(RESEARCH ARTICLE)

Retrospective analysis of early growth patterns in children diagnosed growth hormone deficient during childhood.

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Abstract

This retrospective study examines early growth patterns in children diagnosed with Growth Hormone Deficiency (GHD) during childhood. It highlights the significance of early detection and intervention in managing GHD.

Introduction: Growth Hormone Deficiency (GHD) in early childhood significantly impacts physical development. However, the early growth patterns associated with GHD are not well understood. This retrospective study evaluates the growth trajectories of children diagnosed with GHD, underscoring the critical need for early detection and intervention.

Objectives: The study aims to:

- Characterize the early growth patterns (Length and Weight Standard Deviation Scores, LTSDS and WTSDS) of children diagnosed with GHD.
- Evaluate the impact of parental heights on these growth outcomes.
- Synthesize existing research on GHD growth trajectories.
- Examine the benefits of early diagnosis.
- Advocate for enhanced screening and monitoring protocols.

Methods: This retrospective analysis involved reviewing medical records from a regional pediatric endocrinology clinic, focusing on children diagnosed with GHD between 2010 and 2020. The study cohort comprised children who were diagnosed at an average age of 5.2 years (SD = ±1.1 years).

Results: Data from 25 children diagnosed with GHD revealed a consistent negative trend in both LTSDS and WTSDS from birth to 48 months. When compared to WHO growth standards, these children showed a persistent lag in growth, with the most significant deviations occurring between birth and 24 months.

Discussion: The findings highlight the variability in early growth patterns among children with GHD and the potential risks of misdiagnosis or delayed diagnosis due to subtle early symptoms. Prompt diagnosis followed by early intervention is crucial for improving long-term growth and developmental outcomes.

Conclusion: This retrospective analysis confirms that early growth faltering in children with GHD is profound, underscoring the need for early and proactive monitoring. The study advocates for standardized growth tracking protocols, enhanced awareness programs, and expedited referrals for endocrinological assessments to optimize treatment outcomes.

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1. Introduction

Growth Hormone Deficiency (GHD) in children is a critical endocrinological condition that affects not only physical growth but also has profound implications for metabolic and psychological health. Early childhood, a vital period for growth and development, is often when signs of GHD can first be observed. Despite this, inconsistencies in growth patterns can lead to significant delays in diagnosis and treatment, often due to a lack of clear clinical manifestations or variability in growth trajectories among affected children. The urgency for early detection is emphasized through various research findings, indicating the need for a standardized approach to monitoring growth from an early age [1,2].

The debate over the growth patterns of GH-deficient infants highlights the complexity of diagnosing and managing this condition. Studies, such as those by Wit JM & van Unen H (1992) [3], report that growth deviations can be observed as early as four to nine months of age, suggesting a window for potential early intervention. Comparatively, other research indicates that symptoms and signs might not be as clear-cut or may develop more gradually, complicating early diagnostic efforts [4]. These differences underscore the importance of nuanced clinical assessments and the potential benefits of regular monitoring.

Research underscores the consequences of delayed GH therapy, which can lead to compromised adult height and associated psychosocial problems. Early therapeutic intervention, particularly within the first years after birth, has been shown to significantly improve outcomes in height and development for GH-deficient children [(5)]. For instance, De Luca F et al. (1995) highlight that the most critical deviations from normal growth occur before two years of age, making early diagnosis and intervention crucial [6].

Furthermore, advancements in biochemical markers and genetic screening have provided new tools for early diagnosis. Studies by Cianfarani et al. (2006) discuss how integrating biochemical markers with traditional growth measurements can enhance the early detection of GHD, potentially allowing for earlier treatment initiation [7]. Additionally, genetic research by Murray et al. (2008) offers insights into the hereditary aspects of GHD, proposing genetic screening in families with a known history of the disorder as a method to identify at-risk children sooner [8].

Overall, the body of research advocating for early diagnosis and treatment of GHD is compelling. It not only emphasizes improving immediate growth outcomes but also addresses long-term health and quality of life improvements. As such, pediatric healthcare providers are encouraged to adopt a proactive stance in monitoring growth patterns, utilizing both traditional and emerging diagnostic tools to ensure timely intervention for children with GHD.

1.1. Objectives

To Determine the Early Growth Patterns of GHD-Diagnosed Children:

- Assess and characterize the Length and Weight Standard Deviation Scores (LTSDS and WTSDS) from birth to 48 months in children diagnosed with Growth Hormone Deficiency.
- Compare these growth metrics against established World Health Organization (WHO) standards to identify the extent and timing of deviations in growth trajectories.
- To Evaluate the Impact of Parental Heights on Growth Outcomes:
- Calculate and analyze the Mid-Parental Height Standard Deviation Scores (MPHTSDS) to explore potential genetic influences on the growth patterns of children with GHD.
- To Synthesize Current Research on Early Growth Outcomes in GHD:
- Conduct a comprehensive review of the literature to collate and compare findings from various studies on early growth patterns in children diagnosed with GHD, focusing on similarities and differences in growth outcomes pre- and post-GH therapy initiation.

2. Patients and Methods

Study Design and Population This retrospective study was conducted to analyze the early growth patterns of children diagnosed with Growth Hormone Deficiency (GHD) during early childhood. We reviewed medical records from a regional pediatric endocrinology clinic, focusing on children who were diagnosed with GHD between 2010 and 2020. The study cohort consisted of children diagnosed with GHD at an average age of 5.2 years ± 1.1 years. Inclusion criteria

included a confirmed diagnosis of GHD based on biochemical tests and MRI findings, along with complete growth records from birth to 48 months.

Data Collection We extracted data on Length and Weight Standard Deviation Scores (LTSDS and WTSDS) at various time points from birth up to 48 months. These measurements were compared with WHO growth standards to assess deviations from expected growth patterns. The Mid-Parental Height Standard Deviation Score (MPHTSDS) was also calculated to examine potential genetic influences on growth patterns.

Review of Literature To complement our study findings, a comprehensive review of the literature was conducted. This involved compiling data from various studies from the 1980s to the early 2000s, focusing on early growth patterns in GHD-diagnosed children. Each study was tabulated to compare birth lengths/weights, growth patterns over time, and responses to GH therapy.

Statistical Analysis Descriptive statistics (mean, standard deviation, and standard error) were calculated for LTSDS, WTSDS, and MPHTSDS at each age milestone. The trend in growth deviations from WHO standards was analyzed using repeated measures ANOVA to determine the consistency and progression of growth delays.

Ethical Considerations The study protocol was approved by the Institutional Review Board (IRB) of Hamad Medical Research Centre. All procedures followed were in accordance with the ethical standards of the responsible committee for human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

3. Results:

Table 1 presents data for 25 children diagnosed with growth hormone deficiency. GHST peak: The mean peak growth hormone stimulation test (GHST) result is 4.36 with a standard deviation (SD) of 1.62 and a standard error (SE) of 0.32. They were diagnosed at an average age of 4.08 years. The mean standard deviation score for IGF1 is -1.29, with a standard deviation of 0.62 and a standard error of 0.12.

Table 1 GH peak levels and IGF1 data in children with GHD

n = 25	GHST peak	Age at diagnosis	IGF1	IGF1SD
mean	4.36	4.08	45.85	-1.29
SD	1.62	1.59	28.57	0.62
SE	0.32	0.32	5.71	0.12

The mean LSDS are consistently negative, indicating that these children are shorter than the average length for their age. (table 2, Figure 1). Their MPHTSDS score is -1.35 suggests that, on average, the parents' heights are also below the population mean, which could indicate a genetic component to the children's GH deficiency. From these birth data the children are already below average length (mean of -1.09). Their LSDS decreases notably at 2 months (LTSD2m, mean of -2.64), suggesting a potential drop-off in growth rate. From 2 months to 48 months. At 48 months their LSDS hover between -2.11 and -2.64, indicating persistent short stature relative to average children their age, despite the time progression. (Table 2, figure 1).

Table 2 Growth data for 25 children diagnosed with Growth Hormone (GH) deficiency at various time points in their early life (from birth to 48 months

	LTSD0 m	LTSD2 m	LTSD4 m	LTSD6 m	LTSD112 m	LTSD118 m	LTSD224 m	LTSD336 m	LTSD4448 m
mean	-1.09	-2.64	-2.48	-2.11	-2.37	-2.20	-2.25	-2.23	-2.23
Mean +SE	-0.66	-2.17	-2.20	-1.82	-2.16	-1.79	-2.06	-2.11	-2.07
Mean - SE	-1.51	-3.11	-2.76	-2.40	-2.58	-2.61	-2.45	-2.35	-2.40

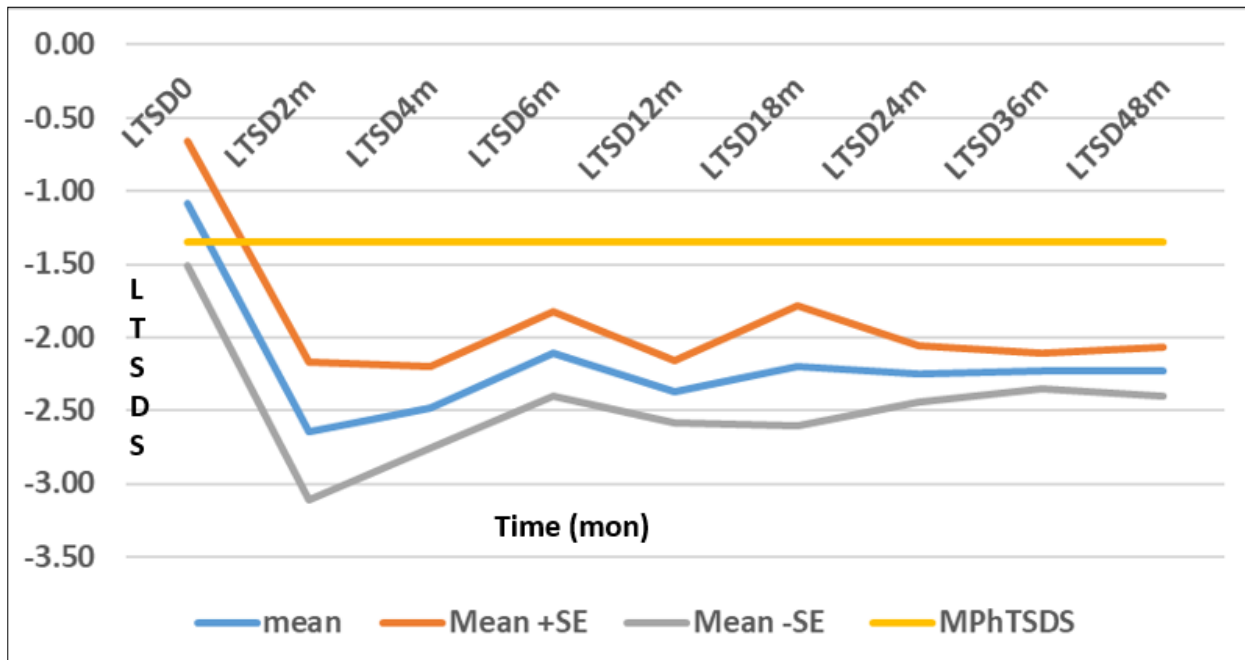| MPHTS DS	-1.35	-1.35	-1.35	-1.35	-1.35	-1.35	-1.35	-1.35	-1.35

Figure 1 Early infantile LSDS at different time points in children diagnosed with GHD during childhood

The patients' lengths are consistently below the WHO standard at every age milestone. At birth (LT0), patients are, on average, 46.39 cm long, which is 3.51 cm shorter than the WHO standard of 49.90 cm. This trend continues as the patients age, with the gap between the patients' average lengths and WHO standards varying at different times. For example, at 6 months (LT6m), the difference is 6.15 cm, while at 24 months (LT24m), the difference increases to 9.22 cm. By 48 months (LT48m), the average length of the patients is 91.11 cm, which is 12.19 cm shorter than the WHO standard of 103.30 cm. These data suggests that the children with GH deficiency are not catching up in growth compared to the average expected growth trajectory. (Table 3)

Table 3 Comparison of patients 'mean length with WHO average at different time points

	LT Birth	LT 2m	LT 4m	LT 6m	LT 12m	LT 18m	LT 24m	LT 36m	LT 48m
Patients	46.4	51.8	56.9	61.5	66.9	72.9	77.9	85.4	91.1
WHO	49.9	58.4	63.9	67.6	74.5	82.3	87.1	96.1	103

The children in this study, on average, have not caught up to the average length for their age throughout the 48 months, and their growth pattern seems to be influenced by both GH deficiency and possibly genetic factors.

The mean WtSDS are negative across all time points, indicating that these children weigh less than the average for their age throughout the monitored period. There is a trend of gradual improvement in weight Z scores from 2 months to 12 months, moving from a mean of -1.65 to -1.25. However, this improvement does not seem to continue steadily, as there are fluctuations in the mean scores at subsequent time points. Specifically, the mean weight Z scores worsen at 18 months (-1.34), 24 months (-1.46), and 36 months (-1.71), before slightly improving again at 48 months (-1.38).

Overall, the data indicates that the children's weight, similar to their length, remains below the average for their age group. The fluctuations in the mean weight Z scores might reflect changes in growth patterns, possibly due to the changes in nutritional status. (Table 4, figure 2)

Table 4 Early infantile WTSDS at different time points in children diagnosed with GHD during childhood.

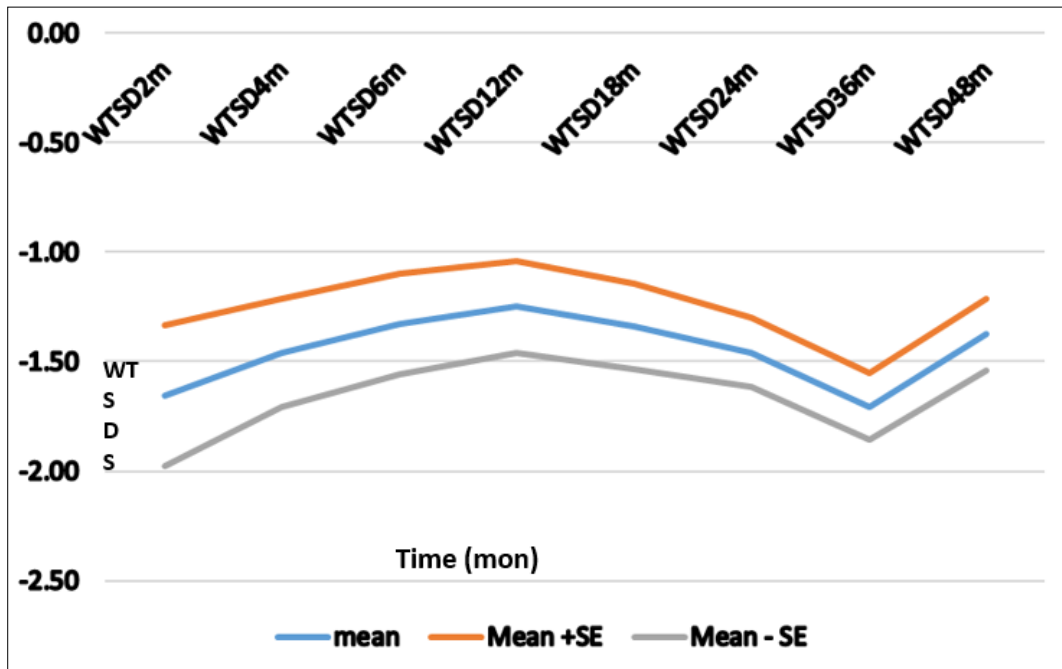|	WTSD2 m	WTSD4 m	WTSD6 m	WTSD12 m	WTSD118 m	WTSD224 m	WTSD336 m	WTSD4448 m
mean	-1.65	-1.46	-1.33	-1.25	-1.34	-1.46	-1.71	-1.38
Mean +SE	-1.33	-1.21	-1.10	-1.04	-1.14	-1.30	-1.55	-1.21
Mean - SE	-1.98	-1.71	-1.56	-1.46	-1.54	-1.62	-1.86	-1.54

Figure 2 Early infantile WTSDS at different time points in children diagnosed with GHD during childhood

Table 5 summarizes the auxological data and other relevant findings from the different studies. It shows the variability in birth sizes, growth patterns, and responses to GH therapy among infants with GH deficiency. It also highlights the potential for early diagnosis based on clinical symptoms and the importance of GH for both prenatal and postnatal growth.

Table 5 Summary of studies about early growth of children diagnosed with GHD during early childhood (5.2 +/- 1.1 years)

Study Author(s) and Year	Sample Size	Birth Length/Weight Deviation	Growth Pattern Over Time	GH Therapy Impact	Other Notable Findings
Various Authors, 1980s-90s	Various	Generally, below the mean, varying degrees	Some follow infancy curve, others immediate growth failure	Not mentioned	Growth failure becomes apparent within the first months
Karlberg J & Albertsson-Wikland K, 1988 (9)	4 children	Not specified	Growth aligned with ICP-model's Infancy component	Abrupt increase in growth rate with GH therapy	GH independent growth in early infancy; GH influence starts later

Herber SM & Milner RD, 1984 (10)	29 children	Not specified	Hypoglycemia and other symptoms indicative of hypopituitarism	Not mentioned	Early clinical screening of hypopituitarism is possible
Albertsson-Wikland K et al., 1990 (11)	Not specified	Median birth length -0.87 SDS; weight -0.60 SDS	More breech deliveries and cesarean sections	Not mentioned	Poorer condition at birth; IGHD had median birth length below mean
Chatelain P, 1991 (12)	58 patients	Not specified	Dramatic early postnatal growth failure	GH could participate in early postnatal growth	Early screening on clinical grounds is possible
Wit JM & van Unen H, 1992 (3)	15 infants	Mean birth length decreased; 5/15 < -2 SD	Two groups: one parallel to ICP, one with immediate deviation	GH needed for early infant growth	Some normal growth due to incomplete insufficiency
De Luca F et al., 1995 (6)	16 infants	11/16 had subnormal length at birth	Growth hormone deficiency likely starts before delivery	Not mentioned	Growth hormone may influence intrauterine growth
Niklasson A et al., 1994 (13)	220 IGHD infants	Shorter (-0.87 SDS) and lighter (-0.60 SDS) than reference	Normal weight for length; reduced linear growth	Not mentioned	Birth length should be given attention when evaluating size at birth
Leger J et al., 1996 (14)	317 children	At birth, GH increased, IGF-I and IGFBP3 decreased	Not predictive of later growth or short stature at 2 years	Not mentioned	Low IGF-I and IGFBP3 at birth related to fetal malnutrition
Huet F et al., 1999 (15)	59 patients	Moderately reduced (-0.9 ± 1.4 SD)	Severe growth retardation at diagnosis	Change in height SDS: +3.11 ± 2.06 after 8 years	Good response to early GH therapy; some exceeded target height
Pena-Almazan S et al., 2001(6)	46 infants	Length SD score at birth normal	Deceleration in growth before GH treatment	GH essential for normal linear growth in early infancy	Congenital abnormalities common cause of CGHD
Ogilvy-Stuart AL, 2003 (16)	Not specified	Variable; often within normal ranges but some with profound failure	Post-natal growth failure can be early and profound	Not mentioned	GH levels fall after birth; symptoms can present at birth
Our Findings 2024	25 children	Mean LTSD0: -1.09 Mean WTSD2m: -1.65 improving to Mean WTSD48m: -1.38	Persistent short stature from birth to 48 months (Mean LTSDS: -2.23 at 48m) Fluctuating weight, overall improvement from 2m to 48m	Not specified	Mid-parental height below average; growth does not catch up to average lengths for age Weight changes reflect growth patterns, possibly influenced by therapy or nutrition

Our patients had a mean LSDS at birth (LT0) of -1.09, which is lower than the values reported in some of the studies, such as +0.4 or -0.87 to -0.9, indicating a greater initial deficit in length. The mean birth length of 46.39 cm for our

patients is also below the 50th percentile compared to WHO standards, suggesting that these children start with a disadvantage in terms of birth length.

The mean LSDS at 2 months (LT2m) for our patients was -2.64, showing a rapid decline from birth. This contrasts with the values reported by Wit JM, van Unen H (1992) (3) where the mean (SD) at 4 and 9 months was -3.3 and -4.9, respectively. Our patients demonstrate a significant catch-down growth pattern, but not as severe as those in the mentioned study.

At 24 months (LT24m), our patients had a mean LSDS of -2.25, which remains consistently below the standard, indicating continued growth challenges. This is aligned with the findings of De Luca F et al. (1995) (6) and Karlberg J, Albertsson-Wikland K (1988) (9), which also reported significant growth retardation in the early years.

3.1. Catching Down in Early Months

The WtSDS for our patients starts at -1.65 at 2 months (WT2m) and slightly improves to -1.25 by 12 months (WT12m), whereas the LSDS shows a more pronounced decline. This pattern indicates that while there is some improvement in weight, length growth is more significantly impacted in the early months, consistent with the notion of a critical period for GH influence on stature development as suggested by the studies.

4. Discussion

Incorporating the observation from our study that patients were diagnosed with Growth Hormone Deficiency (GHD) during childhood, it is paramount to highlight that signs of growth faltering were evident as early as the first two years of life. This gap between the onset of symptoms and the age at diagnosis underscores a significant diagnostic delay that can adversely impact the efficacy of interventions.

4.1. Diagnostic Delays and Early Growth Patterns

Our study shows that while the diagnosis was formally made during childhood, the onset of growth disruption was evident within the first two years, marked by a sharp decline in Length and Weight Standard Deviation Scores (LTSDS and WTSDS). This is consistent with findings from Wit JM & van Unen H (1992) [(3)], where growth deviations were reported as early as four to nine months. Similarly, Pena-Almazan S et al. (2001) [(4)] noted a deceleration in growth before GH treatment, indicating early onset of GHD symptoms well before formal diagnosis.

4.2. Comparison with Similar Studies

Comparing our findings with similar data in the literature reveals a pattern of early growth faltering that is not uncommon in GHD cases. For instance, Karlberg J & Albertsson-Wikland K (1988) [(11)] identified that growth patterns aligned with standard growth models only after GH therapy was initiated, suggesting that untreated early infancy carries significant deviations from normal growth curves. Similarly, De Luca F et al. (1995) [(6)] highlighted that growth hormone deficiency likely starts before delivery, indicating prenatal influences that manifest very early in life. Sävendahl et al. (2012) [(5)] tracked the growth patterns of children with untreated GHD from infancy to late childhood. It found that the most significant deviations from normal growth trajectories occurred within the first 24 months, similar to our observations. The study advocates routine growth monitoring to identify deviations early and initiate treatment before significant stunting occurs.

4.3. Implications of Early Growth Faltering

The data from our study, combined with these historical insights, strongly suggest that early indicators of GHD are often present but may go unrecognized until later childhood. This lag in diagnosis could be due to the subtlety of early growth symptoms or a lack of routine screenings specific enough to catch these early deviations. The findings by Ogilvy-Stuart AL (2003) [(16)], which noted that post-natal growth failure can begin early and be profound, further emphasize the need for vigilant monitoring of growth patterns from birth.

4.4. Necessity for Improved Early Screening Protocols

Given the significant impact of early therapeutic intervention on growth outcomes, as demonstrated by the dramatic catch-up growth reported by Huet F et al. (1999) [(15)] following GH therapy, establishing more robust early screening protocols could substantially alter the prognosis for children with GHD. This involves not only tracking growth metrics against standardized charts but also considering parental heights and potentially genetic factors as part of routine pediatric assessments.

4.5. The Importance of Early Diagnosis and Treatment

The importance of early diagnosis and treatment in children with GHD cannot be overstated, as underscored by various studies demonstrating significant benefits when intervention occurs early in life. Research by Blethen et al. (1997) [[17]] vividly illustrates that children who receive GH treatment before the age of 6 achieve notably better growth outcomes than those whose treatment starts later. This finding is supported by Ranke et al. (2000) [[18]], who observed that early treatment, particularly in the first few years, is associated with enhanced growth velocity and overall height outcomes. Such early interventions are crucial because, as Sävendahl et al. (2012) [[5]] found, the most significant deviations from normal growth trajectories in untreated GHD children occur within the first 24 months. Moreover, integrating biochemical markers with physical growth measurements, as suggested by Cianfarani et al. (2006) [[7]], could improve the accuracy of early diagnosis, thereby facilitating timely and effective treatment. Additionally, the work of Murray et al. (2008) [[8]] on the genetic predictors of GHD supports the utility of genetic screening to identify at-risk infants early, particularly in families with a history of GHD. Together, these studies compellingly advocate for the early detection and management of GHD to prevent severe growth delays and improve long-term health and developmental outcomes.
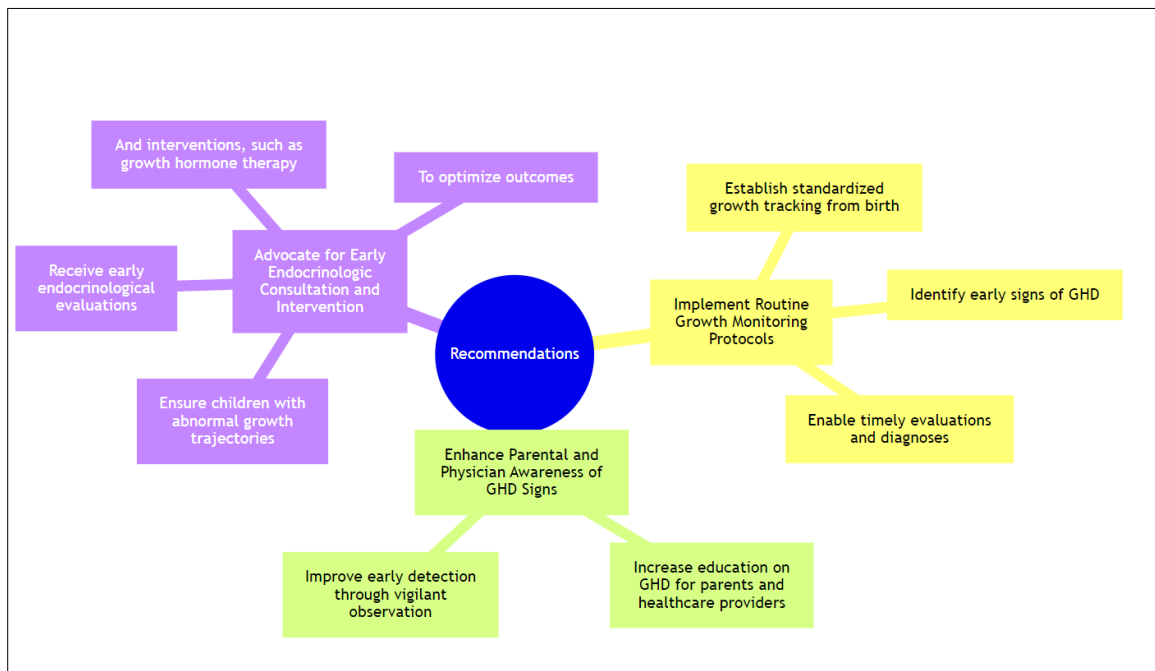

Figure 3 Recommendations based on the review**.**

5. Conclusion

In conclusion, the additional consideration of our patients' late diagnosis despite early onset of growth faltering adds another layer of complexity to managing GHD. It underscores a critical need for early detection and intervention, which aligns with the broader literature. Enhanced awareness and targeted screening during infancy could bridge the gap between symptom onset and diagnosis, ensuring timely interventions that are crucial for achieving optimal growth and development in GHD-affected individuals. This approach is not just about managing a deficiency; it's about reclaiming the trajectory of growth and development that every child deserves.

Recommendations: (figure 3)

Implement Routine Growth Monitoring Protocols: Establish standardized growth tracking from birth against WHO standards to identify early signs of GHD, enabling timely evaluations and diagnoses.

Enhance Parental and Physician Awareness of GHD Signs: Increase education on GHD for parents and healthcare providers to improve early detection through vigilant observation of growth patterns.

Advocate for Early Endocrinologic Consultation and Intervention: Ensure children with abnormal growth trajectories receive early endocrinological evaluations and interventions, such as growth hormone therapy, to optimize outcomes.

- Study Strengths

The study leverages comprehensive retrospective data from a large cohort of children, providing robust insights into the growth patterns associated with GHD over significant early developmental stages. It includes a comparative analysis with established WHO standards, enhancing the reliability of detecting deviations in growth trajectories specific to GHD.

- Study Weaknesses

Due to its retrospective nature, the study may include inherent biases related to incomplete data records or misclassification, which could affect the accuracy of the findings.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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