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Leg Movement Rate before and after a Caregiver- Provided Intervention for Infants at Risk of Developmental Disability: A Pilot Study

Protocol: Intervention: Leg Movement Rate

Significance

Infants with developmental delay often experience lifelong functional limitations in motor, cognitive and social domains. A strictly-defined, conservative estimate recently determined that ~9% of infants in the US are eligible for early intervention services because they are at risk for developmental delay. Diagnoses of developmental delay are typically made at 18 to 24 months of age[1] and current practice is to provide infrequent, low intensity therapies or no intervention across infancy[2-4]. In infants born preterm, for example, low intensity developmental interventions have generally demonstrated short-term benefits that are not sustained into the school years[5-8]. Basic science evidence supports that early and intense therapy intervention is more effective at promoting optimal neuromotor structure and function[9-11]. Given this information, dosing of pediatric physical therapy intervention is a current topic of high interest in the field[12], and researchers are starting to investigate the feasibility of different approaches for providing early, intense interventions[13,14]. Although these approaches are laudable and strongly theoretically based there is a fundamental gap: we do not know what amount and type of movement experience is necessary and sufficient to have a positive effect on the development of infant neuromotor control. This proposal will address this fundamental question by increasing the leg movement experience of infants at risk for developmental delay to an evidence-based minimum threshold for quantity and type of movement and measuring the association between amount of leg movement experience and motor development rate.

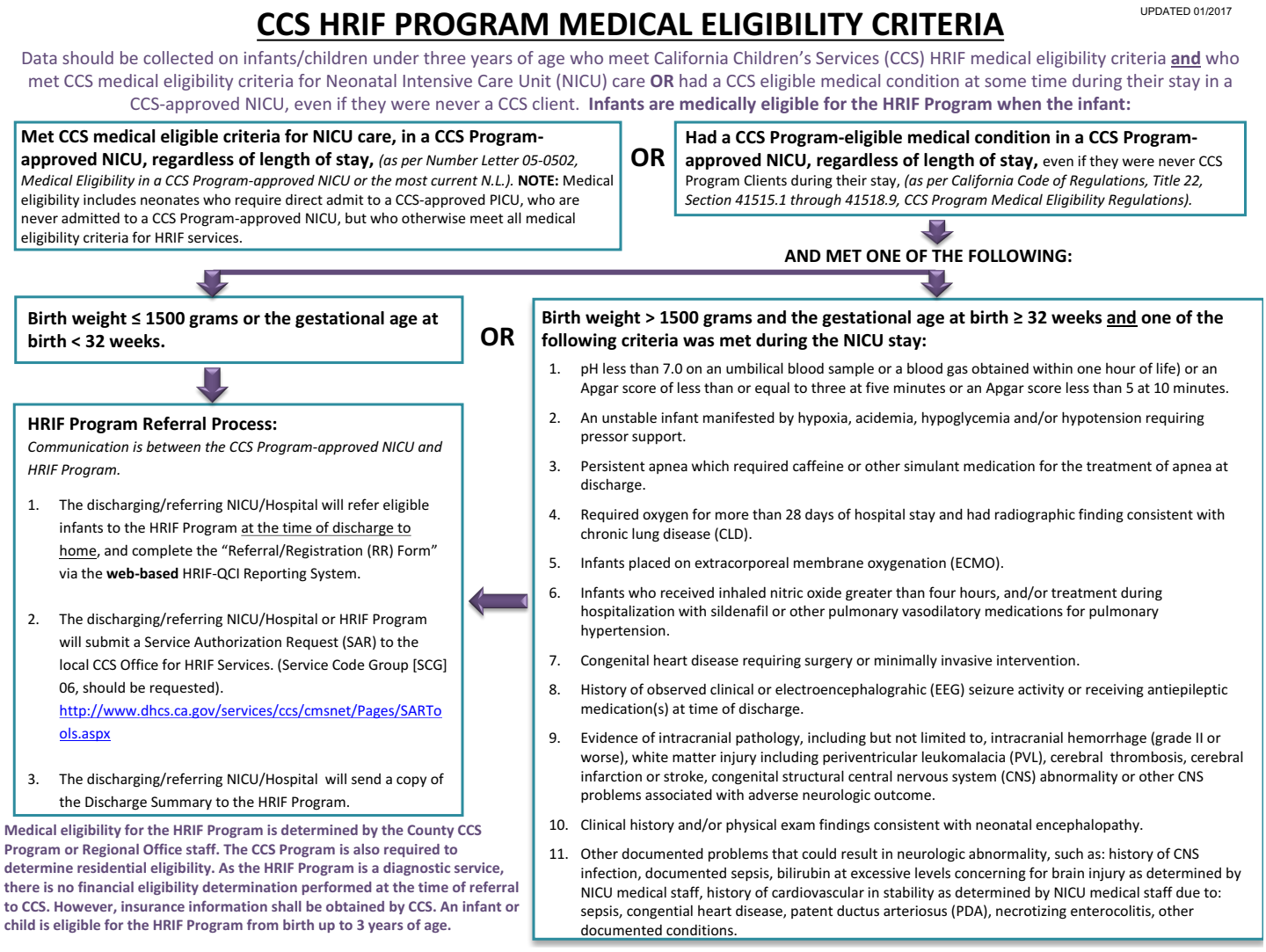
The intervention promotes movement experience from 3 months to sitting onset, based on our pilot data that indicate infants at risk for developmental delay who demonstrate a leg movement rate below 1200 movements per hour of awake time across a day are more likely to have a poor neuromotor outcome than infants who demonstrate a leg movement rate above 1200 movements per hour of awake time. Further, infants at risk for developmental delay move their legs significantly less and make a higher proportion of unilateral movements than infants with typical development. The goal of the intervention is to increase infant movement experience above the quantity threshold while consisting of the prescribed type (1200 movements per hour of awake time with variety of type of movement) in order to provide sufficient and necessary experience for learning neuromotor control.

Approach

Recruitment. Participants will be a representative sample of 12 infants AR recruited using 4 methods. 1) The infants will be recruited with fliers placed around USC campuses and public spaces such as local libraries. Fliers will also be distributed in person and/or electronically via email to local early intervention providers, on social media sites including facebook and instagram, and on the website of the Division of Biokinesiology and Physical Therapy. The parent or legal guardian will be asked to contact research staff by phone or email for further information about the research study, including further discussion of the inclusion criteria. When the parent or legal guardian contacts research staff, the research staff will give more specific information about the study and answer any questions. If they choose to participate after the initial contact, a written consent form will be mailed to them. This will allow the parents and/or legal guardians to discuss their participation with others before signing the written consent. 2) A licensed healthcare provider at CHLA or an early intervention provider, with the permission of the parent or legal guardian, will provide the research staff with the name and phone number of the parent of a potential infant participant who is under their professional care. Research staff will call the parent or legal guardian and give more specific information about the study and answer any

questions. If they choose to participate after the initial contact, a written consent form will be mailed to them. This will allow the parents and/or legal guardians to discuss their participation with others before signing the written consent. 3) Research staff will attend the High Risk Follow-Up Clinic at CHLA. A licensed healthcare provider at CHLA, with the permission of the parent or legal guardian, will introduce the research staff to the family. The research staff will give more specific information about the study and answer any questions. If they choose to participate after the initial contact, a written consent form will be mailed to them. This will allow the parents and/or legal guardians to discuss their participation with others before signing the written consent. 4) A CHLA Clinical Research Coordinator (CRC) will coordinate with the High Risk Follow Up Clinic and potentially the NICU to review infants' medical records for eligibility and speak to families of potential participants. With the permission of the parent or legal guardian, the CRC will provide the research staff with the contact info. Research staff will call the parent or legal guardian and give more specific information about the study and answer any questions. If they choose to participate after the initial contact, a written consent form will be mailed to them. This will allow the parents and/or legal guardians to discuss their participation with others before signing the written consent.

Inclusion Criteria. Infants will be 3-6 months of adjusted age at the first visit, +/- 30 days. Infants will be defined as at risk in accordance with the definition below (confirmed by the PI or the CHLA CRC) [15]:



CCS HRIF PROGRAM MEDICAL ELIGIBILITY CRITERIA

UPDATED 01/2017

Data should be collected on infants/children under three years of age who meet California Children's Services (CCS) HRIF medical eligibility criteria **and** who met CCS medical eligibility criteria for Neonatal Intensive Care Unit (NICU) care **OR** had a CCS eligible medical condition at some time during their stay in a CCS-approved NICU, even if they were never a CCS client. **Infants are medically eligible for the HRIF Program when the infant:**

Met CCS medical eligible criteria for NICU care, in a CCS Program-approved NICU, regardless of length of stay, *(as per Number Letter 05-0502, Medical Eligibility in a CCS Program-approved NICU or the most current N.L.).* **NOTE:** Medical eligibility includes neonates who require direct admit to a CCS-approved PICU, who are never admitted to a CCS Program-approved NICU, but who otherwise meet all medical eligibility criteria for HRIF services.

OR

Had a CCS Program-eligible medical condition in a CCS Program-approved NICU, regardless of length of stay, even if they were never CCS Program Clients during their stay, *(as per California Code of Regulations, Title 22, Section 41515.1 through 41518.9, CCS Program Medical Eligibility Regulations).*

AND MET ONE OF THE FOLLOWING:

Birth weight ≤ 1500 grams or the gestational age at birth < 32 weeks.

OR

Birth weight > 1500 grams and the gestational age at birth ≥ 32 weeks and one of the following criteria was met during the NICU stay:

1. pH less than 7.0 on an umbilical blood sample or a blood gas obtained within one hour of life) or an Apgar score of less than or equal to three at five minutes or an Apgar score less than 5 at 10 minutes.
2. An unstable infant manifested by hypoxia, acidemia, hypoglycemia and/or hypotension requiring pressor support.
3. Persistent apnea which required caffeine or other simulant medication for the treatment of apnea at discharge.
4. Required oxygen for more than 28 days of hospital stay and had radiographic finding consistent with chronic lung disease (CLD).
5. Infants placed on extracorporeal membrane oxygenation (ECMO).
6. Infants who received inhaled nitric oxide greater than four hours, and/or treatment during hospitalization with sildenafil or other pulmonary vasodilatory medications for pulmonary hypertension.
7. Congenital heart disease requiring surgery or minimally invasive intervention.
8. History of observed clinical or electroencephalograhic (EEG) seizure activity or receiving antiepileptic medication(s) at time of discharge.
9. Evidence of intracranial pathology, including but not limited to, intracranial hemorrhage (grade II or worse), white matter injury including periventricular leukomalacia (PVL), cerebral thrombosis, cerebral infarction or stroke, congenital structural central nervous system (CNS) abnormality or other CNS problems associated with adverse neurologic outcome.
10. Clinical history and/or physical exam findings consistent with neonatal encephalopathy.
11. Other documented problems that could result in neurologic abnormality, such as: history of CNS infection, documented sepsis, bilirubin at excessive levels concerning for brain injury as determined by NICU medical staff, history of cardiovascular in stability as determined by NICU medical staff due to: sepsis, congential heart disease, patent ductus arteriosus (PDA), necrotizing enterocolitis, other documented conditions.

HRIF Program Referral Process:

Communication is between the CCS Program-approved NICU and HRIF Program.

1. The discharging/referring NICU/Hospital will refer eligible infants to the HRIF Program at the time of discharge to home, and complete the "Referral/Registration (RR) Form" via the **web-based** HRIF-QCI Reporting System.
2. The discharging/referring NICU/Hospital or HRIF Program will submit a Service Authorization Request (SAR) to the local CCS Office for HRIF Services. (Service Code Group [SCG] 06, should be requested). http://www.dhcs.ca.gov/services/ccs/cmsnet/Pages/SARTools.aspx
3. The discharging/referring NICU/Hospital will send a copy of the Discharge Summary to the HRIF Program.

Medical eligibility for the HRIF Program is determined by the County CCS Program or Regional Office staff. The CCS Program is also required to determine residential eligibility. As the HRIF Program is a diagnostic service, there is no financial eligibility determination performed at the time of referral to CCS. However, insurance information shall be obtained by CCS. An infant or child is eligible for the HRIF Program from birth up to 3 years of age.

Exclusion Criteria. Infants with congenital malformations of the legs will be excluded.

Procedures. A parent or legal guardian will sign an informed consent form prior to their infant's participation. They will receive the consent form to review and will have any questions answered before scheduling a visit. At the time of the visit, they will inspect all equipment and toys have any questions answered before signing the consent form. A caregiver will be present and engaged throughout the data collection visit, which lasts approximately 1 hour in their home, or, if they prefer, in our laboratory. Infants will receive $20 compensation and souvenir photos for each visit.

Data Collection. All infants will be assessed in their homes once per month (+ or – 5 days), from 3-6 months of corrected age until sitting onset (can maintain independent sitting > 30 s) or 9 months corrected age, whichever occurs first. We have chosen this as our intervention endpoint because 1) once sitting is established, the way in which infants use their legs shifts drastically (from mostly supine and some prone free movement to primary use as postural stability) and 2) if they are not sitting independently by 9 months corrected age it is straightforward clinically to identify significantly delay. The goal of our intervention is to get them on the "right track" early, not to provide intervention once a significant delay has occurred. We have chosen to start our intervention at 3 months of corrected age, as this is just before relationships have been observed between leg movement frequency and later functional outcomes (as described in the siginificance section). *Sensor Data.* To record leg movement rate, infants will wear custom leg warmers with a pocket that securely holds a movement sensor at each ankle from the morning visit until bedtime. The caregivers will remove the leg warmers and sensors when they put their infant to bed for the night (~10-12 hours later). We will return to pick them up the next day. Amount and type of leg movements will be determoned using our exitisting, validated software algorithms. *Assessments.* We will measure the infant's weight, length, head circumference, thigh and shank lengths and circumferences. We will document medical and therapy interventions being received and assess motor skills using the Alberta Infant Motor Scale (AIMS), a standardized, norm-referenced observational scale[16]. We will record 5 minutes of spontaneous movement video to have a visual reference for data. We will record the caregiver teaching the child a novel task and assess the caregiver-infant interaction using the Nursing Child Assessment Teaching Scale (NCAST), a evidence based standardized-assement tool[17].

Intervention. At each visit, the caregiver will be reminded of the infant's movement. The research team will spend 15 minutes interacting with the caregiver to determine possible ways to achieve the goal of 1200 movements per hour of awake time, with a variety of movements. Strategies to increase leg movements will be encouraged based on the infant's developmental level and what they demonstrate a response to, including: shake a toy when infant moves legs, sing a line of a song when infant moves legs, change the position of the infant to encourage more leg movement, or lightly tickle the legs and feet of the infant. The intervention will use the GAME (Goals - Activity - Motor Enrichment) protocol, a motor learning, environmental enrichment intervention that has recently been shown to be effective for improving motor skills in infants at high risk of cerebral palsy compared to standard care. The intervention is based on the principles of active motor learning, family centred care, parent coaching and environmental enrichment. Intervention was customised to parent goals and enrichment style and the child's motor ability. To increase the dose of motor practice families were provided with a home program containing suggested activities according to identified goals[14,18,19]. We are expanding this effective intervention by applying it to a new population (infants broadly at risk as opposed to specifically at risk for cerebral palsy) and by specifically quantifying the dose of leg movement experience (amount and type). Otherwise, all intervention will be consistent with the established, published protocol. A customized logbook of all exercises with demonstration pictures of the baby, instructions, and tracking (amount and type) will be provided to the family each visit. Example Intervention Strategy. The research team and family determine that the baby likes Mom smiling and singing "You are my sunshine". They decide that every time the baby's diaper is changed, Mom will demonstrate by assisting the baby with

producing alternating kicks while smiling and singing for 10 total alternating kicks (5 each leg) and then encouraging the baby to perform alternating kicks (not assisting) for 15 seconds and responding with singing and smiling if he or she does. Five sets will be performed each diaper change. Fidelity. Caregivers will keep logbooks of the amount and type of movement experience they provide. This will assist our efforts to create a manual of intervention strategies for future grant proposals. Despite best intentions, however, logbooks are often incomplete; the GAME study reported ~ 50% completion [19]. Our main fidelity measure in this study will be the movement rate and proportion of unilateral movements demonstrated by the infants across days and months. We will be able to compare these data to our existing obervational data to measure the intervention effect size.

Follow Up: Families will be contacted by email or phone every 3-4 months from after the last visit until 24 months of corrected age for updates on their child's medical and developmental status.

Statistical test and analyses were performed using SPSS (Version 24; IBM, Corporation, Armonk, NY, USA). We first checked all variables for normality by plotting histograms and visually inspecting the data. Given the sample size and visual inspection of the variables, we chose to analyze our data using non-parametric statistics. The median and range were used to represent all descriptive statistics for the first and last visit. Wilcoxon Signed Ranked tests (alpha = 0.05) were used to compare the leg movement rates, adherence, and NCAST-Teaching total score to test for significant differences between the first and last visits. Spearman rank order correlations (alpha = 0.05) were used to test for significant relationships between quality of caregiver-child interaction and adherence to the intervention and leg movement rate at all visits.

Sample size justification. We determined our sample size of 12 for this pilot intervention study based on our observational pilot data. In our pilot data, we found large effect sizes (Cohen's d = 0.8 – 1.3) for leg movement quantity (movements per hour of awake time) between 12 infants with TD and 24 infants AR (anticipate ~12 good and ~12 poor neuromotor outcomes). With the planned primary comparison of leg movement of those who received intervention (N = 12) versus those who did not (N = 24), we should be able to detect an effect of Cohen's d of 1.0 at 9 months, with alpha = 0.05 and 80% power.

Potential Risks

Wearable Sensors: There is a small risk of skin irritation from wearing the legwarmers all day. Parents will be able to visually see their infants' feet at all times (they are not covered) and can remove the legwarmers briefly as desired to inspect their infant's skin. Although the movement sensors are small, they are not small enough to present a choking hazard. They measure 1.4 inches by 1.9 inches, larger than the standard choking hazard guidelines.[20]

Storage of Materials. There is a small risk of disclosure of participant's personal information. Data collected from participants includes biological data of leg movement activity, video recordings and health status information. All information collected will be kept private and secure. Password protection and secure internal computer networks and REDCap, a HIPAA-compliant database system hosted by USC, will be used to collect and store data. Hard copies of data, including 2 backup copies on external hard drives, will be stored in a locked, waterproof, fireproof safe in a locked room in a secured building (keys, identification cards) on a secured campus (identification cards, security patrol). Unique identifier codes will be used to separate all data collected from any personal identifying information. Laboratory members will have access to data identified by code for analysis and manuscript preparation, while only the PI and Research Assistant (RA) will have access to identifying information for participant tracking purposes.

Intervention. As is typical with trying to get an infant to perform any desired behavior, there is a risk that

the infant will become distressed as the caregiver attempts to get the infant to move his or her legs more (the intervention). Caregivers will be encouraged to soothe their infant and try the intervention again at a later time of the day. If the infant still becomes distressed, the caregiver will make a note of this and not perform the distressing activity further.

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