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REVIEW PAPER

Inherited glycosylphosphatidylinositol deficiency disorders: a new group of inherited metabolic disorders

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ABSTRACT

Inherited glycosylphosphatidylinositol deficiency disorders (IGDs) are a group of rare congenital disorders of glycosylation with multisystemic involvement. The underlying cause is an abnormal structure of glycosylphosphatidylinositol, which plays a significant role in the attachment of proteins to the cellular membrane. These glycosylphosphatidylinositol-anchored proteins are an important part of receptors, function as hydrolytic enzymes, and play a crucial role in molecules adhesion, immune response, embryogenesis and neurogenesis. Patients present a variety of symptoms including developmental delay with intellectual disability, abnormalities of the central nervous, skeletal, circulatory, gastrointestinal, and urinary systems, facial dysmorphia as well as hearing and visual impairment. Elevated alkaline phosphatase is a characteristic biochemical feature. The current state of knowledge connects the highly differentiated course of clinical presentation with the heterogenic molecular background evaluated in the next-generation sequencing methods. We present a comprehensive review of the pathogenesis, clinical symptomatology and management options in IGDs.

KEY WORDS:

congenital disorders of glycosylation, inherited glycosylphosphatidylinositol deficiency disorders, glycosylphosphatidylinositol-anchored proteins, next-generation sequencing.

INTRODUCTION

Inherited glycosylphosphatidylinositol deficiency disorders (IGDs) are a group of rare and relatively recently discovered multisystem diseases, categorized as a subclass of congenital disorders of glycosylation (CDG) [1]. The underlying cause of these diseases is an abnormal structure of glycosylphosphatidylinositol (GPI), which plays a significant role in the attachment of proteins to the cellular membrane. These glycosylphosphatidylinositol-anchored proteins (GPI-APs) are an important part of receptors, function as hydrolytic enzymes, and play a crucial role in molecule adhesion, immune response, embryogenesis and neurogenesis [2, 3]. The first disease associated with the molecular origin of GPI deficiency was paroxysmal nocturnal hemoglobinuria in 1993 [4]. In this condition clonal hematopoietic stem cells are affected, leading to hemolytic anemia, thrombosis, smooth muscle dystonia, and occasionally bone marrow failure. Nevertheless, this disease is not considered an inborn error of metabolism, because it is a result of an acquired somatic mutation. Over the next 30 years, more than 20 new

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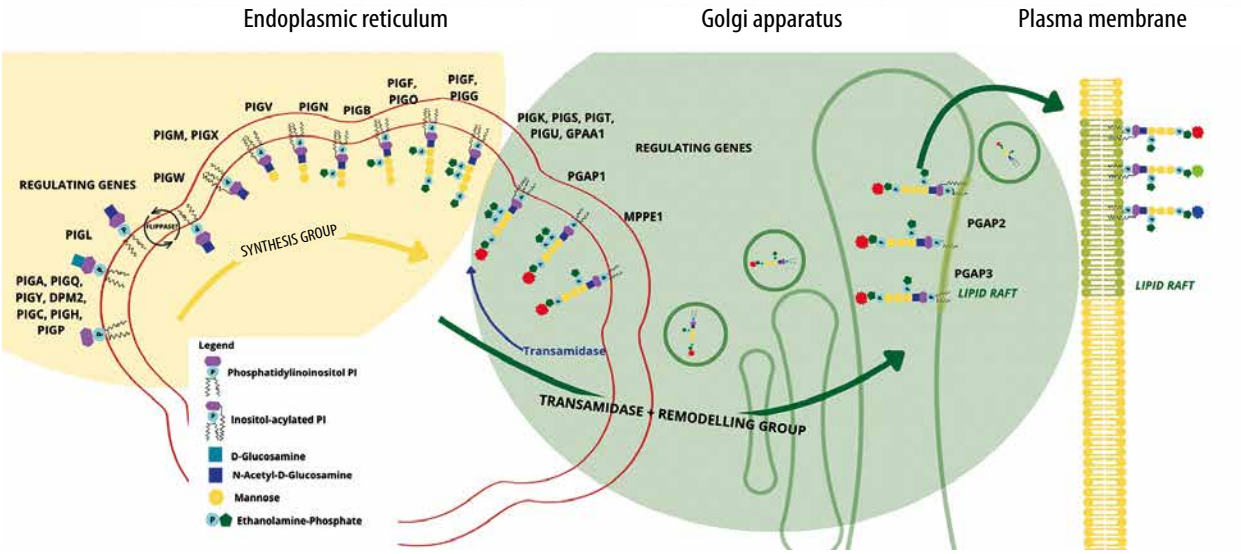

FIGURE 1. GPI biosynthesis pathway. Emphasis on synthesis stage genes (yellow) and transamidase + remodeling stage genes (green). Own work based on LC Carmody *et al.* [1]

inherited diseases related to GPI deficiencies were described. Patients with IGDs may present with a wide spectrum of clinical symptoms including developmental delay with intellectual disability, abnormalities of the central nervous system, skeletal, circulatory, gastrointestinal, and urinary system, dysmorphic facial features as well as hearing and visual impairment. Laboratory tests may reveal deviations from normal levels of alkaline phosphatase (ALP), which is often increased [2]. It is suggested that IGDs might be responsible for approximately 0.15% of developmental delay occurrences [5]. Heterogenous clinical phenotypes make the final diagnosis challenging. Molecular testing is therefore the most effective way to identify these diseases. Currently, only symptomatic treatment is available.

ETIOLOGY AND PATHOGENESIS

Glycosylphosphatidylinositol is a glycolipid composed of phosphatidylinositol and a core glycan which consists of ethanolamine phosphates, three mannoses as well as *N*-acetylglucosamine [6]. Over 150 different human proteins are attached to GPI as a post-translational modification [7]. Their size varies from just 12 amino acids to more than 200 kDa [8, 9]. Glycosylphosphatidylinositol-anchored protein synthesis requires at least 16 reactions, which can be divided into three stages: GPI synthesis, attachment of a nascent protein to the GPI anchor mediated by GPI transamidase, and remodeling, which is crucial to achieve stabilization of the anchor within the cell membrane [1, 10]. Initially, the GPI core formation takes place within the endoplasmic reticulum (ER), followed by multiple fatty acid remodeling stages occurring both in the ER and the Golgi apparatus. Finally, mature GPI-APs are delivered to the cellular membrane. The involvement of 27 genes in this process is widely acknowledged [6]. Pathogenic variants in at least 22 genes associated with GPI biosynthesis have been identified as the cause of IGDs [6, 11]. Mutations in consecutive *PIGA*, *PIGC*, *PIGH*, *PIGP*, *PIGQ*, *PIGY*, *PIGL*, *PIGW*, *PIGM*, *PIGV*, *PIGN*, *PIGB*, *PIGO*, *PIGG* genes disrupt GPI synthesis in the ER and variants in *PIGK*, *PIGS*, *PIGT*, *PIGU*, *GPAA1* alter GPI transamidase function. Abnormalities of *PGAP* genes affect the sorting and remodeling of the GPI-APs in the ER (*PGAP1*) and the Golgi (*PGAP3*, *PGAP2*) (Figure 1) [1, 2, 6]. The most common causes of IGDs are mutations in *PIGN*, *PIGA*, *PIGT*, *PIGV* and *PGAP3* genes [12]. Among pathogenic variants, the majority of cases are transmitted in autosomal recessive inheritance. However, *PIGA* mutations are inherited in an X-linked recessive manner. Pathogenic variants can disrupt GPI-APs structure and reduce their presentation. Abnormal GPI-APs are degraded or released into the serum [10].

CLINICAL AND BIOCHEMICAL FINDINGS

Clinical symptoms of IGDs predominantly manifest within the nervous system. The most common manifestations include developmental delay or intellectual disability, early-onset seizures and muscle tone abnormalities (usually hypotonia) [5]. According to Carmody *et al.* [1], neurodevelopmental abnormalities are apparent in 83% of patients, more often if mutations involve genes responsible for the latter steps of GPI-APs synthesis. Approximately half of the patients are unable to sit or stand independently, and a similar percentage have speech difficulties [13]. Intellectual delay varies in severity, commonly from moderate to profound [11]. Affected individuals may

FIGURE 2. Patients with variants in *PIGV* gene

present various types of seizures. Motor convulsions are found to be much more prevalent than non-motor, and focal onset is more common than generalized. Myoclonic and epileptic spasms were identified as the two predominant forms of focal motor seizures. Epilepsy onset usually occurs in the first two years of life, with a median age of 6–7 months, but cases with a first seizure episode in adulthood have also been described [11, 13]. Patients with mutations in synthesis stage genes usually present seizures earlier than those with transamidase and remodeling stage pathogenic variants. While electroencephalography (EEG) commonly reveals interictal epileptiform discharges, no distinctive features for IGDs were identified [13]. Many individuals are resistant to antiseizure medications and status epilepticus is frequently observed [14]. Hypotonia affects 64–72% of IGDs cases, whereas hypertonia is limited to a small percentage of patients [11, 13]. Other neurological symptoms include dystonia, ataxia, tremors, reflex anomalies and choreiform movements. Their clinical presentation may vary from mild to severe in each case [2]. Some affected individuals present behavioral abnormalities such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and hyperventilation [13].

Dysmorphic features occur in more than 80% of patients but are characterized by significant phenotypic heterogeneity. The prevailing abnormalities in head morphology encompass microcephaly, bitemporal narrowing, depressed glabella, malar flattening, micrognathia, telecanthus, hypertelorism, upslanted palpebral fissures, posteriorly rotated ears, large ear lobes, wide nasal bridge, depressed nasal bridge, high arched palate and widely spaced teeth [13]. The facial phenotype of patients with a mutation in some of the specific genes associated with IGDs is similar (Figures 2 and 3). Some patients may present hand anomalies such as deep plantar creases, short hands and fingers, clinodactyly, camptodactyly, hypoplastic or absent fingernails. Skeletal defects may also include scoliosis, hip dysplasia, reduced mineralization, and delayed bone age [2].

FIGURE 3. Patient with variant in *PIGT* gene

Patients with IGDs might struggle with multisystem involvement. Heart anomalies frequently comprise atrial or ventricular septal defect, patent foramen ovale, patent ductus arteriosus and valvular heart disease. A few patients develop cardiomyopathy [15, 16]. Gastrointestinal disorders include Hirschsprung disease, anteriorly placed anus as well as constipation and gastroesophageal reflux [2, 13]. Nephrological symptoms encompass ureteral dilatation, hydronephrosis, renal dysplasia and cysts [13]. In the ophthalmological examination cortical visual impairment, strabismus and nystagmus can be found. Some mutations can also predispose to hearing loss [2].

The hallmark biochemical deviation in IGDs, although not present in all genetic variants, is abnormal alkaline phosphatase (ALP) concentration. Enzyme GPI

transamidase enables protein attachment to the mature GPI anchor. This metabolic pathway can be disrupted by pathogenic variants of the GPI genes, affecting the latter phases of GPI biosynthesis (*PIGO*, *PIGV*, *PIGN* mutations). In such cases, GPI transamidase is unable to bind peptides to the immature anchors, and these proteins are released into the serum. This process may lead to hyperphosphatasia [2, 11]. Elevation of ALP concentration in such cases can vary widely from approximately 1.1 to 17 times the age-adjusted upper limit of the normal range [12]. Alternatively, mutations of the genes responsible for the initial stages of GPI biosynthesis usually result in peptide degradation in ER and normal or reduced (in *PIGT* mutation) ALP concentration in the blood. However, it is worth mentioning that some patients with *PIGY*, *PIGA*, *PIGL*, *PIGW*, *PGAP2* and *PGAP3* variants with hyperphosphatasia have also been described [2].

The most common anomalies on brain magnetic resonance imaging (MRI) are cerebral atrophy with a frontotemporal predominance, cerebellar and hippocampal atrophy, ventriculomegaly, thin corpus callosum, delayed myelination, white matter loss as well as restricted diffusion of the central tegmental tracts. Cerebral volume loss is usually progressive, indicating a neurodegenerative process, and is significantly associated with severe developmental delay. In a small percentage of patients, craniosynostosis is confirmed based on radiological investigations [13].

Despite differences in ALP concentration, some other genotype-phenotype correlations can be determined. Patients with *PIGT* mutations more often present gastrointestinal involvement and motor symptoms. Pathogenic variants in the *PIGA* gene significantly increase the risk of scoliosis, cardiac and renal involvement. Intractable epilepsy is common in patients with PIGN-IGD and PIGA-IGD [13]. Individuals with *PIGM* variants may have dilated superficial facial veins and vein thrombosis [17]. Hypoplastic fingernails and finger anomalies appear more frequently in *PIGV* pathogenic variants [18]. Ear anomalies and colobomas may differentiate *PIGL* mutations from other IGDs [19]. Patients with *PIGL* variants more often present hearing impairment, as well as cardiac and urologic malformations [2]. Conversely, seizures and facial dysmorphism are less frequent in PGAP1-IGD [20]. Autistic behavior has been described only in *PIGH* and *PGAP3* mutations, and diaphragmatic hernia only in *PIGN* and *PIGA* mutations [12, 13, 21, 22]. Megacolon was reported in *PIGV*, *PIGO* and *PGAP2* pathogenic variants [12]. No significant correlation was found between genotype and either dysmorphology or seizure type [13].

Several syndromes associated with IGDs symptoms have been defined. Six GPI anchor deficiencies (PIGV, PIGO, PGAP2, PGAP3, PIGW, PIGY) have a clinical phenotype of hyperphosphatasia with mental retardation syndrome (HPMRS from 1 to 6, Mabry syndrome) characterized by moderate to severe intellectual disability, dysmorphic features, hypotonia, seizures and persistent hyperphosphatasia. It is important to highlight that the syndrome's phenotype can be variable to some extent and, for example, certain patients may have only borderline elevation of ALP. Mutations in *PIGN*, *PIGA*, *PIGT* and *PIGQ* genes may lead to multiple congenital anomalies: hypotonia-seizures (MCAHS) syndromes with facial anomalies, developmental delay, neurologic symptoms and variable congenital malformations involving the urinary system. Presentation of MCAHS is usually more severe than HPMRS. Another syndrome caused by *PIGL* pathogenic variants, featuring coloboma, congenital heart disease, ichthyosiform dermatosis, mental retardation and ear anomalies, is known as CHIME syndrome [10, 12, 23].

DIAGNOSIS

The diverse clinical IGD presentations pose difficulties in reaching a final diagnosis. In some cases, elevated alkaline phosphatase levels may be a valuable finding. Glycosylphosphatidylinositol deficiency cannot be identified by the analysis of transferrin isoforms like some other CDG [3]. Therefore, molecular investigation becomes the most beneficial diagnostic approach. Next-generation sequencing (NGS) using a panel of genes associated with IGDs, or whole exome sequencing (WES), is the preferred test due to its rapid and comprehensive evaluation of multiple genes. Analyzing the surface expression of GPI-APs by flow cytometry in the patients' fibroblasts or blood granulocytes may provide information on how specific variants impact GPI synthesis [24]. However, decreased expression levels of GPI-APs (e.g. CD16, CD24, CD55, CD59), as well as fluorescently labelled aerolysin (FLAER), which attaches directly to the proper anchors, do not appear to be sufficiently reliable as biomarkers, considering their normal levels in some pathogenic variants [10]. Their expression may also vary depending on the tissue: evaluation of GPI-AP appears to be more sensitive in fibroblasts than in blood cells [12]. Nevertheless, flow cytometry should be considered, particularly in cases with variants of uncertain significance accompanied by IGD clinical symptoms.

MANAGEMENT

Affected individuals need multidisciplinary care including neurologist, ophthalmologist, laryngologist, cardiologist, gastroenterologist, nephrologist and orthopedist support. All patients should undergo a baseline abdominal ultrasound examination and echocardiography to detect any potential malformations. EEG investigation is required. MRI of the head is also worth considering. A child's development, vision and hearing need to be regularly evaluated. If chronic constipation is present, Hirschsprung disease and anal abnormalities must be ruled out [12].

Therapeutic options in IGDs are limited, and patients usually receive only supportive treatment. The majority of children require early developmental support, including physiotherapy and speech therapy. Comprehensive physical therapy is essential for preserving patients' mobility. Some affected individuals present feeding difficulties requiring enteral nutrition. Pharmacological therapy is primarily directed towards patients with seizures. Valproic acid, levetiracetam, and topiramate in standard doses are preferred anti-epileptic drugs in IGDs. Less frequently, phenobarbital, clobazam, carbamazepine and clonazepam are administered [11]. Some patients with PIGA-IGD and epilepsy may benefit from a ketone diet [25]. The introduction of the histone deacetylase inhibitor butyrate can successfully resolve seizures caused by a mutation in the *PIGM* promotor [26]. A deficiency of GPI-anchored enzyme called tissue non-specific alkaline phosphatase (TNSALP) may disrupt the dephosphorylation of pyridoxal-5-phosphate to pyridoxal and reduce its transport through the blood-brain barrier. Lower vitamin B_6 concentration in the brain leads to decreased synthesis of the neurotransmitter GABA and intractable seizures. Considering this aspect, some patients with *PIGV*, *PIGA*, *PIGL* or *PIGO* deficiency might benefit from oral vitamin B_6 supplementation in the form of pyridoxine or pyridoxal-5-phosphate [14, 27]. According to Bayat *et al.* [14], the dose of both forms may be started at 10–15 mg/kg/day, administered twice daily. If no significant adverse effects are observed within 1 or 2 weeks, the dosage can be increased to 20–30 mg/kg/day.

The prognosis for many patients with IGDs is poor and associated with global developmental delay and intellectual disability. The neurodegenerative process is often progressive. The predominant causes of death are respiratory failure due to airway infection and the consequences of epileptic seizures, as well as complications after surgical procedures performed because of congenital defects [13].

CONCLUSIONS

Inherited glycosylphosphatidylinositol deficiencies are heterogeneous disorders with a predominant neurological presentation. This group of diseases should be considered in patients with neurodevelopmental abnormalities, hypotonia, seizures, and multiorgan involvement, especially if cerebral or cerebellar atrophy is present. The final diagnosis requires a genetic confirmation and may be established using NGS techniques, such as a panel of targeted genes or WES. Management usually involves multidirectional supportive care with anti-epileptic pharmacotherapy. Further research is needed to improve therapeutic options for patients with this rare group of disorders.

DISCLOSURES

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