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Breastfeeding Status and Response to Growth Hormone Therapy in Children with Isolated Growth Hormone Deficiency

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Abstract: This study aimed to evaluate the association of breastfeeding status and duration with growth parameters, biochemical markers, and response to growth hormone (GH) therapy in children with isolated growth hormone deficiency (IGHD). In this retrospective study, the medical records of 162 children aged 3–17 years diagnosed with IGHD between January 1, 2019, and December 31, 2024, were reviewed. Overall, 67.9% of the children were breastfed, with a mean duration of 16.4 ± 8.6 months. No significant differences were found between breastfed and non-breastfed children regarding baseline growth and biochemical parameters or treatment response ($p > 0.05$). Overall, 62.96% of the patients achieved a favorable treatment response, which showed no significant association with breastfeeding duration. In multivariable analysis, GH treatment duration emerged as the sole independent predictor of treatment response (OR = 1.355, 95% CI: 1.026–1.791, $p = 0.032$). In conclusion, neither breastfeeding status nor duration was significantly associated with growth trajectories or GH therapy response in children with IGHD, whereas GH treatment duration was a key determinant of therapeutic success.

Keywords: Breastfeeding, Growth hormone therapy, Isolated growth hormone deficiency

Introduction

Isolated Growth Hormone Deficiency and Growth

Isolated growth hormone deficiency (IGHD) represents one of the primary endocrine etiologies of pediatric growth failure. Growth hormone therapy is the cornerstone treatment aimed at accelerating growth velocity in children with IGHD; however, therapeutic responsiveness is modulated by various patient-specific clinical characteristics and treatment-related factors (Dattani & Preece, 2004; Witkowska-Sędek et al., 2018).

The Role of Breast Milk and Bioactive Components in Pediatric Growth

Early life nutrition represents one of the crucial determinants of postnatal growth and development. Breast milk contains essential macronutrients and micronutrients, as well as a multitude of bioactive components—including growth factors (e.g., IGF-1), hormones, and cytokines—that support childhood growth and maturation (Yi & Kim, 2021; Szyller et al., 2024). Beyond basic nutritional support, human milk functions as a dynamic biological system that modulates metabolic programming and long-term endocrine regulation during early development (Table 1).

Among the extensive array of bioactive molecules in human milk, the principal components exerting decisive effects on neonatal development, tissue repair and immunological response are categorized and detailed in Table 1 (Ballard & Morrow, 2013). However, evidence regarding the association between breastfeeding status, breastfeeding duration, and subsequent growth outcomes or response to GH therapy in children with IGHD is

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limited. Although the effects of breastfeeding on overall childhood growth have been widely investigated, studies specifically examining whether early-life breastfeeding parameters are associated with long-term growth parameters and therapeutic response to GH therapy in children with IGHD remain scarce. Therefore, this study aimed to evaluate the potential effects of breastfeeding status and duration on growth parameters and response to GH therapy in children diagnosed with IGHD. In addition, clinical and biochemical variables that may influence treatment response were evaluated using multivariable analysis. Through this approach, the study aimed to contribute to a better understanding of the relationship between early-life nutritional history and treatment response in children with IGHD.

Table 1. Human milk bioactives and functions

Component Category	Key Bioactive Factors	Biological Function and Effect on Growth
Cellular Components	Macrophages, Stem cell	Protection against infection, T-cell activation, tissue regeneration and structural repair
Growth Factors	IGF-1, IGFBP-3, EGF, VEGF	Stimulation of somatic growth and tissue maturation; upregulation of red blood cell mass and hemoglobin synthesis.
Immunoglobulins	IgA/sIgA, IgG, IgM	Antimicrobial activity and activation of phagocytosis; anti-inflammatory effects and regulation of allergic responses.
Cytokines	IL-6, IL-7, IL-8, IL-10, IFN- γ , TGF- β , TNF- α	Regulation of inflammatory responses, enhancement of thymic output and neutrophil recruitment, induction of antibody synthesis, and promotion of immune tolerance.
Antimicrobial	Lactoferrin, Lactadherin	Acute-phase immune response, iron-chelating capacity, antibacterial, antiviral, and antioxidant activities.

Method

Study Design and Participants

This retrospective study reviewed the medical records of children diagnosed with IGHD between January 1, 2019, and December 31, 2024, at the Pediatric Endocrinology Clinic of Aydın Adnan Menderes University Hospital. A total of 162 children aged 3–17 years were included in the study.

Data Collection

Demographic characteristics, birth characteristics, anthropometric measurements, breastfeeding status and duration, vitamin D prophylaxis, IGF-1, IGFBP-3, and data related to GH therapy were obtained from the medical records. Information on breastfeeding status and duration was collected through telephone interviews with parents and based on parental self-report.

Assessment of Treatment Response

Response to GH therapy was evaluated based on the change in height SDS (Δ height SDS), calculated as the difference between height SDS at the last follow-up and at diagnosis. As illustrated in Figure 1, patients were categorized into two distinct response groups: those with a Δ height SDS ≥ 0.5 were classified as favorable responders, whereas those with a Δ height SDS < 0.5 were categorized as inadequate responders.

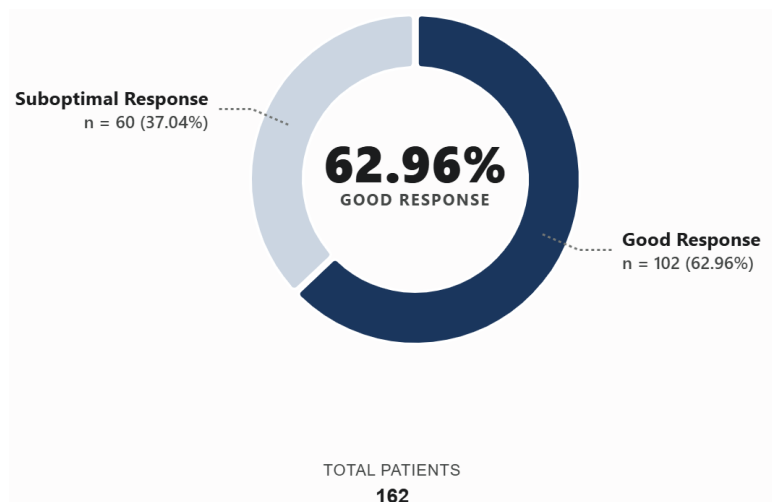


Figure 1. Distribution of treatment response status based on delta (Δ height SDS ≥ 0.5) height SDS

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0. The chi-square test was used to compare categorical variables, the Mann–Whitney U test for comparisons between two groups of continuous variables, and the Kruskal–Wallis test was used for comparisons among more than two groups. Associations between continuous variables were assessed using Spearman’s correlation analysis, and multivariable logistic regression analysis was performed to identify independent factors associated with treatment response. A p-value < 0.05 was considered statistically significant.

Results and Discussion

A total of 162 children aged 3–17 years diagnosed with IGHD were included in the study.

Table 2. Baseline demographic and clinical characteristics of participants

Variable	Total (n=162)
Age, years	10.2 $\pm$ 2.7
Male, n (%)	88 (54.3)
Female, n (%)	74 (45.7)
Breastfed, n (%)	110 (67.9)
Breastfeeding duration, months	16.4 $\pm$ 8.6

As summarized in *Table 2*, the study cohort demonstrated a balanced gender distribution with a predominant history of infant breastfeeding. Among the breastfed participants, the duration of breastfeeding was sustained for an average of over 16 months. Comparative analysis of baseline anthropometric and biochemical parameters revealed no statistically significant differences between breastfed and non-breastfed children regarding age at diagnosis, height SDS, weight SDS, vitamin D levels, IGF-1 SDS, or IGFBP-3 SDS ($p > 0.05$). These findings indicate that the baseline anthropometric and biochemical characteristics of the two groups were overall comparable at the time of diagnosis.

In a study by Clayton et al. (2024), participants were categorized into three groups based on early-life feeding patterns: exclusively breastfed, partially breastfed/mixed-fed, and exclusively formula-fed. In their study, exclusively breastfed children demonstrated lower weight SDS compared to formula-fed peers. Such discrepant findings in the literature suggest that the impact of breastfeeding on early growth parameters may vary according to the target population, age at clinical evaluation, breastfeeding duration, and confounding socioeconomic factors including maternal education, economic status, and environmental conditions during early development. This finding indicates that the distinctive impact of breast milk on growth parameters may vary depending on time and developmental stages. Anthropometric differences driven by bioactive components in human milk during infancy and early childhood tend to gradually attenuate as children grow and environmental dietary factors diversify. Particularly in evaluations conducted at older ages, such as at the time of diagnosis, individual genetic potential,

lifestyle, socioeconomic conditions, and underlying chronic or endocrine conditions become the primary determinants of the growth trajectory, rather than the mode of infant feeding.

When comparing breastfed and non-breastfed children, no statistically significant differences were found regarding GH treatment duration, GH dose, baseline growth parameters, or treatment response ($p > 0.05$). A favorable treatment response was observed in 61.5% of the non-breastfed group and 63.6% of the breastfed group ($p = 0.796$). Adverse drug effects were observed only in the non-breastfed group, and the difference between the groups was statistically significant.

In this study, no adverse drug effects were observed in the breastfed group, whereas adverse effects were reported in 3.8% of patients in the non-breastfed group, and this difference was statistically significant. This finding may suggest a potential role of breastfeeding in treatment tolerability. According to large-scale data from the KIGS cohort, pediatric GH therapy is generally well tolerated, with the majority of adverse events being mild and transient. Treatment-related adverse effects have been reported at low rates, while events requiring discontinuation of therapy have rarely been reported (Maghnie et al., 2022). However, the paucity of prior research evaluating breastfeeding patterns in this context precludes a direct comparative analysis with existing literature. Moreover, due to the retrospective nature of our study and the scarce evidence exploring the interaction between infant feeding history and GH therapy-related adverse events, these observations do not establish definitive causality.

The observed outcomes must therefore be interpreted with discretion, acknowledging that unmeasured confounders—such as age at diagnosis, medication adherence, and socioeconomic background—could have partially skewed these observational findings. Evaluation of breastfeeding duration revealed no statistically significant correlation with height SDS gain, weight SDS gain, first-year growth velocity, or final height SDS ($p > 0.05$). This finding is consistent with previous literature reporting that although breastfed infants may exhibit different weight gain trajectories compared to formula-fed counterparts, linear growth (height) remains unaffected (Akova et al., 2012).

In the multivariable logistic regression analysis, age at diagnosis and baseline vitamin D levels were not identified as independent predictors of favorable treatment response ($p > 0.05$). In contrast, duration of GH therapy emerged as an independent and significant predictor (OR=1,355; %95 GA: 1,026–1,791; $p=0,032$). Specifically, each additional year of GH treatment was associated with an approximately 1.36-fold increase in the odds of achieving a favorable response, independent of potential confounders. This finding highlights that therapeutic success is closely tied to treatment continuity and sustained GH exposure. As emphasized by Darendeliler (2009), long-term compliance and continuous therapy remain critical determinants for maintaining an optimal cumulative growth response in pediatric patients.

Conclusion

In conclusion, neither breastfeeding status nor its duration showed a significant association with clinical parameters or response to growth hormone therapy in pediatric IGHD patients. Notably, although adverse events were observed solely in non-breastfed patients, suggesting a potential protective effect of breastfeeding on treatment tolerability, this finding warrants cautious interpretation due to the retrospective nature of the study. Additionally, the duration of growth hormone therapy emerged as a critical independent predictor of treatment success.

Recommendations

Larger-scale, multicenter, and prospective studies are required to fully elucidate the impact of breastfeeding status and duration on growth trajectories and therapeutic responsiveness in pediatric patients with IGHD. Future research should also evaluate the potential influence of seasonal variations, vitamin D status, and the specific bioactive composition of breast milk on growth and treatment outcomes. Furthermore, since the duration of GH therapy emerged as a key determinant of treatment response, long-term and regular monitoring of growth parameters throughout therapy remains essential.

Scientific Ethics Declaration

* Ethics committee approval for this study was obtained from the Non-Interventional Clinical Research Ethics Committee of Aydın Adnan Menderes University, Institute of Health Sciences (Date: [25.03.2026], Approval No: [2026/27]). Institutional permission was also granted by Aydın Adnan Menderes University Hospital. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

* The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

Conflict of Interest

* The authors declare that they have no conflicts of interest.

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