A comprehensive study of the natural history of OPMD: An essential step towards clinical trial readiness and evidence-based interventions

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Scientific summary

Oculopharyngeal muscular dystrophy (OPMD) is a progressive hereditary neuromuscular disease with a late onset, generally after 40 years. Main manifestations of the disease are ptosis, dysphagia and proximal muscle weakness. Dysphagia is considered as the most disabling symptom since its original description. However, weakness leading to decreased walking capacity and impaired balance, has recently been described as potentially having major impacts on quality of life in OPMD. However, natural history of the disease is not known, and only one study addressed lower limb functions in a small cohort of 14 patients. As stated by the Food and Drug Administration, natural history studies are essential to provide the scientific foundation to build drug development programs, which require a deep understanding of the disease. The earlier the data are available over the longest period of time, the more informative it is to design efficacy trials. Objectives. 1) Document motor performances, mobility limitations, and participation restrictions related to daily activities, and compare them with reference values and between age groups, and document their progression over a 3-year period. 2) Document the relationships between motor performance, mobility limitations and participation restrictions related to daily activities. 3) Document validity and reliability of selected outcome measures (Year 2). Methods. Objectives 1-2. Multicentric longitudinal study with 120 participants with OPMD according to a stratified random sample according to sex and age. Participants will be assessed by trained healthcare professionals using standardized operating procedures and will include motor performances (quantitative muscle strength, balance, fatigue and dysphagia), mobility limitation (short and long-distance walk), participation restrictions in daily activities and social roles. Objective 3. A repeated measures design with a subset of 50 participants assessed at three different occasions. Intra-rater reliability will first be documented by administrating outcome assessments twice by the same rater, two weeks apart. Then a third session will take place two weeks later to assess inter-rater reliability. Statistical analyses. Objectives 1-2. Descriptive statistics will be performed for the whole group and compared between sexes. Progression of each variable will be analyzed using repeated measures ANOVA. Performance will also be compared to reference values or predicted values (depending of the measure). Correlations will be performed between mobility and participation outcome measures. Objective 3. Construct validity will be documented using a priori hypothesis testing made by the research team. For that, we will compare the results between groups of participants with a different age and mobility level using ANOVA and correlate the results with the participants' age and disease duration using Pearson correlation. Intra and inter-rater reliability will be determined using Intraclass Correlation Coefficients (ICCs). Our team is composed of leading researchers and clinicians with world leading expertise in regard to the disease, outcome measures and natural history study design

who have successfully completed several OPMD-related projects. The project will support trial readiness and ensure that we are able to inform prognosis regarding the key problems related to OPMD.