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Health-related Quality of Life Among Patients with Phosphomannomutase 2 Congenital Disorder of Glycosylation in Georgia

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ABSTRACT

Background: Phosphomannomutase 2 congenital disorder of glycosylation (PMM2-CDG) is the most common form of CDG, a group of rare, multisystemic genetic conditions with diverse clinical presentations. While the disease burden is profound, data on health-related quality of life (HRQL) in affected individuals remain scarce.

Objectives: This study aimed to assess HRQL in children with PMM2-CDG in Georgia using the Patient-Reported Outcomes Measurement Information System (PROMIS).

Methods: Ten children aged 5–13 years with genetically confirmed PMM2-CDG were enrolled. Caregivers completed the PROMIS questionnaires across five domains: anxiety, depression, fatigue, pain interference, and physical function.

Results: Children with PMM2-CDG showed notable impairments in health-related quality of life, particularly in physical function, which was significantly below the norm (M = 24.1). Fatigue levels were modestly elevated (M = 53.53), suggesting increased tiredness.

Conclusions: These findings reveal the significant impact of PMM2-CDG on HRQL in children, highlighting the need for integrated care approaches and further longitudinal studies to guide therapeutic priorities and policy planning.

Keywords: Health-related quality of life, HRQL; patient-reported outcomes measurement information system, PROMIS; phosphomannomutase two congenital disorder of glycosylation, PMM2-CDG.

BACKGROUND

Congenital disorders of glycosylation (CDG) represent a heterogeneous group of monogenic metabolic disorders resulting from defects in various steps of the glycosylation pathway.[1] To date, nearly 190 genetic defects have been identified as causative. The first CDG to be characterized at the molecular level is PMM2-CDG (OMIM 212065, previously known as CDG-Ia), which has been reported in approximately 1,000 patients worldwide.[2] The clinical manifestations in affected individuals reflect the role of glycosylation in the development and function of multiple organ systems.[3] PMM2-CDG has a severe clinical presentation and life-limiting consequences. Currently, there are no validated, disease-specific health-related quality of life (HRQL) instruments available to assess the heterogeneous clinical burden of PMM2-CDG. It presents a challenge for determining disease severity and the impact of treatment on the disease course. Over the past decade, significant progress has been made in developing novel treatments for CDG. Innovative interventions focusing on the primary genetic and biochemical defects, as well as their clinical consequences, have progressed from laboratory research to practical, patient-centered therapies, making the HRQL construct is even more relevant. HRQL is a dynamic and multidimensional concept involving physical, emotional, mental, and social functioning. One approach used to evaluate HRQL is the Patient-Reported Outcomes Measurement Information System (PROMIS)—a set of person-centered measures that assess and monitor physical, mental, and social health in both adults and children.[4] PROMIS includes self-report measures for adults, as well as measures for children aged 8–17, and parent proxy-report measures for children aged 5–17.

As mentioned above, there is a general lack of studies on HRQL in individuals with PMM2-CDG,[5-7] and no clinical or epidemiological studies have been conducted in Georgia to date. This study aimed to evaluate HRQL in children with PMM2-CDG in Georgia using the PROMIS.

METHODS

The study involved ten individuals aged 5 to 13 years. Patients and their caregivers were recruited through the physician network and rare disease organizations. The caregivers completed the PROMIS parent proxy-report questionnaires at the time of enrollment. Sociodemographic characteristics are summarized in Table 1. Five domains – anxiety, depression, fatigue, pain interference, and physical function – were evaluated using parent proxy profile instruments. PROMIS

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scores were obtained and converted to standardized T-scores (mean=50, standard deviation=10) for each domain. Descriptive statistics, including means and standard deviations, were calculated for all PROMIS domains. The study was conducted between January 2024 and July 2024. Ethical approval was obtained from the institutional review board, and written informed consent was obtained from parents or legal guardians before participation, in accordance with national and international ethical standards and guidelines.

TABLE 1. Sociodemographic characteristics of the study patients

Characteristic	N (%)
Total N	10
Age groups	
5–9 years	6 (60)
10–13 years	4 (40)
14–17 years	0 (0)
Gender	
Male	5 (50)
Female	5 (50)

RESULTS

PROMIS domain scores are summarized in Table 2. The physical function domain showed the most significant deviation from the normative mean (M=24.1), indicating considerable impairment in mobility and physical capability. Scores for pain interference (M=44.12) and anxiety (M=48.75) were slightly below the population mean, indicating relatively mild disturbances. Fatigue scores (M=53.53) were modestly elevated, indicating increased tiredness and reduced energy levels among participants. Depression scores (M=49.43) remained within normative range but trended toward higher emotional distress.

TABLE 2. PROMIS mean scores

Domain	M
Anxiety	48.75
Depression	49.43
Fatigue	53.53
Pain Interference	44.12
Physical Function	24.1

DISCUSSION

This study provides the first data on health-related quality of life (HRQL) in children with PMM2-CDG in Georgia, assessed using the PROMIS instrument. The most affected domain, physical function, aligns with the known neuromuscular and multisystem involvement of PMM2-CDG, which frequently manifests with hypotonia, ataxia, and developmental delays.[1] Fatigue also emerged as a prominent concern, consistent with reports describing energy deficits due to impaired glycoprotein synthesis and mitochondrial dysfunction in PMM2-CDG.[6] The absence of strong associations between HRQL scores and gender or disease duration may reflect the small sample size and the chronic, non-linear progression of the disorder. PMM2-CDG often exhibits variable disease trajectories, with intermittent periods of stabilization and progression, which can complicate the interpretation of simple time-related correlations. Clinically, the pronounced impairments in physical function and fatigue highlight the need for multidisciplinary management strategies. From a health policy perspective, our findings underscore the importance of integrating HRQL assessments into routine care and rare disease registries to enhance care planning and resource allocation.

CONCLUSIONS

PMM2-CDG has a significant impact on the physical and psychosocial well-being of affected children in Georgia. PROMIS is a practical and sensitive instrument for assessing this burden and could facilitate both clinical follow-up and cross-country research collaborations. Addressing the complex needs of these children requires integrated, multidisciplinary care pathways and sustained policy attention. Future longitudinal studies with larger cohorts are needed to track changes in HRQL over time and evaluate the effectiveness of targeted interventions.

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