

PEDIATRIC LEUKODYSTROPHIES**INTRODUCTION**

Leukodystrophies (LDs) are genetic disorders which primarily involve the white matter of the brain and spinal cord. They comprise a heterogeneous group in terms of genetic etiology, cellular pathology, imaging hallmarks, and clinical presentation. All LDs are characterized by the loss or dysfunction of oligodendrocytes and astrocytes, which comprise the glial cells of the central nervous system, and the consequent loss of myelin, the insulating substance of the brain; as such, myelin loss is the defining feature of all leukodystrophies. LDs are best known as affecting children, but they can appear in patients of all ages. Their overall prevalence has been estimated to be roughly 1:7,500 live births, although this is likely an underestimate, because of several newly described genetic forms and adult variants. Motor weakness with progressive spasticity are common features of the LDs, but their clinical symptoms can include vision loss, incoordination and imbalance, seizures, and cognitive impairment, among others. The clinical course of most LDs can be highly variable, from early death to relatively mild disease, depending upon the gene and specific mutation involved. For most LDs, treatment is primarily supportive. For LDs arising due to enzyme deficiency, such as globoid cell leukodystrophy (Krabbe disease), hematopoietic or umbilical cord derived-stem cell transplants (HSCT/USCT) can slow disease progression by donor cell provision of the deficient enzyme; generally though, the benefits of this approach are limited to early cases with mild disease. For other LDs, enzyme replacement therapy may be effective. For most LDs however, early white matter damage and myelin loss limits the effectiveness of these approaches.

RATIONALE AND EXPERIMENTAL EVIDENCE OF CELL-BASED THERAPIES FOR LEUKODYSTROPHIES

Human neural and glial progenitor cells (NSCs and GPCs) can be isolated from fetal brain tissue, and can be generated from pluripotent stem cells as well. They offer the potential to produce new astrocytes and oligodendrocytes, and to thereby remyelinate the injured or diseased white matter. Upon transplantation into mice lacking myelin, these cells differentiate into astrocytes and oligodendrocytes in a context-dependent manner, thereby restoring myelin and rescuing these animals, which would otherwise succumb to their disease. In order to obtain the large numbers of human glial progenitor cells needed for clinical trials, protocols to derive GPCs from human pluripotent stem cells have been developed. In preclinical animal studies, these stem cell-derived GPCs have demonstrated similar efficacy to those derived from human brain tissue.

WHAT IS THE CLINICAL STATUS OF CELL-BASED THERAPIES FOR LEUKODYSTROPHIES?

Currently, most patients with LDs can only be offered supportive treatment; few disease-modifying or curative strategies are available. Metabolic LDs due to enzymatic dysfunction, including the lysosomal storage diseases such as globoid cell leukodystrophy, and peroxisomal disorders like adrenoleukodystrophy, may be offered HSCT/USCT. However, the benefits of this approach are limited to mild and early-diagnosed cases; this approach cannot restore cells already lost, or repair damage that has already occurred. For that purpose, cell replacement therapy with human neural or glial progenitor cells is under development. This approach was first trialed in a phase I safety study in patients with Pelizaeus-Merzbacher disease, a congenital leukodystrophy characterized by mutations in the gene coding proteolipid protein (PLP), which is required for myelination. This study provided the first proof of principle that human NPCs transplanted into the cerebral white matter are well tolerated and could engraft the white matter of affected children. Yet the use of fetal tissue-derived cells hindered the further development of this strategy. As a result, more recent efforts have focused on the use of glial progenitor cells derived from human pluripotent stem cells.

WHAT DOES THE NEAR FUTURE HOLD?

HSCT and enzyme replacement therapies may be appropriate for some leukodystrophies characterized by enzyme deficiency, if diagnosed early enough. For most leukodystrophies though, whether caused by non-enzymatic genetic abnormalities in glial structure or myelin production, or diagnosed too late to prevent white matter loss, these currently available approaches are ineffective. For these cases – which comprise the vast

majority of LD patients - alternative approaches based on the transplantation of healthy neural or glial progenitor cells are under development. In particular, grafts of pluripotent stem cell-derived glial progenitor cells, intended to replace lost cells and thereby restore lost myelin, may offer an effective treatment approach, and one with curative intent. Going one step further, patient-derived iPSCs may then permit the use of genetic editing to correct underlying mutations, allowing autologous transplantation of a patient's repaired cells back into the brain. Similarly, genetic editing may permit the removal of immune recognition molecules from transplanted progenitor cells, to allow their safe integration without the need for immunosuppressive therapies. While these second-generation technologies are already under development, in the near future we may reasonably expect the transplantation of unmodified human glial progenitor cells for the treatment of the childhood leukodystrophies to advance to phase 1 safety trials, pending FDA approval.

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