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Minireview

Quantitative neuroimaging in mucopolysaccharidoses clinical trials

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ABSTRACT

The mucopolysaccharidosis (MPS) disorders are rare lysosomal storage disorders caused by mutations in lysosomal enzymes involved in glycosaminoglycan (GAG) degradation. The resulting intracellular accumulation of GAGs leads to widespread tissue and organ dysfunction. In addition to somatic signs and symptoms, patients with MPS can present with neurological manifestations such as cognitive decline, behavioral problems (e.g. hyperactivity and aggressiveness), sleep disturbances, and/or epilepsy. These are associated with significant abnormalities of the central nervous system (CNS), including white and gray matter lesions, brain atrophy, ventriculomegaly, and spinal cord compression. In order to effectively manage and develop therapies for MPS that target neurological disease, it is important to visualize and quantify these CNS abnormalities. This review describes optimal approaches for conducting magnetic resonance imaging assessments in multi-center clinical studies, and summarizes current knowledge from neuroimaging studies in MPS disorders. The content of the review is based on presentations and discussions on these topics that were held during a meeting of an international group of experts.

1. Introduction

The mucopolysaccharidosis (MPS) disorders are a group of lysosomal storage disorders, each characterized by the deficiency of a specific lysosomal enzyme involved in glycosaminoglycan (GAG) degradation. The resulting progressive accumulation of GAGs in cells and tissues leads to multi-organ dysfunction [1]. All MPS disorders are inherited in an autosomal recessive manner, except MPS II which is X-linked. Frequent manifestations of MPS include short stature, musculoskeletal abnormalities, hepatosplenomegaly, cardiorespiratory disease [1,2], and/or central nervous system (CNS) abnormalities [2,3]. However, there is great heterogeneity in the type, frequency, and progression rate of clinical manifestations between and within the different MPS disorders [1,2].

CNS signs and symptoms also vary between the different MPS disorders and seem to be related to the type of accumulating GAG [4]. Patients with MPS I, II, III, and VII, particularly those with rapidly progressing phenotypes, often present with brain abnormalities resulting in impaired cognitive development, hyperactive and/or aggressive behavior, sleep disturbances, and seizures [2,4–10]. In all these disorders, heparan sulfate is stored in the cells [4,11,12]. While in MPS IV and VI the main GAGs accumulating are keratan sulfate and dermatan sulfate, respectively, these patients do not present with significant cognitive impairment but can develop spinal cord compression and/or hydrocephalus [1–3,13].

In MPS disorders with CNS involvement, CNS imaging can function as a non-invasive tool for early diagnosis and monitoring of disease progression. In addition, it can help to select the most appropriate therapeutic intervention(s) and to monitor treatment efficacy [14–16]. Magnetic resonance imaging (MRI) has been used frequently in MPS clinical studies [3,17], mostly using qualitative or semi-quantitative endpoints [18–22]. More recently, advanced MRI techniques and post-processing software have provided quantitative MRI data that could be correlated with clinical outcomes, and thus may serve as biomarkers in clinical studies [14,15]. However, the use of MRI in clinical studies requires production of high quality and reliable data. To obtain these, it is important to apply the right approach from protocol design onward [23].

This review discusses the best approach to perform MRI in clinical studies, with focus on MPS, and summarizes current knowledge from neuroimaging studies in MPS disorders. Its content is based on information from an expert meeting on the brain in MPS, held on April 28–30, 2016 in Stockholm, Sweden, attended by 39 MPS experts from centers around the

Abbreviations: AD, axial diffusivity; CNS, central nervous system; CSF, cerebrospinal fluid; DTI, diffusion tensor imaging; FA, fractional anisotropy; FLAIR, fluid-attenuated inversion recovery; GAG, glycosaminoglycan; GM, gray matter; HCP, human connectome project; MD, mean diffusivity; MPS, mucopolysaccharidosis; MPS IH, MPS I Hurler; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NODDI, Neurite Orientation Dispersion and Density Imaging; PVS, perivascular space; RAFFn, Relaxation Along a Fictitious Field in the rotating frame of rank n; RD, radial diffusivity; WM, white matter

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world. Additional relevant literature was obtained from PubMed searches using search terms “Mucopolysaccharidoses”[Mesh] AND neuroimaging (free text) (41 items) and “Mucopolysaccharidoses”[Mesh] AND “MRI” (62 items). Publications not available in English were excluded. Searches were performed without date restriction. Additional publications were identified from reference lists within the most relevant MPS-related papers focusing on CNS imaging. The literature search was completed in August 2016.

2. Magnetic resonance imaging approach for multi-center studies

MRI is considered a valuable tool to study disease pathology and monitor disease progression in several disorders, including MPS [3,21]. Ideally, MRI studies provide high quality data that are consistent over time and across centers. However, biological variability and physical measurement variability can influence the robustness and reliability of MRI outcomes [14,23]. Consequently, meticulous attention should be paid to each step in the image acquisition process and analysis. This entails careful protocol development and testing, site qualification and training, ongoing site monitoring for protocol compliance, and quality control. Finally, use of appropriate analysis software and correct data archiving procedures are important [23].

2.1. Protocol design, site selection, and protocol training

Guidance on the design of imaging studies is provided by the Food and Drug Administration in the ‘Clinical trial imaging endpoint process standard guidelines for industry’ published in 2015 [24].

When developing an MRI protocol for a multi-center clinical study, the ultimate goal is to obtain reproducible and robust results across sites. In order to achieve this, each site should be able to meet the study requirements and their flexibility to accommodate different scanner vendors and scanner models, coil models, and scanner software versions must be guaranteed [23]. Not only different scanners, but also differences in analysis and post-processing of images can introduce variability. Standardized archiving and reporting of MRI data remain challenging due to the multitude of software (packages) available [25]. Ideally, only sites using the same scanner hardware and software should be selected. However, when studying rare diseases like MPS, patients need to be recruited from all over the world, and the significant disabilities usually associated with their disorders make it difficult to travel long distances. Consequently, these studies often include different sites using different scanner hardware and software. In order to minimize variability in results and allow comparison between sites and studies, harmonization of MRI protocols is essential and the selected MRI protocol needs to be designed for optimal within- and between-site reproducibility [15,23,24,26]. Some examples of harmonized protocols across different MRI platforms that are used in the Human Connectome Project (HCP) studies (www.humanconnectomeproject.org) [27] can be found at http://protocols.humanconnectome.org/HCP/3T/imaging-protocols.html or the Alzheimer's Disease Neuroimaging Initiative (ADNI) MRI protocols at http://adni.loni.usc.edu/methods/documents/mri-protocols/. In MPS and rare disorders studies in general, the selection of study sites is usually driven by the ability to recruit patients and to implement the study-specific MRI protocol. Similarity of the MRI equipment at study sites, such as scanner platform and magnetic field strength, and study personnel expertise are other important factors to be considered while selecting study sites. When a site is considered able to comply with the selected MRI protocol, site personnel should receive proper training on the protocol and data handling procedures [23,24]. Prior to study start, the protocol needs to be tested on a phantom and/or human volunteer. The site should only be approved when training and test results are of acceptable quality [23,24].

2.2. Monitoring of image quality

After site approval, adherence to the protocol and quality requirements must be continuously monitored. Any important event that could affect image quality (e.g. loss of key imaging personnel such as the radiologist or MRI technician, system software upgrades, or other changes in MRI equipment) should be reported to the principal investigator. In addition, at sites with few patients where time between subsequent study visits can be long and personnel involvement in the study is limited, important aspects of the protocol and data handling, such as MRI equipment used, MRI sequences and their parameters, and adherence to the MRI acquisition protocol, can be re-assessed before an upcoming study visit. Evaluation of MRI data should start as soon as possible in order to detect and address artifacts or system problems early on [23].

2.3. Selection of the study population

When selecting patients for MRI studies, the presence of MRI contraindications must be evaluated at the pre-screening visit. Potential contraindications for MRI that should be considered for MPS patients include MRI incompatible (or ferromagnetic) metal implants (e.g. knee or hip prostheses, screws for spine surgery from compounds other than titanium or stainless steel), cochlear implants, and cardiac pacemakers. Some implanted devices such as programmable shunts or metal materials used for orthodontic treatments and orthopedic C-spine surgeries contain MRI safe compounds. However, their proximity to the examined head or C-spine may complicate the subsequent MRI analysis due to data contamination by a susceptibility artifact that projects into the brain or C-spine scans resulting in challenging or impossible data analysis and making derived data results less reliable or not usable. In addition, the need and tolerance for anesthesia must be evaluated. This is especially important for MPS patients, in whom anesthesia can be associated with severe complications due to a presence and/or an exacerbation of pre-existing airway, cardiac, and spine conditions [28]. Typical problems that may arise in MPS patients during anesthesia include difficulty/inability to intubate; airway obstruction after anesthesia induction and extubation due to narrow airways; exacerbation of cardiac valve disease, coronary artery disease, or diastolic dysfunction; and spinal cord compression and/or ischemia due to spinal canal narrowing or atlantoaxial instability [28]. Sedation may be required for young patients and patients with behavioral problems who have difficulty lying down in an MRI scanner for a considerable amount of time. Unsedated scans can be collected while a subject is distracted via audio and video systems. For the correction of slight motion artifacts in the MRI data, motion-correction techniques are applied in the data post-processing. Finally, for progressive diseases such as MPS, it is important to have data from untreated age- and gender-matched patients, e.g. from a natural history study, or healthy controls to interpret the MRI results. This is especially crucial when using MRI as a clinical outcome to evaluate the effect of treatment. As neurological abnormalities are generally not reversible, the patient's age and/or degree of impairment at baseline should be considered to determine whether a treatment effect is still achievable. In general, it can be very challenging and in some cases almost unattainable (e.g. severe MPS I patients are almost all treated by hematopoietic stem cell transplant by 2 years of age) to find appropriate untreated control subjects due to the rarity of the MPS disorders and the fact that withholding or postponing treatment cannot be considered as it is against ethical principles. The rarity of MPS also confounds the performance of larger scale studies in these patients.

2.4. Selection of magnetic resonance endpoints

MRI endpoints can be either qualitative or quantitative. Traditionally, MRI studies in MPS have provided information on CNS anatomy based on qualitative ratings of scans by a radiologist [29], e.g.