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Perspective

Gaucher Disease in Childhood: Clinical Classification and the Emerging Landscape of Gene Therapy

Stefan Bittmann[1,2], Elisabeth Luchter[1], Elena Moschüring-Alieva[1]

[1]*Department of Pediatrics, Ped Mind Institute, Department of Pediatrics, Hindenburgring 4, D-48599 Gronau, Germany*

[2]*Honorary Professor (Hon.Prof.), School of Medicine, Shangluo Vocational and Technical College, Shangluo, 726000, Shaanxi, China*

***Corresponding author:** Stefan Bittmann, Department of Pediatrics, Ped Mind Institute, Department of Pediatrics, Hindenburgring 4, D-48599 Gronau, Germany and Honorary Professor (Hon.Prof.), School of Medicine, Shangluo Vocational and Technical College, Shangluo, 726000, Shaanxi, China.

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Abstract

Gaucher disease was known after Philippe Charles Ernest Gaucher (1854-1918), who described the disease the first time in 1882 in a 32 years-old woman as a medical student. He died in 1918 with the age of 63 years due to pneumonic infection. Gaucher disease is the most often found lysosomal storage disease with a prevalence of 1-9/100000 newborns. Gaucher Disease (GD) is a rare, autosomal recessive lysosomal storage disorder caused by mutations in the GBA1 gene, leading to a deficiency in the enzyme glucocerebrosidase. This deficiency results in the accumulation of glucosylceramide within macrophages, primarily affecting the spleen, liver, bone marrow, and, in severe cases, the central nervous system. In pediatric populations, GD manifests across a broad clinical spectrum, categorized into non-neuronopathic (Type 1), acute neuronopathic (Type 2), and chronic neuronopathic (Type 3) forms. While Enzyme Replacement Therapy (ERT) and Substrate Reduction Therapy (SRT) have revolutionized the management of systemic manifestations, they fail to cross the blood-brain barrier effectively, leaving a critical therapeutic void for neuronopathic variants. Gene therapy has emerged as a transformative approach, offering the potential for a definitive, long-term cure. This paper reviews the pathophysiology and clinical classification of pediatric GD, evaluates current therapeutic limitations, and explores the perspectives, clinical trials, and future outlook of gene therapy in children over the next decade.

Keywords: Gaucher disease, Pediatric oncology, Lysosomal storage disorders, Glucocerebrosidase, Neuronopathic Gaucher disease, Gene therapy, Adeno associated virus (AAV)

Introduction

Gaucher Disease (GD) represents the most prevalent lipidosis and one of the most common lysosomal storage diseases globally, with an overall incidence of approximately 1 in 40,000 to 100,000 live births, rising significantly to 1 in 850 within the Ashkenazi Jewish population [1]. The underlying molecular pathology involves biallelic mutations in the GBA1 gene, located on chromosome 1q21, which encodes the lysosomal enzyme acid β-glucosidase [2]. In healthy individuals, G Case catalyzes the degradation of glucosylceramide into glucose and ceramide. A deficiency in this enzyme leads to the progressive accumulation of undegraded glycolipids within the lysosomes of monocyte-macrophage lineage

cells. These lipid-laden cells, macroscopically known as "Gaucher cells," infiltrate vital organs, leading to a complex multi-systemic disease characterized by hepatosplenomegaly, cytopenias, skeletal abnormalities, and severe neurological deterioration in specific subtypes [3]. In children, the diagnosis of GD presents significant clinical challenges due to phenotypic heterogeneity. Pediatric patients often present with failure to thrive, severe bone pain, abdominal distension, and delayed puberty [4]. Over the past three decades, the management of systemic GD has relied heavily on intravenous enzyme replacement therapy and oral substrate reduction therapy. Although these interventions successfully mitigate hematological and visceral symptoms, their inability to cross the blood-brain barrier limits their efficacy against neurodegenerative forms (*Schiffmann* et al., 2020). Consequently, gene therapy—utilizing both ex-vivo hematopoietic stem cell modification and in vivo viral vector-mediated delivery—is currently being investigated as a groundbreaking frontier to provide systemic and neurological correction for affected children.

Classification of Gaucher Disease in Childhood

Historically and clinically, GD is classified into three major phenotypes based on the absence or presence and rate of progression of neurological involvement.

Type 1 GD is the most common form, accounting for over 90% of cases in Western populations. Although classified as non-neuronopathic, its onset frequently occurs during childhood. Clinical Presentation: Pediatric patients typically manifest with painless splenomegaly, hepatomegaly, anemia, and thrombocytopenia, which often leads to easy bruising and epistaxis. Skeletal Manifestations: Bone involvement is a hallmark of pediatric Type 1 GD, characterized by osteopenia, Erlenmeyer flask deformities of the distal femur, avascular necrosis, and debilitating bone crises caused by localized bone marrow ischemia [5]. Growth: Growth retardation and delayed onset of puberty are highly prevalent due to chronic inflammation and metabolic stress. Type 2 Gaucher Disease (Acute Neuronopathic)

Type 2 GD is the most severe form, with symptom onset usually occurring within the first six months of life. It is characterized by rapid, relentless neurodegeneration. Neurological Features: Infants present with brainstem dysfunction, oculomotor abnormalities (strabismus, saccadic palsy), hypertonia, opisthotonos, dysphagia, and trismus [6]. Systemic Features: Massive hepatosplenomegaly and ichthyosiform skin abnormalities are frequently observed. Prognosis: The disease progresses rapidly, with death typically occurring before the age of two due to respiratory failure or aspiration pneumonia. Type 3 Gaucher Disease (Chronic Neuronopathic)

Type 3 GD presents with a highly variable phenotype that emerges during childhood or adolescence. It features a slower, more chronic neurological progression than Type 2. The earliest and most consistent sign is Horizontal Supranuclear Gaze Palsy (HSGP). Patients may subsequently develop ataxia, myoclonic epilepsy, spasticity, and progressive cognitive decline (*Shipley* et al., 2013). Type 3 is further subclassified into Type 3a (predominant neurological symptoms), Type 3b (extensive visceral and skeletal involvement with limited neurological progression), and Type 3c (cardiovascular calcifications, corneal opacities, and mild splenomegaly).

Mechanisms of Gene Therapy in Gaucher Disease

Two primary modalities dominate the research and clinical trial landscapes:

Ex Vivo Lentiviral-Gene Therapy

This approach involves harvesting autologous hematopoietic stem and progenitor cells ($CD34^+$ cells) from the patient, transducing them ex vivo with a lentiviral vector carrying a functional GBA1 gene, and reinfusing them following myeloablative or reduced-intensity conditioning. Transduced microglial precursor cells can cross the blood-brain barrier, engraft within the central nervous system, and secrete functional GCase. This enzyme is then taken up by neighboring deficient neurons through cross-correction (*Soria*, et al., 2019). Clinical trials, such as those evaluating AVRO-RD-02, have demonstrated safety, robust engraftment, and significant reductions in toxic substrates (glucosylsphingosine) in Type 1 patients, paving the way for applications in Type 3 cohorts.

In Vivo Adeno-Associated Viral (AAV)-Gene Therapy

This approach utilizes engineered AAV vectors administered systemically or directly into the central nervous system (e.g., intracerebroventricular, cisterna magna, or intrathecal delivery) to directly transduce post-mitotic neurons and astrocytes. Highly neurotropic serotypes, such as AAV9 and AAV-PHP.B, are utilized for their superior ability to penetrate the blood-brain barrier following intravenous or targeted infusion. In vivo approaches are highly relevant for pediatric Type 2 and Type 3 patients, where rapid intervention is required to arrest neurodegeneration before irreversible structural damage occurs [7].

Critical Challenges and Technological Solutions

While the future is promising, translating pediatric Gaucher gene therapy into standard clinical practice requires overcoming several biological barriers:1. Immunogenicity and Neutralizing Antibodies Pediatric patients exposed to AAV vectors can develop robust immune responses [8-44]. Pre-existing neutralizing antibodies (NAbs) against specific AAV capsids can bind to the vector and completely block transgene delivery [45]. Current research focuses on creating next-generation synthetic capsids that evade immune recognition, alongside transient immunosuppression protocols to ensure safe vector administration [46]. For Type 2 and Type 3 GD, systemic intravenous vector delivery does not yield sufficient therapeutic concentrations within the central nervous system

[47]. In addition to direct intracisternal injections, scientists are designing novel, engineered AAV capsids capable of crossing the BBB via receptor-mediated transcytosis following standard intravenous injection [48]. Ex vivo lentiviral therapies historically carried a risk of insertional mutagenesis, where the viral vector integrates near proto-oncogenes [49]. Furthermore, traditional busulfan-based bone marrow conditioning causes profound cytopenias and long-term toxicity in growing children [50]. The field is shifting toward non-genotoxic antibody-drug conjugates (ADCs) for targeted bone marrow depletion, drastically lowering conditioning toxicity for pediatric patients [51]. Rather than adding extra copies of a gene, emerging fields like CRISPR-Cas9 base editing and prime editing aim to correct specific GBA1 point mutations directly within the native genome [52-57]. This ensures that GCase remains under normal, physiological regulatory control, removing the risks associated with viral integration or transgene over-expression.

Future of Gene Therapy in Gaucher Disease

The next decade, several key milestones and challenges will shape the delivery of gene therapy to pediatric Gaucher patients. The clinical success of gene therapy, particularly for Type 2 and Type 3 GD, depends heavily on early intervention. Over the next few years, the widespread integration of GD into universal newborn screening programs will allow infants to undergo gene therapy prior to the onset of clinical neurodegeneration. Next-generation synthetic AAV capsids with enhanced BBB tropism are being engineered. This will allow for non-invasive, high-efficiency central nervous system transduction via standard peripheral intravenous delivery. Managing the immune response against the viral vector and the newly expressed, foreign GCase enzyme remains a primary focus. Pediatric patients will require tailored, transient immunosuppression regimens to prevent neutralizing antibody formation and T-cell-mediated clearance of transduced cells. Determining whether a single childhood intervention provides lifelong expression or if pediatric liver growth dilute episomal AAV vectors over time is critical. This issue highlights the potential necessity for integration-targeted CRISPR/Cas9 configurations in future iterations. Gaucher disease in childhood presents a severe clinical spectrum that demands therapeutic options capable of addressing both systemic and neurological pathology. While conventional therapies have successfully managed systemic symptoms, they remain inadequate for neuronopathic variants. Gene therapy represents a major advancement in addressing this unmet medical need. Through ex vivo lentiviral stem cell modification and in vivo neurotropic AAV vector delivery, upcoming clinical strategies aim to achieve definitive, long-term disease modification. Continued clinical trials, refined vector designs, and the expansion of newborn screening will be crucial in establishing gene therapy as a standard curative option for pediatric Gaucher disease over the next decade. The landscape of pediatric Gaucher disease treatment is on the verge of a historic shift. Over the next decade, one-time gene therapies will likely transition from clinical trials to approved first-line therapies. For Type 1 pediatric patients, this means a childhood free from frequent hospital visits and the long-term threat of skeletal damage. For the devastating neuronopathic Type 2 and 3 variants, advanced neurotropic vectors represent the first real opportunity to cross the blood-brain barrier, preserve cognitive function, and extend life expectancy. Continuing clinical trials, rigorous safety monitoring, and optimized delivery systems will be essential to fully unlocking these curative strategies.

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Conflict of Interest

None.

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