Editorial

Metabolome alterations: a tool to assess efficacy in clinical trials for neuronopathic lysosomal disorders?

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When setting a clinical trial, one of the main difficulties is to establish which measurements of treatment efficacy will be informative. Studies in animal models allow tissue extraction, for example, and therefore *in situ* quantification of molecule, a possibility that usually is not available in clinical studies. This is especially true when the disease studied is rare, because frequently little is known regarding the natural history of disease progression, being assessment of the brain function particularly difficult. Mucopolysaccharidosis IIIB (MPS IIIB) is a rare lysosomal storage disorder presenting predominantly severe progressive neurological disease, with no treatment currently available. Ongoing clinical trials report that neuronopathic MPSs require consistent protocols to measure functional outcomes and recent studies are still debating about reliability, metrics, cross-cultural validation, sensitivity and feasibility of cognitive and adaptive measurements (1).

Having that in mind, Fu and colleagues (2) looked for metabolome alterations in MPS IIIB mouse serum both in early and late stages of the disease. They identified 18 metabolites altered as early as 2 months of age. Among these compounds, six amino acids and nine lipids were altered, including aspartate and fructose, for example. As the disease progressed, alterations were greater, both in their number and in their amplitude, and included a total of 231 metabolites. Molecules easily detectable by most clinical laboratories such as glucose, glutamate, glutamine and phenylalanine, were among the metabolites with altered levels. More importantly, they treated the mice with an AAV vector carrying the NAGLU transgene (rAAV9-hNAGLU). The mice not only showed impressive phenotype correction, but also the metabolomic changes responded well to a systemic rAAV9-hNAGLU gene delivery, going back to normal levels.

These results gain importance when considering that younger MPS IIIB mice have mild disease manifestations (3), but already present metabolomic alterations early in life. Most clinical trials in humans are designed to introduce a treatment intervention before cognitive decline shows up. In this context, the identification of early alterations in the disease and how they behave with treatment could be very informative.

It is important to point out, however, that it becomes imperative to establish a "metabolomic signature" in human patients. This signature could then be used as a reliable surrogate marker of treatment efficacy, once it is proven to reflect brain disease. Another source would be the cerebrospinal fluid (CSF), albeit more invasive.

The understanding of these alterations could be important not only for MPS IIIB, but also for other similar diseases. Once the patterns of alterations are identified, they can be used along functional outcomes as surrogate markers of efficacy in clinical trials.

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