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Applications of Biomarkers in Mucopolysaccharidosis Type IVA

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Description

Mutations in the N-acetylgalactosamine-6-sulfatase (GALNS) gene cause mucopolysaccharidosis type IVA (MPS IVA), a lysosomal storage disease. Skeletal dysplasia and the clinical symptoms of MPS IVA are produced by a disturbance of the cartilage and its extracellular matrix, resulting in an imbalanced growth pattern. Enzyme Replacement Therapy (ERT) with recombinant human GALNS has shown to be effective in daily activities and endurance tests. However, there is no evidence that ERT improves bone lesions or bone growth in MPS IVA patients, and there is no link between therapeutic efficacy and keratan sulphate levels in the urine, which build in MPS IVA patients. Proteomics methods, both qualitative and quantitative, were used. To find potential disease biomarkers, we investigated leukocyte samples from healthy controls (n=6) and untreated (n=5) and ERT-treated (n=8, obtained before and after treatment) MPS IVA patients. We chose a collection of proteins dysregulated in MPS IVA patients with ERT from 690 proteins found in leukocytes. Lactotransferrin, coronin 1A, neutral alpha-glucosidase AB, and vitronectin were discovered as possible protein biomarkers, all of which may alter bone and cartilage metabolism. To confirm the validity of these proteins as prospective MPS IVA indicators, more research into cartilage and bone changes in MPS IVA is needed.

Mutations in the GALNS gene cause Morquio A syndrome, also known as mucopolysaccharidosis type IVA, an autosomal recessive disorder. A lack of N-acetylgalactosamine-6-sulfatase [1-3] causes Keratan Sulphate (KS) and Chondroitin-6-Sulfate (C6S) to accumulate in many tissues, primarily bone, cartilage, heart valves, and cornea. Systemic skeletal dysplasia with inadequate ossification and subsequent growth imbalance [4] is characterised by short stature and neck, cervical instability, spinal cord compression, tracheal obstruction, prominent chest, kyphoscoliosis, laxity of joints, hip dysplasia, and knock knees. In untreated individuals, respiratory failure is the leading cause of death in their second and third decades of life.

In clinical practise, two therapies for MPS IVA are currently available: Enzyme Replacement Therapy (ERT) and Hematopoietic Stem Cell Transplantation (HSCT). The notion of cross-correction underpins ERT and HSCT, in which lysosomal enzymes are taken up by deficient recipients' cells and lysosomes *via* the mannose-6-phosphate receptor. For MPS IVA, ERT using the recombinant enzyme GALNS (elosulfase alfa) is a well-established treatment. Elosulfase alfa, like other kinds of ERT for Lysosomal Storage Disorders (LSDs), has a number of drawbacks. It requires weekly 4-6 hour infusions; it is cleared quickly due to its short half-life (35 minutes in humans, 2 minutes in mice); it is costly; avascular cartilage penetration is restricted; and patients can develop an immunological response to the infused enzyme [5].

Furthermore, elosulfase alfa clinical trials have showed no improvement in bone development and pathology. Recent research has found that the presence of KS, KS sulfation level, chondroitin-6-sulfate levels, and the presence of collagen type II in blood are all potential indicators for bone and cartilage pathology in MPS IVA patients. Although urinary KS levels have been used in clinical trials as a potential biomarker, there is no evidence that lower urinary KS levels correspond with clinical improvement. Urinary KS is produced by the kidneys and does not reflect the extent of bone and other important tissue deterioration in MPS IVA. As a result, urine KS is a pharmacokinetic marker rather than a surrogate biomarker.

Conflict of Interest

None.

References

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