button that lights something up

Other stomping activities:

- Give your child different textures and consistencies to step on such as gel cushion, air mattress, water bag, bag of rice, bean bag, bag of Styrofoam pellets, corn flakes in bag, play-dough
- Let your child chase you and step on your toes
- Encourage your child to stomp her/his foot to the beat of music or clapping

Riding toys

- Sit your child on a riding toy and let him/her push with both feet
- Sit your child on a riding toy with foot supported on unaffected side and encourage her/him to push with the affected side
- Stand your child on scooter with unaffected foot on platform and encourage him/her to push with the affected leg

Just Learning to Step…
Walking with Support…
Walking with No Help…

Climbing

- Encourage your child to crawl onto or over low objects or furniture
- Create an obstacle course using things like cones, hoops, or boxes to climb over, in, through
- Help your child to climb stairs and encourage leading with the affected leg
- Place several thick books on the floor in a line with space between and have your child step up onto then down from each book.
- Pile cushions up to make a ‘mountain’ for climbing
- Help your child to climb up a ladder on a bunk bed or play structure

Jumping

- Support your child under the arms and bounce him/her jolly jumper style
- Have your child jump down from low height with support
- Pile pillows on the floor for your child to jump on or over
- Put mats or hula hoops on the floor for you child to jump onto or into
- Place sticky notes on the wall for your child to jump up and grab