EPOS RESEARCH GRANT

Clubfoot-Calf study: 3D ultrasound of the calf in children with clubfeet.

Purpose

To compare the musculus gastrocnemius medialis (GM) with 3D ultrasound between children with and without clubfeet in order to gain more knowledge about the etiology and prognosis of clubfeet.

Hypothesis

We hypothesize that the calf muscle of children with clubfeet has a diminished muscle volume, cross section and muscle and tendon length.

Methodology

Primary research question:
What is the difference in GM muscle volume on 3D ultrasound in children aged 2-5 years with and without clubfeet?

Secondary research questions:
What is the difference in GM muscle geometry on 3D ultrasound in children aged 2-5 years with and without clubfeet?
Is there a correlation between morphological features of the GM on 3D ultrasound and clinical scores, including Pirani and Dimeglio score, foot function and Patient Related Outcome Measures (PROMs)?

Setting: The OLVG, Amsterdam

Participants: Forty children between the age of 2-5 years with unilateral (20 children) and bilateral (20 children) idiopathic clubfeet will be selected from the clubfoot population visiting the OLVG. Children will be excluded if they have undergone any orthopaedic surgery of the lower limb other than an achilles tenotomy. A convenience sample of 20 typically developing children (TD) in the same age range as the children with clubfeet will take part as controls. For all groups, we will exclude children with other pathologies of the musculoskeletal system.

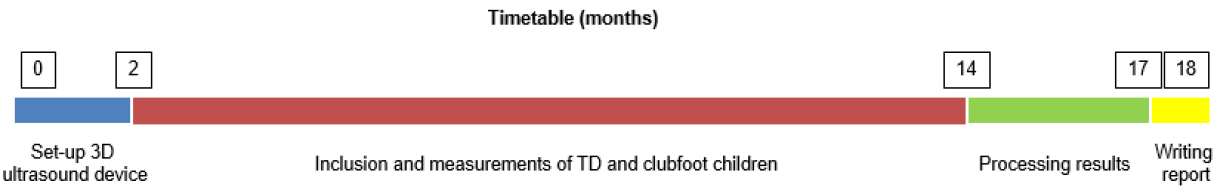
Exposures: We will perform a 3D ultrasound of the GM muscle (https://www.jove.com/t/55943/3d-ultrasound-imaging-fast-cost-effective-morphometry-musculoskeletal).[5] Treatment of the clubfoot or clubfeet is as defined by the Dutch Clubfoot guidelines.[8]

Main Outcomes and Measures:
Our main outcome will be gastrocnemius medialis muscle volume, which will be measured by 3D ultrasound as done before by us and our colleagues.[5,9] Also the geometry will be measured like this.
During the 3D ultrasound examination, a probe will be moved (swept) in a transverse orientation with respect to the leg in a longitudinal direction over the skin superficial to the GM. Location and orientation of the probe will be registered by a motion capture system and

synchronized with ultrasound images to construct a three-dimensional voxel array (i.e. 3D ultrasound image), using custom software.
Other baseline characteristics will be recorded (other medical history, clubfoot treatment, position in utero, APGAR score, pregnancy duration, PROMs) and a physical examination will be performed (weight, height, leg length, fibula length, hip abduction, spine deformities, feet scores (pirani en dimeglio), ankle dorsiflexion and plantar flexion, diameter of upper leg and calf and feet length). This will be used to find a correlation between morphological features of the GM on 3D ultrasound and clinical scores.

Statistics:
Sample size estimation: Our primairy outcome is difference in GM volume. To quantify a difference in GM muscle volume with a mean difference of 8 mL and a SD of 2 mL, with a power of 97.9% we would need two children in each group if there would be two groups (without loss to follow-up) based on previous experiments.[9] We are treating around 20 patients with clubfeet every year, so 80 children aged 2-5 years with a unilateral clubfoot or bilateral clubfeet in total. We will include 20 patients with an unilateral clubfoot and 20 patients with bilateral clubfeet. We want to compare this to the same amount of TD children. This will make 20 patients in each group.
General statistical plan: two types of statistics will be used:
I. Typically developing-clubfoot (unilateral)-clubfeet (bilateral) group comparisons using means and standard errors.
One way ANOVA will be used to test for significance of differences in mean values of unilateral clubfoot, bilateral clubfeet and TD groups regarding anthropometric data and GM geometrical characteristics measured at 0 Nm.
II. Regression analysis using individual data of subjects.
Pearson's product-moment coefficients of correlations will be used to assess relations between age, and geometrical and anthropometric characteristics, using individual data. Differences in slopes will be tested using Sigma Plot.
For ANOVA and Pearson's correlations we will use SPSS with the level of significance set at $p < 0.05$.

Time frame
Permission has already been obtained from the medical ethics committee of Amsterdam University Medical Center and local approval has been granted in the OLVG by the Scientific Research Advisory Committee. Setting up and testing the setup for performing 3D ultrasound measurements will take 2 months, after which the inclusion and performance of measurements will start. About 20 new patients per year are treated for clubfoot in the OLVG. There are currently about 80 patients with the age of 2-5 years being treated in our facility. All patients come for annual outpatient check-ups. Taking into account an inclusion rate of 50%, performing ultrasounds will take approximately 12 months. After taking the measurements, the scans will be reconstructed and analyzed. It is expected that the total duration of reconstruction and analysis will take 2 months, after which 1 month is taken into account for the statistical tests and possible run-out. Finally, 1 month is counted for writing the article.



Collaborations:
The OLVG and Amsterdam University Medical Center (AUMC) work together as a specialized and certified clubfoot center. Currently the clubfoot treatment is performed at the OLVG by Dr. M. Witbreuk. This work is assisted by dr. M. Koolen (orthopedic resident, interested in pediatric orthopedics) and drs. F. de Nies. For this research project, there will be a close collaboration with the department of child rehabilitation of the AUMC and the Vrije Universiteit Amsterdam, including Prof. Dr. A. Buizer, Prof. Dr. R. Jaspers and Dr. G. Weide, who are all involved in the research of calf muscles of children with cerebral palsy using 3D ultrasound. Furthermore, the OLVG will collaborate with the department of radiology, including Dr. H.J. van der Woude (radiologist) and the clinical physics department, including Dr. V. Lagerburg. Finally, the orthopedic scientific research department 'Joint Research' will be involved for substantive research support.

Future: During the treatment of clubfoot, muscle morphology of the calves is not routinely examined. This measurement could provide insight into whether morphological features are a part of the etiology and evaluate the success of treatment. Ultimately, the hope is that 3D ultrasound can improve or redirect the treatment of clubfoot by investigating whether it is a diagnostic tool that can identify clubfoot with a higher risk of failure of therapy or relapse. In further research, out of the scope of this grant, we would like to perform a prospective follow-up study.

Short literature review

Clubfoot is a well-recognized foot deformity estimated to affect approximately 1 in 1,000 live births.[1] Approximately one-half of cases present with bilateral deformity; unilateral cases are predominantly right-sided.[2] Several studies searched for the cause of a clubfoot, but seemed not to be succesful.[3] Post mortem studies in a limited number of fetuses, neonates and children with clubfeet have shown atrophy of the muscles in the calves.[3,4] It is thought that either muscle or central nervous system anomalies can cause the muscle atrophy, resulting in weakness of the calves and bone deformities. There is limited literature available describing studies where the muscle characteristics are measured. One study presents muscle mass measurements in the affected and non-affected leg by means of MRI or post-mortem examination.[4] This study showed that atrophy and shortening of the muscles remain present in children and adults treated for their clubfoot.[4] Demonstrating muscle atrophy, but especially geometry differences in children with clubfeet may contribute to a better understanding of the etiology of a clubfoot. Also, it might give us a prognostic tool for its treatment.
With a recently developed 3D ultrasound technique the muscle volume, cross section and muscle and tendon length of the calf muscle can be measured.[5] The methods and results are ready to be used in clinical decision-making, as shown by the results in cerebral palsy (disorder with muscle abnormalities as a result of brain damage). In children with cerebral palsy in which the lower extremity is affected, the gait pattern is characterized by an 'equine gait'. Children

walk on their toes, with the foot in pointed position and their ankle in plantar flexion in the stance phase and limited push-off force. Without treatment, the gait pattern and ankle movement generally deteriorate with age. The course of cerebral palsy has many similarities with that of a clubfoot or clubfeet. The 3D ultrasound technology is portable, easily available and non-invasive and now allows for in-depth assessments of muscle volume, physiological cross-sectional area, fascicle length, and tendon length of the musculus gastrocnemius medialis (GM) and the musculus vastus lateralis muscle.

In a clubfoot there seems to be an excess of collagen synthesis with retracting fibrosis in the medial and posterior tarsal ligaments, in the deep fascia, the tendo Achilles, and the posterior tibial tendon. These changes induce severe equinus, medial displacement of the navicular, heel varus and foot adduction.[6] The effects on the tibialis posterior are provoked by the musculus gastrocnemius and soleus, which are smaller and shorter in a clubfoot than in a normal foot.[4] There is a negative correlation between the size of the leg muscles and the severity of the abnormality. In the most severe clubfoot, the gastrosoleus is seen as a small muscle in the upper third of the calf. Excessive collagen aggregation in the ligaments, tendons and muscles may be present until the child is 3 or 4 years old and may be the cause of relapse.[6] However, we do not know exactly how the tendons develop and how they correlate to the muscle characteristics. Therefore, it is not clear how the changing geometry of the muscles in children with a clubfoot affects the function of the ankle. We do know that a neglected clubfoot causes an enormous physical, social, psychological and financial burden on the patient, their families and the community.[7] Globally, a neglected clubfoot is the most serious cause of physical disability among congenital musculoskeletal abnormalities.

A different muscle geometry is not something that is looked at standardly in assessing and treating children with a clubfoot. Measuring this could give us an insight in whether muscle atrophy and/or geometry is indeed a part of the etiology of a clubfoot or clubfeet. This may adjust the various aspects of treatment during the first five years of life.

In our Clubfoot Expertise Centre we have the possibility to perform prospective examinations in children with clubfeet by means of 3D ultrasound examination of the clubfoot or clubfeet compared to the normal foot and the foot of typically developing children.

References

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