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George W. Gaiser
For Pedal-with-Pete Foundation
994 Dussel Rd.
Kent, OH 44240

Dear Mr. Gaiser,

In response to your letter dated December 3, 2008 requesting a grant proposal in the field of cerebral palsy research, I have enclosed a proposal entitled "In Vivo Assessment of Quadriceps Muscle Plasticity in Children with Cerebral Palsy".

We are confident that the goals and objectives of this proposal are complementary to the mission of the Pedal-with-Pete Foundation to improve the quality of life for persons with cerebral palsy. Securing funding from your organization will significantly strengthen and support our ongoing research with children who have cerebral palsy.

Thank you in advance for your review of our proposal.

Sincerely,

Noelle Moreau, Ph.D., PT
Principal Investigator

12/17/08
R. Darren McCants, Director
Office of Research and Sponsored Programs

Project Title: In Vivo Assessment of Quadriceps Muscle Plasticity in Children with Cerebral Palsy
Principal Investigator: Noelle G. Moreau, PhD, PT

Scientific Summary

Background: Cerebral palsy (CP) is the most common physical disability originating in childhood, occurring in 3.6 per 1,000 live births. Although the primary deficit in CP is injury to the brain, secondary impairments affecting muscle function such as weakness, contractures, and spasticity are often far more debilitating and lead to worsening disability throughout the lifespan. Some have suggested that these muscle changes in CP may be irreversible; however, it is now known that muscles are one of the most 'plastic' tissues in the body. In fact, recent evidence suggests that gross muscle hypertrophy and architectural changes within muscle fibers can occur as early as 3-5 weeks after resistance training in healthy adults. Our preliminary data are the first to show increases in rectus femoris cross-sectional area (16%-72%) and fascicle (bundle of fibers) angle (8%-120%) in 3 children with CP after 5 to 6 weeks of intensive adaptive sports participation, thus supporting this claim. It is also unknown how effectively muscles in CP can adapt to training stimuli that target specific muscle architectural parameters, such as fascicle length and cross-sectional area. These parameters have been observed to be decreased in CP, suggesting loss of sarcomeres in-series (fiber shortening) and in-parallel (muscle atrophy). We propose here that specific training-induced muscle architectural adaptations can occur in CP, leading to improved motor function.

Hypotheses and Specific Aims: The first Specific Aim is to demonstrate whether 8 weeks of intensive resistance training can produce significant alterations in muscle architecture in children with CP. To test this aim, 20 children with CP will participate in 1 of 2 intensive quadriceps resistance training protocols of similar duration and intensity: traditional strength training (ST) and velocity-enhanced training (VT). We hypothesize that significant increases in strength and muscle thickness and/or cross-sectional area (CSA) will occur in both groups in response to training. The second Specific Aim will test whether VT, which will include resistance training at increasingly higher velocities, will induce specific architectural adaptations not observed with traditional strength training. *Velocity-based training has been shown to increase muscle fiber length in normal muscles, resulting in improved muscle power and joint excursion.* We hypothesize that fiber length will increase in addition to increases in muscle size in the VT group. We also hypothesize that the VT group will demonstrate improved knee excursion, muscle power and rate of force development, important for *functional activities*, as compared to the ST group. The third specific aim is to determine if changes in muscle architecture will translate to improvements in gait, functional activities, and self-perception. We hypothesize that both groups will demonstrate increases in gait velocity, improvements in activity and participation, and improved self-perception and self-esteem; however, only the VT group will demonstrate improved knee excursion in gait and step lengths.

Design: Twenty subjects with CP between the ages of 10-17 years will be randomly assigned to the ST or VT group. Both interventions will target the quadriceps muscles and will be conducted on an isokinetic dynamometer, 3 x/wk for 8 weeks. Subjects will be tested before and after the training program. Ultrasound (US) imaging will be used to non-invasively obtain CSA, muscle thickness, fascicle angles, and fascicle lengths at rest. Preliminary data from our lab taken on repeated US images had reliability coefficients (ICC) ranging from 0.89 to 0.99. Quadriceps strength, power, and rate of force development will be tested on an isokinetic dynamometer. Gait data will be collected with computerized 3D gait analysis system. The Physical Self-Description Questionnaire (PSDQ) will be used to measure self-perception related to physical competence and self-esteem. The Pediatric Outcomes Data Collection Instrument (PODCI) will be used to measure activity and participation in the community. Mixed-model ANOVA will used to test for main effects of group and time as well as interactions. Linear regression will be used to relate muscle alterations to gait and muscle function.

Potential Impact: Muscles have been grossly under rehabilitated in CP and other spastic motor

disorders. However, current evidence of muscle plasticity challenges this approach. This study will have an immediate impact on the way that we monitor and treat muscles across all disabilities: 1) Monitoring: rather than invasive or costly measures, such as biopsies and MRI, US provides a non-invasive *in vivo* imaging tool which shows great promise in the rehabilitation field, and 2) Treatment: in addition to providing further support for intensive training protocols in CP, specific paradigms such as velocity training may provide an effective non-surgical alternative for increasing muscle length while improving muscle power, strength, and function.

Previous Research

We recently evaluated children before and after an intensive adaptive sports camp, where subjects attended daily up to a maximum of 6 weeks. The program consists of multiple sports and recreational activities including soccer, basketball, baseball, martial arts, tennis, and dance with every afternoon devoted to swimming instruction including strength and endurance training in the pool. Our data provide support to our hypothesis here that significant linear increases in cross-sectional area (CSA) indicating increased muscle growth, are possible in CP and appear to occur far earlier than literature suggests (Figure 1). However, for this intervention, specific muscle groups were not targeted in an isolated, systematic manner. In this study, the goal is to rigorously control muscle loading and training speeds, so that we can more precisely ascertain the effect of specific training regimens on our outcome measures.

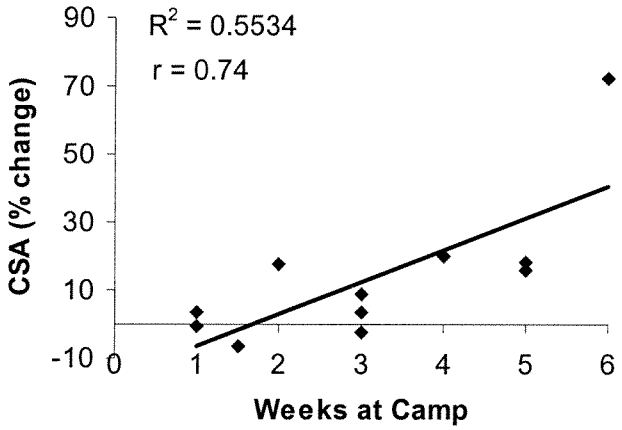

Figure 1. Correlation of % change in rectus femoris CSA (cross-sectional area) with weeks at sports camp

We measured fascicle lengths of the rectus femoris in 18 children with CP and 12 control subjects of similar age (CP: 11.6 ± 3.3 yrs; Control: 11.9 ± 3.9 yrs). We observed a 27% decrease in resting fascicle lengths in the group with CP compared to controls as illustrated in Figure 2. This data provides the first evidence that fiber lengths of the rectus femoris are shorter than their typically developing peers. This finding also supports the rationale behind the use of velocity training in this population to specifically target fiber length of the quadriceps. These projects were funded by the Section on Pediatrics of the American Physical Therapy Association and a training grant from the National Institutes of Health to Washington University, Program in Physical Therapy.

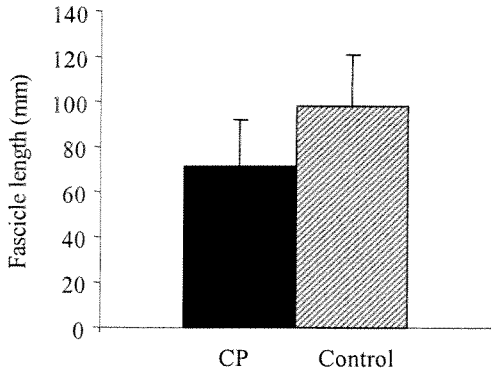

Figure 2. Average Fascicle lengths (mm) of 18 subjects with CP (70.8 ± 21.4) compared to 12 control subjects (97.4 ± 23.1) of similar age (p = .001)

Funding and Budget

This is a 2 year project, which would begin January 1, 2009. My current funding only partially supports this project. **For this proposal, we have included an additional aim (Aim 3) to measure the effect of the intervention on walking ability and quality of life**. More specifically, the funding from Pedal-with-Pete will allow us to measure the direct effects of this intervention on activity and participation in the community as well as the child's self-perception of his or her physical competence and self-esteem, which are areas most often neglected in current studies on children and adolescents with CP. The current funding is being used primarily to cover a small portion of the PI's time and effort, a small portion of a research assistant's time, and supplies.

However, additional monies are needed to cover the total cost of this project. We are requesting $35,000 to primarily cover 1) Physical Therapy services for the intervention portion), 2) a small portion of the PI salary/effort, 3) participant reimbursement for travel and participation, 4) travel to scientific conferences to disseminate research findings, and 5) addition of a control group that does not receive the intervention. We feel this project will be more successful if we can include a control group of 10 participants that do not receive the intervention in order to provide the highest level of scientific evidence; if we can include these new psychosocial instruments and assessments in addition to physical measures; provide the highest level of intervention from licensed physical therapists; and in this time of economic hardship, provide some remuneration to parents for their time and expense to participate for 8 weeks (3 x a week).

If we are unable to receive the full amount of $35,000, we would still be able to use a smaller amount; however, we would need to make adjustments to the budget, which would include reducing the amount of participant remuneration, removing the control group, reducing travel to disseminate research findings, a reduction in the amount of physical therapist's time, and decrease in the PI's effort.

Principal Investigator

Dr. Noelle Moreau began working with children with CP at Shriners Hospital for Children in Shreveport, LA, where she worked as the lead physical therapist in the Motion Analysis Laboratory, where she used advanced 3-D cameras and technology to rigorously analyze walking patterns in children with CP. After four years, she decided to pursue a doctorate in biomechanics at Louisiana State University. Her dissertation topic was "Quantification of Muscle Fatigue in Cerebral Palsy and Its Relationship to Impairments and Function" (See attached CV for related publications). She finished her PhD at the end of 2006 and immediately began a Postdoctoral Research Fellowship at Washington University in St. Louis, Program in Physical Therapy, in January of 2007 to continue work with her mentor, Diane Damiano and also with Dr. Jan Brunstrom at the Cerebral Palsy Center. After completion of her postdoctoral training, she was hired at Medical University of South Carolina as a research Assistant Professor in the Department of Health Professions to continue her line of research. The overarching goal of her current research is to investigate the mechanisms underlying abnormal muscle function in people with CP and the development of effective rehabilitation strategies to enhance muscle function and quality of life.