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Developing outcome measures for pediatric mitochondrial disorders: Which complaints and limitations are most burdensome to patients and their parents?☆

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ABSTRACT

Since some drug intervention effects are only experienced by the patient, organizations such as the Food and Drug Administration prefer clinically meaningful outcome measures. Here, we evaluated which symptoms and limitations in daily life are most burdensome to pediatric patients with mitochondrial disorders and their parents, using two questionnaires. In a study of 78 patients, the most burdensome complaints included fatigue, behavior and speech disturbances, epilepsy and muscle weakness and a high degree of limitations in daily activities was found. Importantly, there was a discrepancy between what symptoms metabolic pediatricians estimated would be most burdensome compared to the patients'/caretakers' opinion. To include feasible and relevant outcome measures in intervention studies, the experience and opinions of patients and caretakers should therefore be heard.

1. Introduction

Mitochondrial diseases are the most prevalent inherited metabolic diseases, with an incidence of approximately 1:5000 live births (Schaefer et al., 2004). Currently, there is no cure for mitochondrial diseases but there are some promising results of pharmacological interventions in cells and animals (Koene and Smeitink, 2009; Koopman et al., 2012; Viscomi et al., 2011; Wenz, 2009) and in some mitochondrial disorders (Hirano et al., 2012; Koga et al., 2012). A recent Cochrane review states that while the number of trials in patients with mitochondrial disorders has doubled since 2006 (Chinnery et al., 2006), the percentage of trials with an adequate trial design remained stable but extremely low (12 out of 1335 studies) (Pfeffer et al., 2012). Therefore, more awareness on how to perform scientifically sound clinical trials and joint ventures to find solutions for the many difficulties associated with these heterogeneous and complex disorders is of major importance.

The careful and systematic selection of outcome measures is necessary for scientifically sound clinical trials (Fig. 1). The US Food and Drug Administration (FDA) stresses that it is required to include outcome measures of importance to patients in every trial. Since the doctors' opinion of the severity of symptoms and disabilities does not necessary agree with that of the patients (Litwin et al., 1998; Schnadig et al., 2008; Vogelzang et al., 1997), we studied which symptoms and limitations are the most burdensome to pediatric patients with mitochondrial disorders and their parents and whether this corresponds to the estimation of their doctors' opinion.

Mitochondrial diseases are complex and heterogeneous multisystem disorders mostly affecting the function and sometimes the structure of the brain, muscles and heart (McFarland et al., 2010). Because of the complexity of these disorders, it seems difficult to determine which symptoms to measure during a clinical trial. We asked patients and their parents about the symptoms that they experience as most bothersome and most wanted to change during future treatment. To identify and classify symptoms and disabilities we used the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) framework (Fig. 2) (Ronen et al., 2011), developed by the World Health Organization (WHO). The ICF-CY checklist was used to inventory symptoms and disabilities in our patient population.

This is, to our knowledge, the first study investigating which complaints and disabilities patients with mitochondrial disorders and their parents experience in daily life.

2. Methods

All pediatric (<18 years) Dutch-speaking patients with a mitochondrial disorder, followed up regularly at the Nijmegen Centre for

Abbreviations: ICF-CY, International Classification of Functioning, Disability and Health for Children and Youth; WHO, World Health Organization; FDA, Food and Drug Administration.

☆ Conflict of interest: JS is founder and CEO of Khondrion BV.

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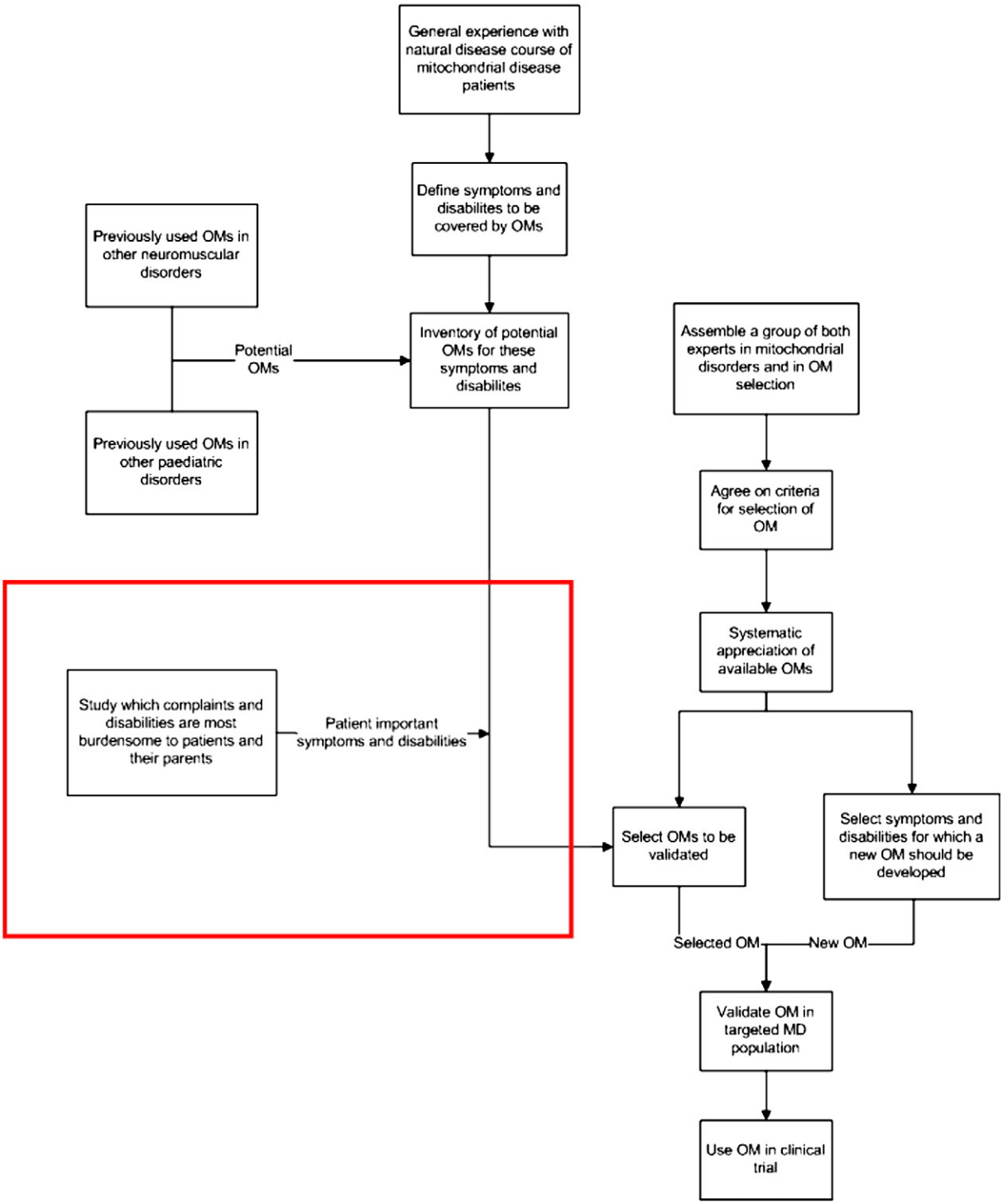

Fig. 1. Flowchart for selecting outcome measure instruments used to determine disease severity and follow-up disease progression to be used in clinical trials for children with mitochondrial disorders. In red marked the position of this study in the flowchart.

Mitochondrial Disorders, were included in this study. Patients were defined as having a mitochondrial disorder when the fresh muscle biopsy showed one or more of the following: i) ATP production 10% under the lower limit of the control range (Rodenburg, 2011), and/or ii) one or more enzyme complex deficiencies (under the limit of the control range), and/or iii) a confirmed pathogenic mitochondrial DNA (mtDNA) or nuclear mutation and/or iv) a mitochondrial syndrome (Leigh or MELAS syndrome, MNGIE, etc.) (Koopman et al., 2012). Patients were grouped as having myopathy, encephalomyopathy, encephalopathy or mainly gastrointestinal involvement based on their most prominent symptom(s), if they did not fit the profile of a specific mitochondrial syndrome.

We sent two questionnaires to all patients who met the inclusion criteria (see Supplementary file 1 (Dutch), translation in English Supplementary file 2). The first questionnaire was designed to assess which symptoms were most burdensome to patients and their parents. It contained three domains: i) the presence of symptoms/complaints in the child; ii) which three symptoms would (the parent expect) the child most like to change mostly; and iii) which three symptoms would the parents themselves like to change? The symptoms and complaints list