

Identification and treatment of gait abnormalities in children and adolescents with Dravet syndrome

Research Protocol for posting on ClinicalTrials.gov PRS

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1. Background

The gait pattern in children and adolescents with DS was first described as "crouch gait" by Rodda et al., using 2D video analysis, clinical examination and X-ray of the lower limbs [1]. Later, Rilstone et al confirmed this "crouch" pattern in adults [2]. In addition to the gait deviations described, the children with DS also showed an enlarged internal hip rotation and a decreased passive knee and hip extension and an increased external tibial torsion and pes plano valgus observed with increasing age [1]. Based on these observations, Rodda hypothesised that a combination of malalignment and muscle weakness of the lower limbs lies at the root of the observed gait disorders [1]. However, this hypothesis can only be confirmed by 3D gait analysis in combination with measurements of muscle strength, which has not yet been carried out.

From the study of Rodda et al. "crouch gait" appears to develop in children with DS between 6 and 12 years [1], followed by a progressive decline in the gait pattern with increasing age [1, 2]. As mentioned, the passive movement limitations and the bony deformities aggravate by increasing age [1]. It is known that "crouch gait" in other patient populations usually arises in early adolescence [3]. This period is characterized by a growth spurt, in which body length and weight increase faster than muscle strength, reflecting the "crouch" pattern [3]. "Crouch gait" is known as a very complex, progressive disorder, profound understanding of the various causal factors is required to adequately treat this pattern. In order to gain full insight into the causes of the abnormal gait pattern, a longitudinal follow-up of patients is therefore necessary to monitor the influence of various factors, such as growth, a possible decrease in muscle force, but also the characteristic psychomotor retardation.

No literature is known on the treatment of gait disorders in patients with DS. Researchers do mention the use of corrective insoles [4], orthopaedic shoes and ankle-foot orthosis [1], mainly based on clinical expertise and results of scientific research in other populations. Orthopaedic procedures are also applied to correct bone-like abnormalities with the aim of optimizing the gait pattern [1]. The effectiveness of these interventions in patients with DS is unknown. To increase the quality of life of the individual patient, it is essential to keep patients with DS active and mobile for as long as possible. Interventions can focus on improving the strength and/or correction of the biomechanics of the gait pattern. It is extremely important to also think about prevention and determine at what age one can already intervene to correct small deviations in biomechanics (e.g. by splints) to prevent children from entering a vicious circle of serious gait disorders, such as "crouch". When drawing up a treatment plan, it is possible to rely on the expertise of the treatment of gait abnormalities in other neuromotor disorders (cerebral palsy, spina bifida), but it is essential to adapt the proposed treatment plan to the specific characteristics of patients with Dravet syndrome.

2. Purpose of the research

The ultimate objective of this project is to draw up adequate, scientifically based, treatment for reduction and, if possible, prevention of gait disorders in children with DS.

3. Method

The research consists of 2 parts: a retrospective part and a prospective part. In the retrospective part, children's developmental status and potential developmental delay is described based on file data. In the prospective part, the children with DS are contacted and their gait pattern is evaluated.

Patient Recruitment:

Dravet syndrome has a prevalence of 1/15,000 to 1/30,000. In Flanders, an estimated 380 people would have been diagnosed with Dravet syndrome. In 2016, 70 patients were medically and paramedically monitored at the University Hospital Antwerp (UZA), at the Child Neurology Department. As this is a rather small patient population, attempts are made to reach all patients within the age range of 3 – 25 years with Dravet syndrome in the geographical area of Flanders and the south of the Netherlands. Approximately 50 participants are being sought, 30 of which are from UZA and 20 from other centres. Children can participate in the study if they are (1) diagnosed with Dravet syndrome, based on the criteria defined by Ceulemans and Cras in 2004 [5] and (2) are 3 years or older, have at least one year of walking experience and are up to 25 years at first inclusion. Exclusion criteria for participation are the prevention of a heavy epileptic seizure (status epilepticus or tonic-clonic seizure for more than 3 minutes) in the 24 hours prior to the study and/or insufficient cooperative for the removal of a 3D gait analysis.

A study officer from the UZA will invite patients who arrive at the Dravet consultation at the Child Neurology Service to participate in the study. In addition, a written call is launched via the newsletter of the parent association Stichting Dravet Syndrome Nederland/Vlaanderen. Interested parties can contact the aforementioned research officer who will provide further information.

Written consent is requested to the parent(s) or legal guardian of the children. The parents and the child are informed prior about the course of the study, expectations and risks.

A control population in accordance with the size and characteristics of the pilot group, of children and (young) adults with typical development or cerebral palsy will be composed of available data from previous research. UZ Leuven makes a database available to this end of gait analyses carried out for research at the KU Leuven [6]. In addition, a second control group will be composed of children and young adults who also have motor and developmental problems, whether or not in combination with epilepsy, due to a genetic condition that is not a mutation in the SCN1A gene.

Research Setting

All studies carried out for this study will take place in the M²OCEAN lab, UZA.

Data Collection Procedures

The research protocol is Figure 1 and a schematic view can be found in the addendum to this research protocol. Prior to the physical examination, parents are asked about the use of technical aids as well as the distance that the child can walk independently, and a classification is made according to the Functional Mobility Scale [7]. The Mobility Questionnaire, research version (MoVra28) is also taken [8].

An essential part of a gait analysis is an extensive physical neurological and clinical physiotherapeutic examination [9] collecting information on joint range of motion, alignment (femoral anteversion, bimalleolar and tibiofemoral angle via goniometry), muscle strength of the lower limbs, as well as about possible foot abnormalities (varus or valgus abnormalities of rear foot) and and hypermobility (Beighton hypermobility scale). Children with DS usually have a severe mental retardation which makes instructions for manual muscle strength tests difficult to understand. The physiotherapeutic exam will therefore be supplemented by the Functional Strength Measurement [10], a strength test designed especially for children with easy to understand assignments. The results of the FSM in children with Dravet syndrome can be compared with available normative values from the literature [10].

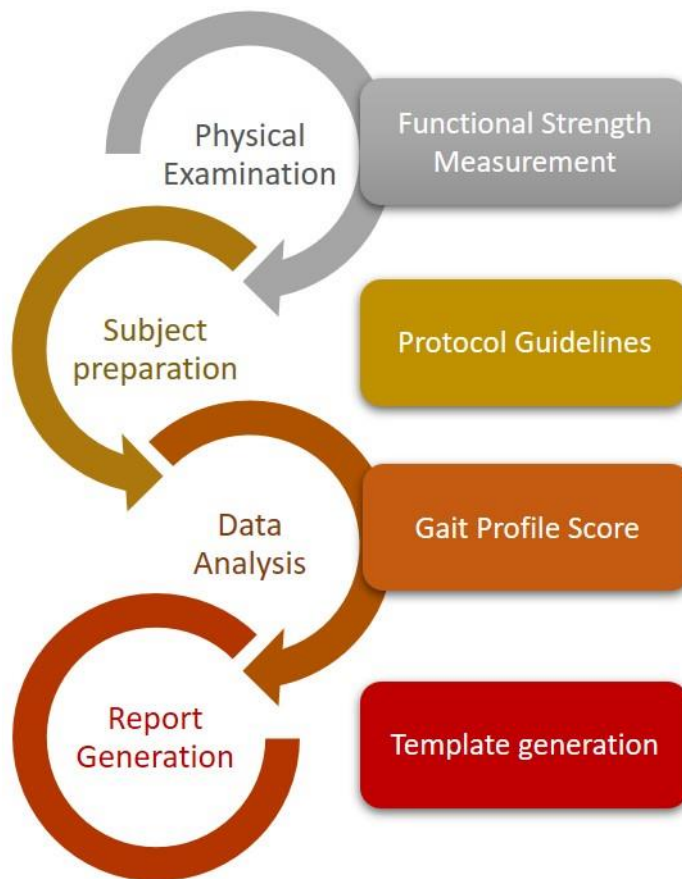


Figure 1: Schematic overview of the research protocol

In order to characterize the biomechanics of the gait pattern, the children will be subjected to an extensive 3D gait analysis. The experimental set-up used has already been validated in several studies [11-13] and consists of an instructed walkway (16 m long), surrounded by 8 cameras (Vicon Motion Systems, T10, 100Hz), in which four force platforms (AMTI type OR 6-7, 0.5 x 0.4 m, 1000 Hz), were built in to register the ground reaction forces of the left and right foot separately. The Helen-Hayes marker set-up [14] (see fig. 2) will be used to follow the kinematics of the lower limbs. The reflective markers (14 mm) are applied to the skin using hypoallergenic tape. The children will be encouraged to walk barefoot on the hiking trail at preferential speed. The over and over again steps are repeated until 3 good left and 3 good right-wing foot contacts are collected on the power plates. In order to achieve a pattern as naturally as possible, the children will receive small assignments (e.g. bringing small cubes or puzzle pieces back and forth) to divert attention from stepping.

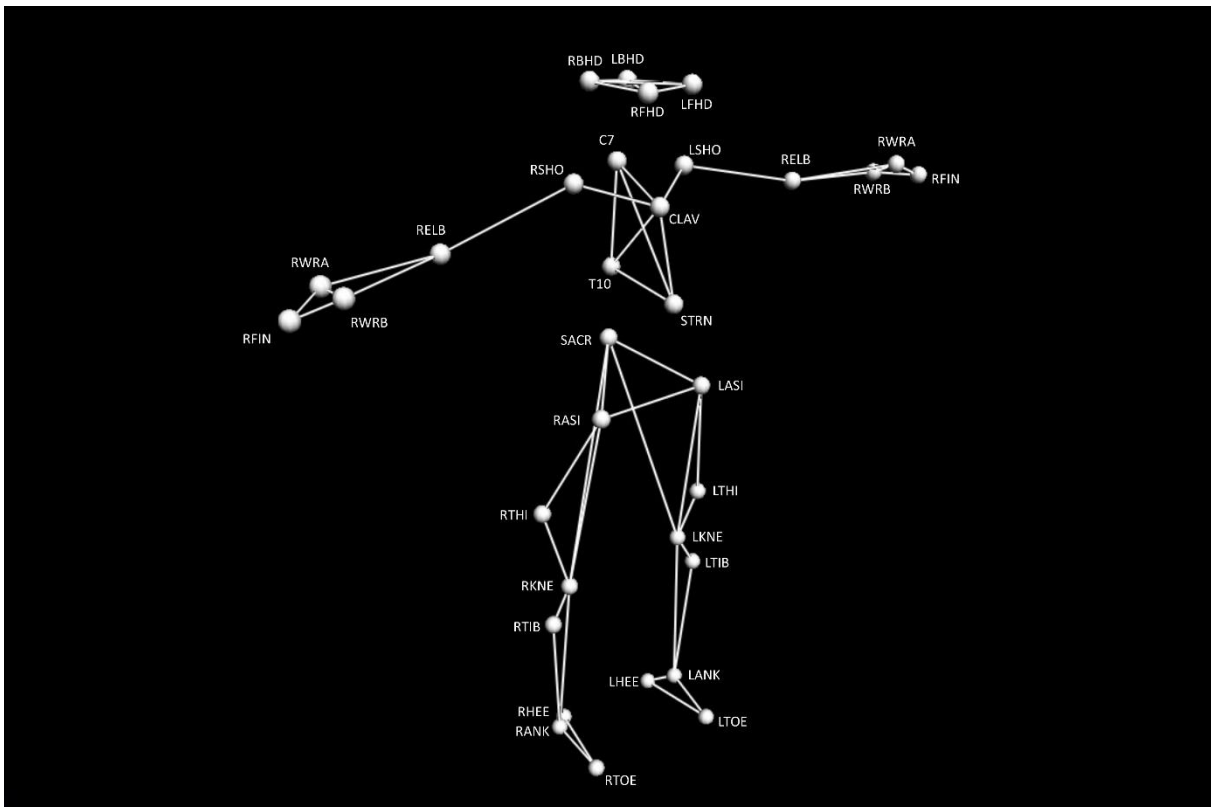


Figure 2: The marker set

Data analysis

Kinematic data, such as the range of motion of the different joints, describe the gait pattern and a comparison with age-specific reference data may determine gait abnormalities. The Vicon Clinical Model (based on the Kadaba [15] and Davis [14]) is used to reconstruct movements of the different body segments and describe and analyze the kinematic time profiles. Joint angles are expressed as YXZ Cardan angles of the most distal compared to the most proximal segment. The angles are zero during the upright stance. These angles display flexion/extension, ad/abduction and internal/external rotation of the joints.

To detect the biomechanical causes of the gait disorder, it is important, using an integrated inverse-dynamic model (Vicon Clinical Model), to determine the forces that control the observed movement. From measured joint kinematics and the ground reaction forces, net joint moments are calculated, which may be considered the cause of the observed movement pattern in a specific joint. The net joint moment is the resulting moment generated by all the structures that span the joint (muscles, ligaments, capsule, skin) [16]. To fully understand how active (muscles) and passive (gravity, ligaments and capsule) forces work together during movement, the inverse dynamic analysis must be supplemented by electromyography (EMG). To the extent of the possible, we will therefore attempt to collect EMG data from the hip extensors, knee flexors and extensors and ankle plantar flexors.

Interventions

No literature has been known to date on the treatment of arising disorders in patients with DS. There are three possible approaches to the prevention and treatment of gait disorders (1) the changes in passive anatomy; (2) changes in active anatomy and (3) the changes in the gait

pattern due to change in internal forces (active and passive anatomical changes) and external forces (ground reaction force, gravity).

Passive changes mean muscle contractures and bone-like abnormalities. Previous research identified both flexion and extension defects, as well as malrotations in children with DS [1]. Prevention of muscle contractures can be done by stretching during physiotherapy as well as by using night equipment for positioning. Active changes mean that we have a loss of strength that was suggested in children with DS [1]. Here too, after sufficient insights into the natural course, preventive, but also corrective action can be done using physiotherapy. Finally, there are also possibilities to directly affect the gait pattern, for example, by using orthotics that can restore biomechanical functions.

Use of orthotics as well as frequency of physiotherapeutic interventions will be listed. On the basis of the results of the 3D gait analysis and the longitudinal follow-up of patients, a decision will be taken on the usefulness and application of any interventions in consultation with the treating neurologist and physiotherapist.

Statistical analysis plan

The statistical analysis will mainly include descriptive statistics. Gait parameters will be compared between DS and healthy controls using a t-test or a non-parametric alternative. Changes in gait pattern, detected by annual retesting, will be evaluated using a mixed models design.

4. Relevance of the research

Knowledge and insights from this project will directly improve quality of life in patients with Dravet syndrome by optimizing the treatment of gait abnormalities, allowing the individual to remain mobile for longer and thus contribute to increased independence and self-reliance of the individual. This sets the research within the strategic cluster 'Health & Well-being' with a focus on prevention and treatment of gait problems in brain disorders based on personalized therapy. A personalised treatment plan can only be achieved if a thorough identification of the gait defects and its causes have been carried out, which can only be done on the basis of 3D gait analysis. Moreover, prevention can only be done and intervened early, when the data of a longitudinal follow-up of the gait pattern are available in children with DS.

5. References

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