LIFE WITH GLYCOGENOSIS IXa: DELAYED DEVELOPMENT AND THE PATH TO THERAPY IN A CASE STUDY

Barbora Lanková[1], Michal Vostrý[1,2], Veronika Kvochová[2], Ilona Pešatová[1], Radka Beranová[2], Ivana Štolová[2]

[1] Faculty od Education, J. E. Purkyně Unviersity in Ústí nad Labem (Czech Republic)
[2] Faculty of Health Studies, J. E. Purkyně Unviersity in Ústí nad Labem (Czech Republic)

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Abstract

This article presents a case study of a child diagnosed with glycogenosis IXa, a rare metabolic disorder caused by a deficiency of phosphorylase b kinase, which disrupts glycogen metabolism and leads to its accumulation in the liver. This condition results in a range of clinical manifestations, including hepatomegaly, hypoglycemia, muscle hypotonia, delayed psychomotor development, and other neurological impairments. The study focuses on a detailed description of the patient's clinical symptoms, which include difficulties with gross and fine motor skills, delayed speech and cognitive development, reduced physical activity, and problems maintaining balance. As part of the proposed therapy, the article highlights the importance of a multidisciplinary approach encompassing medical, rehabilitative, psychological, and educational care. Various rehabilitation methods are discussed, including proprioceptive neuromuscular facilitation (PNF), acral coactivation therapy (ACT), and sensorimotor stimulation, all aimed at increasing muscle tone, improving motor functions, and enhancing coordination. Speech therapy focuses on the development of speech and communication skills, with interventions tailored to the child's individual needs. Pharmacological treatment includes the administration of nootropics to support the development of the central nervous system, and dietary therapy also plays a crucial role, aiming to prevent hypoglycemia and promote growth through a diet rich in proteins and complex carbohydrates. The presented case underscores the significance of multidisciplinary team collaboration and individually tailored therapeutic approaches to ensure optimal care for patients with glycogenosis IXa. The study also opens avenues for further research into the long-term effectiveness of various therapeutic methods, with the goal of improving patients' quality of life and minimizing complications associated with this chronic metabolic disorder.

Key words: glycogenosis, metabolic disorders, psychomotor retardation, multidisciplinary collaboration, helping professions, delayed development,

INTRODUCTION

Glycogen storage diseases (GSDs) are rare congenital disorders characterized by disruptions in glycogen metabolism, leading to its accumulation in tissues or problems with its breakdown (Beauchamp et al., 2007; Lau et al., 2011). Based on specific enzyme deficiencies and affected tissues, 24 types of GSDs have been identified so far (Kanungo et al., 2018). GSD type IXa is caused by a deficiency of enzymes or transport proteins involved in glycogen metabolism. This deficiency of phosphorylase b kinase (PhK) is the cause of GSD type IX. The first description of PhK deficiency in the literature appeared in 1966 (Hug et al., 1966). The protein consists of four subunits (α, β, γ, δ), each encoded by a different gene. Based on the affected gene, GSD type IX is divided into four subtypes (Beauchamp et al., 2007). GSD IXa most commonly has X-linked recessive inheritance, which explains the higher incidence in male patients (Nguyen et al., 2020; Tsilianidis et al., 2013). The incidence of GSD type IX is approximately 1 in 100,000 live births, with IXa accounting for about 75 % of these cases (Davidson et al., 1992; Maichele et al., 1996). Clinically, PhK deficiencies can be categorized based on the primarily affected tissues into hepatic or muscular phenotypes (Beauchamp et al., 2007; Walter et al., 2016). Hepatic phenotypes are more common, while muscle PhK deficiency is relatively rare (Goldstein et al., 1993). Clinical manifestations are highly variable, and their characteristics depend on specific mutations, whose spectrum is very broad (Nguyen et al., 2020). Typical symptoms include hepatomegaly, chronic liver disease, hypoglycemia, hyperlipidemia, and delayed psychomotor development (Nguyen et al., 2020; Fu et al., 2019; Hendrickx et al., 1996; Massese et al., 2022). Increased levels of triglycerides and cholesterol are often observed in GSDs affecting the liver. Due to impaired glucose metabolism, there is fasting intolerance, which triggers increased lipolysis and fatty acid oxidation in mitochondria (Ozen, 2007). Most individuals with PhK deficiency reach normal height, but growth development is characterized by initial retardation during the first 2–3 years, followed by gradual normalization of growth (Schippers et al., 2003; Willems et al., 1990). Short stature is accompanied by a round face resembling a doll's face (Kishnani et al., 2019).

The most common manifestations involving the muscular and skeletal system include muscle weakness and pain, hypotonia, and gross motor skill disorders (Lau et al., 2016; Waheed et al., 2020). Decreased bone mineralization leading to osteopenia is also common (Beauchamp et al., 2007; Kishnani et al., 2019). Some cases also include neurological problems such as epilepsy, ataxia, dysarthria, dysmetria, nystagmus, mild spasticity, autonomic dysfunction, decreased vibration perception in the lower limbs, and delayed cognitive and speech development (Burwinkel et al., 1998; Smith et al., 2020). It is therefore evident that clinical symptoms can have a wide spectrum. Symptoms usually appear in early childhood or childhood (Massese et al., 2022), although asymptomatic forms often predominate. Although GSD IXa is often considered a milder form of glycogen storage disease (Morava et al., 2005) and, due to gene mutation, is regarded as a benign condition (Willems et al., 1990), it can lead to more serious or long-term complications such as liver cirrhosis (appearing already in early childhood), cerebellar atrophy, or increased risk of fractures (Johnson et al., 2012; Schönau, 1996; Smith et al., 2020). Although GSD IX is a significant subgroup of glycogen storage diseases, its diagnosis is often complicated and time-consuming due to rarity, overlapping symptoms with other types of glycogen storage diseases, and genetic diversity (Kim et al., 2015). For reliable recognition of GSD IXa, genetic testing is usually necessary because symptoms are nonspecific and mild, which can lead to diagnostic delays (Fu et al., 2019; Zhu et al., 2023). Diagnosis is further supplemented by clinical history and laboratory tests (Massese et al., 2022). An alternative is liver biopsy, which is invasive and does not allow precise identification of the disease type (Zhu et al., 2023). For patients with GSD type IX over five years old, cardiological examination is recommended at intervals of 1–2 years to monitor possible complications (Roscher et al., 2014).

It is important to note that diagnosis takes an average of six years, indicating persistent difficulties with early recognition of the disease, especially in areas without access to enzyme testing (Fu et al., 2019). Treatment consists of dietary measures, particularly the administration of foods low in simple sugars and high in proteins, primarily in the form of uncooked cornstarch, to prevent hypoglycemia (Zhu et al., 2023; Brown et al., 2015; Karande et al., 2016). The diet should be rich in proteins, which should constitute 2–3 grams per kilogram of body weight, corresponding to approximately 20–25 % of total caloric intake (Derks et al., 2021). Carbohydrates should cover about 45–50 % of daily caloric intake, with each meal containing complex carbohydrates along with proteins for better stabilization of glucose levels (Kishnani et al., 2019). This measure should be followed not only during the day but also through nocturnal feeding (Pennisi et al., 2020). Strict monitoring of glycemia is also necessary. Long-term care also includes monitoring bone density and supplementation with calcium and vitamin D to prevent osteopenia and fracture risk (Ross et al., 2020).

With strict adherence to the dietary regimen and regular monitoring of health status, the prognosis is usually favorable (Massese et al., 2022). Although some experts perceive this disease as asymptomatic or consider its treatment unnecessary, initial symptoms such as nausea and vomiting can negatively impact social and school life. Delayed growth and psychomotor development can then affect the psyche during adolescence, which can ultimately worsen the overall quality of life (Schippers et al., 2003). It follows that the issue of glycogen storage disease IXa affects multiple areas simultaneously, and it is therefore appropriate to present a case study emphasizing a multidisciplinary approach to the diagnosis and therapy of these patients.

CASE STUDY

The patient arrives for examination with his mother and an interpreter, as the family is from Ukraine and the child has had problems since he stopped breastfeeding, specifically observable abdominal growth and other symptoms of the disease. The patient was born in 2020 (he was 3.9 years old at the time of the case study). The first examination was conducted at 2.5 years of age. The processing of anonymized data was in accordance with the Ethics Committee of FZS UJEP and after obtaining verbal consent for the processing of personal data.

Family History: Mother (born 1988): pharmacist, no health issues, non-smoker, no history of drug or toxic substance use. Father (born 1983): bricklayer, non-smoker, no serious health problems or toxic habits. Sibling: girl (born 2011), also suffering from frequent respiratory infections, suspected Henoch-Schönlein purpura, constipation, and frequent illnesses during childhood. From a neurological standpoint, the family history is relatively uncomplicated, but there is a burden associated with infections and overall health instability in the children.

Personal History: The patient's health began to be concerning after the cessation of breastfeeding at the end of 2022. The mother noticed an enlarged abdomen and the presence of hepatomegaly, which led to suspicion of a metabolic disorder. Additionally, there was a slowdown in overall development, especially in motor skills and speech. Symptoms such as hypotonia (reduced muscle tone), hepatomegaly (enlarged liver), and a general reluctance toward physical activity supported the diagnosis of glycogen storage disease type IXa (GSD IXa). Other significant factors in the personal history include frequent infections in the family, which may have contributed to the deterioration of the child's overall health, and the diagnosed GSD IXa.

Clinical Neurological Examination: Examination on February 23, 2023: The patient was examined at the age of 2 years and 5 months. The child was present with an interpreter, as the family is from Ukraine and arrived in the Czech Republic after the outbreak of war. The main complaints concerned the child's physical inactivity, inability to maintain balance, problems with gross and fine motor skills, and overall developmental delay.

Gross Motor Skills: The patient moves slowly, has difficulty walking, falls, and is generally clumsy. Examination reveals muscle weakness, especially in the lower limbs. Fine Motor Skills: The patient plays with toys awkwardly, cannot grasp toys properly, and has difficulty coordinating them.

Cognitive Abilities: Mental development corresponds to a mildly delayed child, but basic reflexes are present. He responds to sounds and can pronounce basic words; however, a delay in speech development is noticeable. Reactions: Primary reflexes are preserved (palmar grasp, Babinski reflex etc.), but finer motor responses are slowed. Muscle hypotonia affects the child's overall ability to manipulate objects.

Important Tests*:* Electroencephalography (EEG) – August 22, 2023: The result shows abnormal activity in the central nervous system. The EEG examination demonstrates mild irregularities that may be related to a metabolic disorder and psychomotor retardation. The neurologist recommends further monitoring. Liver Tests: Hepatomegaly is confirmed, along with elevated liver enzymes, which is a typical symptom of GSD IXa.

Examination on November 14, 2023: During this examination, borderline motor skills are evident. The patient can play but is often observed throwing objects on the ground and then picking them up, which may signal sensory issues or reduced motor control. Objective Findings: Normal neurological findings, but hypotonia persists, especially in the trunk and lower limbs. Conclusions: Overall, the symptoms correspond to a moderately severe form of GSD IXa with persistent difficulties in fine motor skills and hypotonia.

Diagnosis*:* Based on clinical examinations and tests, the patient was diagnosed with glycogen storage disease type IXa (GSD IXa). This type of metabolic disorder is characterized by impaired glycogen storage in the liver, causing hepatomegaly, muscle hypotonia, delayed motor development, and cognitive difficulties. The patient has also been diagnosed with delayed psychomotor development. This developmental deficit is particularly

evident in the areas of gross and fine motor skills, which is a consequence of reduced muscle tone typical of metabolic disorders like GSD IXa.

Recommendations for Treatment

Psychological and Speech Therapy Care: Speech therapy has already been initiated with the aim of developing the patient's speech and communication skills. Regular monitoring and evaluations focused on the further development of speech abilities are recommended. Speech therapy should include special programs tailored to patients with metabolic disorders. Pharmacotherapy: The patient was advised to use nootropics (Equazen), a fatty acid-based preparation that has a positive effect on the development of the brain and central nervous system. Additionally, other nootropics supporting the development of the central nervous system may be utilized if deemed beneficial for the patient. Rehabilitation: Intensive physiotherapy and occupational therapy are crucial for improving muscle tone and coordination of movements. Rehabilitation exercises should focus on developing gross motor skills, especially walking, balance, and fine motor skills (e.g., manipulating objects).

Neurological Monitoring: Regular neurological follow-up is recommended once or twice a year, depending on the patient's development and EEG examination results. This monitoring is important for tracking the progression of glycogen storage disease and any changes in the patient's neurological condition. Prognosis: The prognosis for a patient with glycogen storage disease type IXa depends on many factors, particularly the degree of involvement of the muscular and cognitive systems. Regular monitoring, timely rehabilitation, and adequate therapy can improve the patient's overall development. Glycogen storage disease type IXa is a chronic metabolic disorder that requires lifelong treatment and monitoring; however, early interventions can minimize the impacts on quality of life.

INTERVENTION

Special education and speech therapy intervention

The boy’s speech development is significantly delayed, both in the expressive and receptive components, and therefore all language levels need to be supported. Emphasis should primarily be placed on expanding his vocabulary, especially since his mother tongue is different (Ukrainian). In interventions, it is necessary to build on the child’s current level and realistic possibilities so that his overall development and communication competencies are stimulated. Initially, it is advisable to focus on developing comprehension of speech using simple instructions accompanied by gestures and visualization. Vocabulary development can be supported with the help of real objects, photographs, and pictorial materials. It is then important to repeat words and to add rhythm and melody to speech, for example by using simple poems and rhymes and playing rhythmic instruments. At the same time, the intervention will focus on developing auditory perception (e.g., distinguishing sounds, locating their sources) and gradually strengthening verbal memory—starting with words, then moving on to simple sentences, rhymes, and poems. His speech development and overall progress should also be supported by developing self-care skills and independence, as well as strengthening his emotional and social maturity. This includes developing fine and gross motor skills, graphomotor and visuomotor skills, and strengthening visual perception. All activities should be structured so that there is a calm, stable place for working with the child both at preschool and at home, given that he also has a significantly weakened ability to concentrate. The ability to focus can be enhanced by selecting activities that the child finds enjoyable. In the beginning, it is best to keep activities to just a few minutes, gradually extending their duration. It is also beneficial to schedule frequent relaxation and calming moments and alternate activities more often. Throughout the day, provide positive motivation, praise, and small rewards for completing tasks (e.g., stickers or pictures). Allow the child time for a gradual adaptation. He requires a safe and empathetic environment.

This is a boy with special educational needs, and supporting his speech development through education in a small preschool group using special pedagogical methods focused mainly on the development of speech and language skills is recommended. An individualized approach and intensive speech therapy are essential. In preschool, it is appropriate for the special education teacher to provide methodological support to his parents so that consistent approaches to his development can be ensured in collaboration with the family.

Rehabilitation Interventions

In the therapy of a child with glycogen storage disease type IXa, it is essential to apply various therapeutic methods that effectively contribute to improving motor skills and balance. The main goal of physiotherapeutic intervention is to increase muscle tone and muscle strength, enhance coordination, optimize gait patterns, and prevent issues such as muscle atrophy and falls, which could subsequently cause additional problems. One effective method is proprioceptive neuromuscular facilitation (PNF), which focuses on working with diagonal movement patterns. These patterns stimulate movement in natural diagonal trajectories that correspond to everyday activities, thereby contributing to the functionality of the musculoskeletal system. PNF activates synergistic muscle groups, emphasizes proprioception, and thus enhances body awareness in space and control over movement. Part of this method also includes gentle stretching during muscle activation, which can prevent muscle shortening and atrophy. Muscle strengthening can be supported by using therabands and strengthening techniques like the repeated contraction technique. Specifically, diagonals can be utilized on the lower limbs, pelvis, or trunk. Another effective method is acral coactivation therapy (ACT), which focuses on activating and strengthening muscle groups throughout the body in developmental kinesiology positions. ACT concentrates on improving muscle tone, coordination, and overall motor function. It helps to straighten the spine and strengthen the muscles of the deep stabilization system of the spine, which are crucial for proper postural control and overall functionality of the musculoskeletal system. The method of dynamic neuromuscular stabilization is similar to ACT and also contributes to the activation of stabilizing muscles and improvement of posture.

Sensorimotor stimulation plays a significant role in this therapy as well. Through proprioceptive stimulation, it enhances the body's ability to perceive its position and movement in space, which is essential for maintaining stability and coordination. This stimulation strengthens the deep stabilizing muscles and contributes to better postural control, which is key for maintaining balance and proper posture. Various unstable surfaces are used in therapy, such as Posturomed, balance discs, BOSU, FLOWIN, and different types of unstable segments and wedges, which allow for specific proprioceptive stimulation. These aids create controlled instability, thereby activating stabilizing muscles and improving balance, coordination, and postural stability. In addition to these therapeutic methods, various devices can be included in the intervention, which can motivate the child to engage in more physical activity. For example, the Balance Tutor helps optimize gait patterns and reduce the risk of falls. This technology can also be used in games that involve weight shifting, contributing to improved balance. Another device is the Imoove, which functions as an unstable surface, activating the muscles of the deep stabilization system of the spine and allowing for various exercises to strengthen specific muscle groups. Gait training represents another important component of this intervention, as it improves not only mobility but also the functionality of daily activities. Overall, it can be stated that the combination of various therapeutic methods and devices creates a comprehensive approach to the rehabilitation of children with metabolic disorders, focusing on increasing muscle tone and strength, improving motor skills, and preventing complications.

DISCUSSION

Glycogen storage disease type IXa is a rare metabolic disorder caused by a deficiency of phosphorylase b kinase, leading to impaired glycogen metabolism and subsequent clinical manifestations such as hepatomegaly, hypotonia, and delayed psychomotor development (Beauchamp et al., 2007). In the presented case of a child from Ukraine, symptoms appeared after the cessation of breastfeeding, which aligns with literature indicating that manifestations often occur in early childhood (Massese et al., 2022). Diagnosis of glycogen storage disease IXa is often complicated due to nonspecific symptoms and overlap with other types of glycogen storage diseases (Kim et al., 2015). In our case, the diagnosis was established based on clinical manifestations, laboratory tests, and neurological examination. Genetic testing, considered the gold standard for confirming the diagnosis (Fu et al., 2019), was not mentioned, which may be related to limited availability of these tests for families from war-affected regions. A multidisciplinary approach to treatment is crucial for improving the prognosis of patients with glycogen storage disease IXa (Kishnani et al., 2019).

Initiation of speech therapy and recommendations for physiotherapy and occupational therapy are consistent with recommended practices aimed at enhancing muscle tone, coordination, and motor skills. Rehabilitation interventions such as proprioceptive neuromuscular facilitation and acral coactivation therapy have proven effective in strengthening muscles and improving patients' functional abilities (Hermens et al., 2006). Pharmacotherapy involving nootropics like Equazen may support cognitive functions and central nervous system development, although evidence of their effectiveness in glycogen storage disease IXa is limited. Dietary measures, including a diet rich in proteins and complex carbohydrates, are essential for preventing hypoglycemia and promoting growth (Ross et al., 2020). In our case, dietary intervention was not discussed in detail, which represents a potential area for further improvement in care. The prognosis of patients with glycogen storage disease IXa is variable and depends on the severity of symptoms and the timeliness of intervention (Tsilianidis et al., 2013). Regular neurological monitoring is important for tracking disease progression and adjusting therapeutic approaches. Studies indicate that early rehabilitation can significantly improve motor functions and quality of life in patients (Schippers et al., 2003). In conclusion, the presented case highlights the importance of a comprehensive and individualized approach to patients with glycogen storage disease IXa. Multidisciplinary team collaboration, encompassing medical, rehabilitative, and psychological care, is essential for optimal management of this condition. Further research is needed to better understand the efficacy of various therapeutic methods and to develop standardized care protocols.

CONCLUSION

Glycogen storage disease type IXa (GSD IXa) represents a rare yet significant metabolic disorder characterized by impaired glycogen metabolism due to phosphorylase b kinase deficiency. The presented case underscores the complexity of diagnosing GSD IXa, particularly in populations with limited access to advanced genetic testing, such as families affected by conflict-related displacement. Early recognition of clinical symptoms, including hepatomegaly, hypotonia, and delayed psychomotor development, is crucial for timely intervention and improved patient outcomes. A multidisciplinary approach is essential in managing GSD IXa, encompassing medical, rehabilitative, and psychological care. Initiating speech therapy, physiotherapy, and occupational therapy can substantially enhance motor skills, muscle tone, and overall functional abilities. Rehabilitation techniques like proprioceptive neuromuscular facilitation and acral coactivation therapy have demonstrated efficacy in strengthening muscles and improving coordination, thereby mitigating the risk of complications such as muscle atrophy and falls. Pharmacological interventions, including the use of nootropics, may offer additional support for cognitive and central nervous system development, although further research is needed to establish their effectiveness in GSD IXa specifically. Dietary management remains a cornerstone of treatment, emphasizing the intake of proteins and complex carbohydrates to prevent hypoglycemia and support growth. Regular neurological monitoring and comprehensive dietary planning are imperative for adapting therapeutic strategies to the evolving needs of the patient. The prognosis for individuals with GSD IXa is variable and largely dependent on the severity of symptoms and the promptness of therapeutic interventions. Early and consistent rehabilitation efforts can significantly improve motor functions and enhance the quality of life. However, the chronic nature of GSD IXa necessitates lifelong management and continuous monitoring to address emerging health challenges and optimize patient care. In conclusion, the case highlights the importance of a tailored, multidisciplinary approach in the diagnosis and management of GSD IXa. Enhanced awareness, accessible diagnostic tools, and integrated therapeutic strategies are vital for improving outcomes for patients with this rare metabolic disorder.

Source

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