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Minireview

Cognitive endpoints for therapy development for neuronopathic mucopolysaccharidoses: Results of a consensus procedure

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ABSTRACT

The design and conduct of clinical studies to evaluate the effects of novel therapies on central nervous system manifestations in children with neuronopathic mucopolysaccharidoses is challenging. Owing to the rarity of these disorders, multinational studies are often needed to recruit enough patients to provide meaningful data and statistical power. This can make the consistent collection of reliable data across study sites difficult. To address these challenges, an International MPS Consensus Conference for Cognitive Endpoints was convened to discuss approaches for evaluating cognitive and adaptive function in patients with mucopolysaccharidoses. The goal was to develop a consensus on best practice for the design and conduct of clinical studies investigating novel therapies for these conditions, with particular focus on the most appropriate outcome measures for cognitive function and adaptive behavior. The outcomes from the consensus panel discussion are reported here.

Contents

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1. Introduction

Mucopolysaccharidoses are inborn errors of metabolism characterized by the progressive accumulation of glycosaminoglycans in tissues throughout the body [1]. There are currently eleven known mucopolysaccharidoses, each caused by a different lysosomal enzyme deficiency.

Mucopolysaccharidoses vary in their prevalence and presentation, although most include extensive somatic involvement affecting the heart, lungs, airway, bones, joints, vision, hearing, and gastrointestinal system [1]. In the most severe forms of mucopolysaccharidosis (MPS) types I, II and III, this is accompanied by central nervous system (CNS) dysfunction or decline, becoming evident in the second or third year of life and ultimately resulting in the loss of attained skills. The CNS manifestations of these conditions are devastating to parents, relentless in their decline, and result in premature death. CNS manifestations are also observed in MPS VII; an ultra-rare disease that is not discussed in this article.

Treatments for MPS I and II have been available for several years in the form of hematopoietic cell transplantation (HCT) and enzyme replacement therapy (ERT). Although both have been found to have benefits in addressing and preventing progression of many of the somatic features of these disorders [2–16], only HCT has been found to have any effect on CNS decline owing to the inability of ERT to cross the blood–brain barrier [16–20].

Currently, there are several potential disease-modifying products in pre-clinical and clinical development to address the CNS manifestations of MPS I, II and III, with the ultimate aim of preventing or halting the neurologic decline characteristic of these disorders. The design and conduct of clinical studies to evaluate the effects of novel therapies on CNS manifestations in children with neurodegenerative diseases is challenging. The most appropriate measures of the effects of novel therapies on the CNS are changes in cognitive function and adaptive skills (i.e. the ability to engage in day-to-day activities). Until now there have been a great variety of approaches taken to evaluate cognition and adaptive behavior in patients with mucopolysaccharidoses, which is perhaps understandable given the plethora of psychometric measurement instruments available for these purposes. To enable clinicians, investigators, regulatory bodies and caregivers to fully understand the relative effectiveness of treatments for mucopolysaccharidoses, it is essential that standard protocols are applied consistently to ensure reliable measurement of cognitive outcomes and adaptive behavior in clinical trials. The importance of this was emphasized at a workshop convened by the Food and Drug Administration on cognitive assessment in inborn errors of metabolism and in guidelines developed by the National Institutes of Health (NIH; www.nlm.nih/gov/cde) [21,22]. Owing to the rarity of mucopolysaccharidoses, multinational studies are often needed to recruit enough patients to provide meaningful data and achieve statistical power. However, this brings with it diversity of testing languages and cultures. The availability of the most up-to-date versions of tests also varies between countries, meaning that older versions of a psychometric measurement instrument may be used by some countries within the same study.

To address these challenges, an International MPS Consensus Conference for Cognitive Endpoints took place on 2–3 December 2016, organized by the US and UK MPS Societies and supported by industry. During this meeting an international panel of experts was convened to discuss approaches for evaluating cognitive function in patients with mucopolysaccharidoses. The goal was to achieve consensus on best practice for the design and conduct of clinical studies investigating novel therapies for these conditions, with a focus on the most appropriate outcome measures for cognitive function and adaptive behavior. The outcomes from the consensus panel discussion are reported here.

2. Methods

A modified Delphi technique was used to reach consensus on best practice for evaluating cognitive and adaptive function in patients with mucopolysaccharidoses. This methodology, developed by the Rand Corporation/University of California, Los Angeles (UCLA), CA, USA [23], is based on the original Delphi process [24], which has been widely used to achieve consensus on a specific issue and is increasingly used for the developing of clinical guidelines when there is insufficient evidence [20,25,26]. An overview of the consensus process is shown in Fig. 1.

In consultation with the UK Society for Mucopolysaccharide Diseases and US National MPS Society, an 18-member steering committee was formed and chaired by Elsa Shapiro, PhD. A comprehensive literature review was performed by a member of the steering committee – a psychologist with expertise in another inborn error of metabolism (DJ) – to consolidate the best available published information on the methods used to assess cognitive function and adaptive behavior in patients with MPS diseases, including psychometric properties, usefulness in various settings, and use and sensitivity to change in MPS diseases. Full details and findings from the literature review can be found in Janzen et al. elsewhere in this issue of *Molecular Genetics and Metabolism* [27]. The steering committee discussed and determined the composition of an expert panel to participate in a Delphi consensus process. The final composition of the expert panel included four pediatric neuropsychologists with expertise in mucopolysaccharidoses, two pediatric neuropsychologists with expertise in other neurological conditions, one neurodevelopmental pediatrician with expertise in psychological assessment in mucopolysaccharidoses, six pediatric physicians with expertise in mucopolysaccharidoses, a statistician, and a healthcare attorney/MPS caregiver. All participating clinicians and psychologists have authored peer-reviewed publications on mucopolysaccharidoses, with the exception of two pediatric neuropsychologists who have published extensively on neurocognitive testing in their respective fields.

The expert panel convened for a 1-day face-to-face meeting in London, UK. The meeting was facilitated by an independent clinical epidemiologist with experience of conducting Delphi-style consensus panels. The focus of the meeting was approaches for evaluating cognitive function and adaptive behavior in patients with MPS I, II or III. Methods for assessing behavior were not included in the discussion.

Before the meeting the panel members were provided with information about 14 measurement instruments previously used to evaluate cognitive outcomes in patients with mucopolysaccharidoses; these tools are discussed in detail in Janzen et al. elsewhere in this issue of *Molecular Genetics and Metabolism* [27]. Having reviewed this information, panel members with asked to answer an e-mail survey about:

- Whether they would want to consider these instruments during the consensus meeting, and
- Their assessment of the importance of 14 measurement characteristics on an 11-point scale (0, not important; 10, very important). Measurement characteristics included the psychometric properties of the instruments (e.g. reliability, sensitivity, validity), feasibility, and cross-cultural relevance.