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A Longitudinal Study of Brain Volume Changes in Children With Growth Hormone Deficiency Treated With Recombinant Human Growth Hormone

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Abstract

Recombinant human growth hormone (rhGH) is the standard treatment for isolated growth hormone deficiency (IGHD), but its effects on structural brain development remain incompletely understood. This study evaluated the longitudinal volumetric changes in the pituitary gland and selected brain structures in children with IGHD following rhGH therapy. In this ambidirectional cohort study, 43 children with IGHD underwent MRI at baseline and after a mean follow-up of 1.6 ± 1.2 years following rhGH therapy, with age- and sex-matched controls recruited separately for baseline (n = 20) and follow-up (n = 21) evaluation. Pituitary volumes were manually segmented using 3D Slicer, while subcortical and corpus callosum structures were analysed using automated segmentation (Fastsurfer). At baseline, IGHD participants had significantly smaller pituitary and splenium volumes, while the remaining corpus callosum regions were larger compared with controls. Following rhGH therapy, pituitary and splenium volumes increased significantly ($p < 0.01$), with partial normalisation, while enlarged corpus callosum subregions showed significant volume reduction, indicating region-specific structural adaptation. rhGH therapy is therefore associated with region-specific brain volumetric changes and partial normalisation of structural abnormalities in children with IGHD, and MRI-based volumetry may serve as a useful biomarker for monitoring treatment-related brain structural changes.

INTRODUCTION

Growth hormone deficiency (GHD) is a complex endocrine disorder which affects linear growth, metabolism, bone health and neurocognitive development [1] . The prevalence rates range between 1 in 4,000 to 1 in 10,000 children (1). It may present as isolated growth hormone deficiency (IGHD) or as part of multiple pituitary hormone deficiencies (MPHD) [2]. Recombinant human growth hormone (rhGH) therapy has revolutionized clinical management by enabling catch-up growth and improved adult height [3].

Current diagnostic approaches rely on auxological criteria and biochemical markers. Growth hormone(GH) stimulation tests such as the insulin tolerance test (ITT) or clonidine stimulation are limited by poor reproducibility, inter-assay variability, and arbitrary cut-off values [1, 4]. IGF-1 and IGFBP-3 levels are useful but lack specificity because they are influenced by nutritional status, chronic illness, and pubertal stage. MRI of the hypothalamic–pituitary region forms part of the baseline investigations in isolated growth hormone deficiency to assess for structural abnormalities. Thus, it has potential in being used as an adjunct tool in objective assessment of the pituitary gland at diagnosis, prognostication and in the evaluation of treatment outcome[5-7].

Occasionally MRI may demonstrate pituitary hypoplasia, empty sella, pituitary stalk abnormalities, and ectopic posterior pituitary in children with growth hormone deficiency (GHD)[5, 7-9]. Even in the absence of gross structural abnormalities, quantitative MRI studies have demonstrated smaller pituitary volumes in children with GHD compared with healthy or idiopathic short stature controls[10, 11]. Beyond the sellar region, GH and IGF-1 receptors are widely expressed in the developing brain, where they regulate neurogenesis, synaptic plasticity, and myelination[12-15]. Children with GHD exhibit structural brain alterations, including reduced corpus callosum, hippocampal, and thalamic volumes and altered white-matter microstructure, as well as reduced cortical grey matter volume, surface area, and thickness associated with circulating GH/IGF-I levels, supporting a link between GH–IGF dysregulation and altered brain development[[16, 17].

Longitudinal imaging studies show that recombinant human growth hormone (rhGH) therapy can induce partial structural recovery, with pituitary volume increasing after treatment although remaining smaller than in healthy peers[2]. However, longitudinal evidence remains limited, and the extent to which rhGH-associated recovery extends beyond the pituitary gland to other GH–IGF-1 responsive brain regions remains poorly characterised. We hypothesised that children with IGHD would demonstrate region-specific structural brain alterations at diagnosis, and that rhGH therapy would be associated with measurable, region-specific volumetric change in the pituitary gland and selected brain structures. This study therefore evaluates baseline morphological differences between children with IGHD and healthy controls, and assesses longitudinal treatment-related volumetric changes using MRI-based volumetry.

METHODOLOGY

Study design and ethics

This ambi-directional cohort study incorporated both retrospective and prospective components. Retrospective clinical and imaging data were obtained from patients managed at the Universiti Malaya Medical Centre (UMMC) and Universiti Malaya Specialist Centre (UMSC) between 2019 and 2025. Prospective MRI studies were performed between May 2024 and April 2025 to provide additional

longitudinal data. Retrospective clinical and imaging records were accessed for research purposes by the corresponding author between 1 January 2024 and 1 April 2025, corresponding to the period of participant recruitment. The corresponding author had access to information that could identify individual participants throughout data collection and recruitment, as this was necessary to coordinate prospective follow-up MRI; all identifying information was subsequently removed prior to data analysis. The primary objective was to evaluate volumetric differences in the pituitary gland and selected brain structures in children with isolated growth hormone deficiency (IGHD), both at baseline and after recombinant human growth hormone (rhGH) therapy. This study was approved by the Medical Research Ethics Committee, University of Malaya Medical Centre (MREC ID No. 202392-12831), and was conducted in accordance with the International Council for Harmonisation – Guidelines for Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all participants prior to enrolment.

Participants

Children with isolated growth hormone deficiency (IGHD) were diagnosed based on integrated clinical, auxological, and biochemical parameters, including height and growth velocity ≤2 SD for age, together with a peak GH response <10 μg/L on two separate provocative tests (insulin tolerance test or glucagon stimulation test), in accordance with institutional protocol. Eligible patients had a baseline pituitary MRI performed prior to initiation of recombinant human growth hormone (rhGH) therapy and were followed up for a duration of 1 to 3 years. As post-treatment MRI is not part of routine clinical care for these patients, with treatment response conventionally monitored through height and growth velocity rather than repeat imaging, a follow-up MRI was prospectively arranged for each recruited patient. Children were excluded if they demonstrated multiple pituitary hormone deficiencies, adrenocorticotropic hormone deficiency, hypothyroidism, syndromic features, systemic illness, or any contraindication to MRI. These inclusion and exclusion criteria ensured a homogeneous cohort representing true IGHD without confounders from other endocrine or systemic disorders. The control group consisted of age- and sex-matched paediatric subjects with brain MRI studies who presented with non-specific symptoms such as headache or tinnitus and had no documented growth abnormalities. As it was neither ethical nor practically feasible to rescan healthy children for longitudinal comparison, two separate control groups were established retrospectively: one matched to the baseline age of the IGHD cohort for pre-treatment comparisons (Control A), and a second matched to the reassessment age of the IGHD cohort for post-treatment comparisons (Control B).

MRI acquisition and processing

Baseline MRI studies were performed using clinical scanners either the 3.0 Tesla Signa® Prime, 1.5 Tesla Signa® Explorer systems (GE Healthcare, United States), or the 3.0 Tesla MAGNETOM Prisma system (Siemens Healthcare, Germany). The MRI protocol included sagittal T1-weighted turbo spin-echo (TSE), axial and coronal T2-weighted TSE, coronal T1-weighted TSE, dynamic post-contrast coronal T1-weighted TSE, and post-contrast T1-weighted MPRAGE sequences. The follow-up MRI acquisition was performed between 6 months to 24 months after the baseline study. It was performed using the 3.0 Tesla MAGNETOM Prisma scanner with limited sequences consisting of non-contrast brain images in T1-weighted MPRAGE, T2-weighted TSE, and T2-weighted FLAIR CUBE sequences.

Volumetric segmentation of the pituitary gland and subcortical structures was performed using the T1-weighted MPRAGE sequence, which was consistently acquired at both baseline and follow-up imaging. Additional sequences, including post-contrast and coronal T1 TSE imaging, were acquired as part of the standard clinical MRI protocol but were not used for volumetric analysis. The pituitary gland was manually segmented slice-by-slice using 3D Slicer (Brigham and Women's Hospital, Boston, MA, USA) (Figure 1) by a single reader with prior training in radiology and segmentation. To verify segmentation accuracy, a random subset of segmented images was independently reviewed by a second assessor with eight years of experience in radiology, who evaluated the accuracy of pituitary margin delineation. Automated segmentation of the basal ganglia, thalamus, hippocampus, amygdala, and corpus callosum subregions was performed using FastSurfer (Deep-MI group, Technical University of Munich, Germany) (Figure 2). Each automated segmentation output underwent quality control via manual inspection of orthogonal planes to verify anatomical fidelity and accurate capture of structural boundaries.

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., NY, USA). Graphs and visualisations were generated using Python (version 3.11) with the matplotlib and seaborn libraries. Normality was assessed using skewness, kurtosis, the Shapiro-Wilk test, and visual inspection of histograms, which confirmed that most of the volumetric variables were normally distributed; parametric tests were therefore used for subsequent analyses. Descriptive statistics were used to summarise demographic characteristics of the participants. Between-group comparisons (IGHD vs. controls) were analysed using independent samples t-tests, and within-subject changes (IGHD baseline vs. post-treatment) were assessed using paired t-tests. Given the exploratory nature of this study across multiple brain structures, p-values were not adjusted for multiple comparisons. Effect sizes were calculated using Cohen's d to quantify the magnitude of between-group and longitudinal differences, interpreted as small ($|d| \approx 0.2$), medium ($|d| \approx 0.5$), and large ($|d| \geq 0.8$); a negative value indicates a higher mean volume in the second comparator group (control or post-treatment) relative to the first (IGHD or baseline), and a positive value indicates the converse. All statistical tests were two-tailed, with a p-value of <0.05 considered statistically significant

RESULTS

A total of 43 children with IGHD with a mean age of 10.6 ± 2.5 years met the eligibility criteria for this study. The follow-up period ranged from 1 to 3 years. Two separate age- and sex-matched control groups were employed for cross-sectional comparisons: one matched to the IGHD cohort at baseline and another matched at the reassessment time point. Follow-up MRI was performed after a mean interval of 1.6 ± 1.2 years following initiation of growth hormone therapy, at which time the mean age of the IGHD participants was 12.7 ± 2.1 years.

Table 1: Demographic characteristics of IGHD subjects and age-matched control groups.

		Baseline MRI		Post treatment MRI	
		IGHD (n=43)	**Control A** (n=20)	**IGHD** (n=43)	**Control B** (n=21)
Mean Age (year)		10.0(1.9)	10.6(2.5)	12.5(1.9)	12.7(2.1)
Gender	**Male**	26	11	26	12
	Female	17	9	17	9

Results are presented across multiple tables, organised according to the direction and pattern of volumetric change observed: structures that were smaller in IGHD at baseline (Table 2), structures that were larger in IGHD at baseline (Table 4), and corresponding longitudinal changes following rhGH therapy (Tables 3, 5). This structure was chosen to clearly distinguish region-specific patterns of structural alteration and treatment response. At baseline, the pituitary gland was markedly smaller in IGHD subjects compared to controls ($p < 0.01$, ES = -1.41)(table 2, figure 3(A)), representing the most significant deficit observed. The posterior corpus callosum (splenium) was also significantly smaller in size ($p < 0.01$, ES = -0.75)(table 2, figure 3(C)). Both findings indicate large effect sizes and substantial structural underdevelopment relative to controls. The left and right caudate nuclei were smaller at baseline, although the differences were not statistically significant (left $p = 0.08$, ES = -0.48; right $p = 0.07$, ES = -0.49) (Table 2).

Table 2: Brain structures smaller in the IGHD group compared with controls at baseline.

	IGHD baseline		Control A		p-value	Effect size	IGHD post tx		Control B		p-value	Effect size
	mean	**SD**	**mean**	**SD**			**mean**	**SD**	**mean**	**SD**		
Pituitary	309.9	84.3	441.9	112.3	**<0.01**	-1.41	425.5	91.4	527.9	98.9	**<0.01**	-1.09
Lt Cau	3587.2	426.1	3798.9	465.9	0.08	-0.48	3682.3	417.0	3965.4	500.4	0.02	-0.64
Rt Cau	3709.2	415.8	3923.4	479.1	0.07	-0.49	3794.8	395.0	4072.4	493.2	0.02	-0.65
CC Pos	629.5	267.8	818.1	211.5	**<0.01**	-0.75	771.4	255.6	900.4	258.7	0.06	-0.50

The data are presented as mean volume (mm3) and Standard Deviation (SD). Lt = Left, Rt = Right, Cau=caudate, CC Pos=Corpus callosum posterior (splenium), post tx=post treatment.

Following treatment, the pituitary gland in the IGHD group remained smaller than controls but showed clear catch-up with a smaller ES compared to the baseline ($p < 0.01$, ES = -1.09)(table 2, figure 3(D)). Similarly, the splenium showed narrowing group differences ($p = 0.06$, ES = -0.50)(table 2, figure 3(D)). In contrast, both caudate nuclei remained small compared to controls post-treatment (left $p = 0.02$, ES = -0.64; right $p = 0.02$, ES = -0.65)(Table 2). Within-group longitudinal analysis revealed significant increases in the volume of all four structures. The pituitary gland demonstrated the most robust volumetric gain ($p < 0.01$, ES = -1.51), followed by the left caudate ($p < 0.01$, ES = -0.45), splenium ($p < 0.01$, ES = -0.43) and right caudate ($p = 0.01$, ES = -0.40)(Table 3). These findings indicate strong treatment-related normalization of volume in structures which were initially smaller in the IGHD group compared to the control group.

Table 3: Longitudinal changes in structures smaller in IGHD compared with controls at baseline.

	IGHD baseline		IGHD post tx		p-value	Effect size
	mean	sd	mean	sd		
Pituitary	309.9	84.3	425.5	91.4	<0.01	-1.51
Lt Cau	3587.2	426.1	3682.3	417.0	<0.01	-0.45
Rt Cau	3709.2	415.8	3794.8	395.0	0.01	-0.40
CC Pos	629.5	267.8	771.4	255.6	<0.01	-0.43

The data are presented as mean volume (mm3) and Standard Deviation (SD). Lt = Left, Rt = Right, Cau=caudate, CC Pos=Corpus callosum posterior (splenium), post tx=post treatment.

At baseline, IGHD subjects had significantly larger corpus callosum subregions, specifically the mid-posterior isthmus ($p < 0.01$, ES = 1.12), mid-anterior body ($p < 0.01$, ES = 1.00), central body ($p < 0.01$, ES = 0.78), and anterior (genu) ($p = 0.03$, ES = 0.62). These represented medium to large effect sizes, indicating abnormal enlargement of these callosal substructures. Post-treatment, these differences diminished. The anterior corpus callosum (genu) normalized completely ($p = 0.89$, ES = 0.04). Other callosal segments remained larger but with reduced effect sizes: mid-posterior isthmus ($p < 0.01$, ES = 0.77), mid-anterior body ($p = 0.06$, ES = 0.52), and central body ($p = 0.06$, ES = 0.51)(Table 4).

Longitudinally the corpus callosum subregions decreased in size post treatment (mid-posterior $p < 0.01$, ES = 0.46; central body $p = 0.02$, ES = 0.38; mid-anterior body $p = 0.02$, ES = 0.37; anterior genu $p = 0.01$, ES = 0.39)(Table 5). Meanwhile both the thalami showed a larger volume at baseline, although these differences did not reach statistical significance(right p-value 0.08, ES 0.48; left p value 0.09, ES 0.46). Within-group longitudinal analysis showed robust growth in both thalami (right p-value <0.01, ES -0.50, left p-value <0.01, ES -0.48)(Table 5).

Table 4: Brain structures larger in the IGHD group compared with controls at baseline.

	IGHD baseline		Control A		p-value	Effect size	IGHD post tx		Control B		p-value	Effect size
	mean	SD	mean	SD			mean	SD	mean	SD		
Lt Thal	8033.7	968.3	7607.9	788.8	0.09	0.46	8354.6	871.1	8021.8	949.8	0.17	0.37
Rt Thal	7647.9	818.9	7256.5	785.4	0.08	0.48	7910.1	804.5	7675.9	928.4	0.30	0.28
CC MP	871.7	326.5	549.7	178.0	<0.01	1.12	714.9	243.7	545.7	162.1	<0.01	0.77
CC Cent	1033.4	262.4	830.6	254.8	<0.01	0.78	923.5	206.2	808.8	263.7	0.06	0.51
CC MA	1100.7	367.8	755.1	288.4	<0.01	1.00	949.1	331.5	778.2	321.7	0.06	0.52
CC Ant	992.8	273.4	842.3	162.8	0.03	0.62	874.7	201.8	867.6	147.5	0.89	0.04

The data are presented as mean volume (mm3) and Standard Deviation (SD). Lt = Left, Rt = Right, Cau=caudate, Put=Putamen, GP=globus pallidus, Thal=thalamus, CC MP=Corpus callosum mid posterior (isthmus), CC Cent=Corpus Callosum Central (body), CC

MA=Corpus Callosum Mid anterior (body), CC Ant=Corpus Callosum Anterior (genu).

Table 5: Longitudinal changes in structures larger in IGHD compared with controls at baseline.

	IGHD baseline		IGHD post tx		p-value	Effect size
	mean	sd	mean	sd		
Lt Thal	8033.7	968.3	8354.6	871.1	<0.01	-0.48
Rt Thal	7647.9	818.9	7910.1	804.5	<0.01	-0.50
CC MP	871.7	326.5	714.9	243.7	<0.01	0.46
CC Cent	1033.4	262.4	923.5	206.2	0.02	0.38
CC MA	1100.7	367.8	949.1	331.5	0.02	0.37
CC Ant	992.8	273.4	874.7	201.8	0.01	0.39

The data are presented as mean volume (mm3) and Standard Deviation (SD). Lt = Left, Rt = Right, Cau=caudate, Put=Putamen, GP=globus pallidus, Thal=thalamus, CC MP=Corpus callosum mid posterior (isthmus), CC Cent=Corpus Callosum Central (body), CC MA=Corpus Callosum Mid anterior (body), CC Ant=Corpus Callosum Anterior (genu).

At baseline, the putamen, globus pallidus, hippocampus, and amygdala were not significantly different between IGHD subjects and controls (all $p > 0.1$, ES ≤ 0.4). Within IGHD subjects, several of these structures, most notably the bilateral amygdala and right hippocampus, demonstrated significant longitudinal volume increases following treatment, with moderate effect sizes ($p < 0.01$) (Supplementary table S1, S2). Despite this significant within-group growth, these structures remained statistically comparable to controls at both baseline and post-treatment assessment, suggesting that their developmental trajectory under rhGH therapy proceeded at a rate consistent with, rather than divergent from, normal age-related growth.

DISCUSSION

This study quantitatively evaluated the effects of isolated growth hormone deficiency (IGHD) on brain structural volumes and the longitudinal changes following recombinant human growth hormone (rhGH) therapy. Distinct baseline neuroanatomical alterations were observed in children with IGHD compared with healthy controls. At diagnosis, IGHD subjects exhibited significantly reduced pituitary and splenium volumes, while several corpus callosum subregions were paradoxically enlarged and the caudate nuclei showed a trend toward smaller volumes. Other subcortical and limbic structures, including the thalamus, putamen, globus pallidus, hippocampus, and amygdala, were largely comparable to controls at baseline. Following rhGH therapy, longitudinal analysis demonstrated significant increases in pituitary, splenial, and caudate volumes, with reduced differences relative to controls. Enlarged corpus callosum subregions showed reductions in volume over time, including normalization of the anterior genu. Continued growth were observed in the bilateral thalami, bilateral amygdala, and right hippocampus. Together, these findings indicate that IGHD is associated with heterogeneous structural brain alterations and that rhGH therapy is accompanied by measurable, region-specific volumetric changes across multiple brain regions.

In children with IGHD, pituitary volume was reduced at baseline compared with controls. A cross-sectional trend of reduced age-related growth velocity was also observed within the IGHD cohort. These findings are consistent with Kessler et al. (2016), who demonstrated that pituitary volume was lowest in IGHD, intermediate in idiopathic short stature (ISS), and highest in controls, with minimal age-related increase in IGHD compared with the clearer increase observed in ISS and controls[10]. Similar observations were reported by Low et al. (2023), who described a cross-sectional decreasing trend in pituitary volume with age among IGHD subjects [2]. Together, these findings suggest that impaired pituitary growth may represent a structural feature of IGHD, although the underlying mechanisms remain uncertain.

The splenium of the corpus callosum was significantly smaller in the IGHD group at baseline compared with controls but increased following rhGH therapy, suggesting partial structural recovery. Similar callosal involvement has been reported previously. Webb et al. demonstrated reduced splenial size and white-matter abnormalities in children with growth hormone deficiency, while Zhou et al. and Lin et al. described broader structural and microstructural alterations involving the corpus callosum and other brain regions in paediatric GHD [16, 18, 19]. The volumetric recovery observed after rhGH therapy may reflect the neurobiological effects of growth

hormone and its downstream mediator insulin-like growth factor-1 (IGF-1) on brain development and structural plasticity. Experimental and translational studies have shown that the GH–IGF-1 axis plays an important role in central nervous system development by promoting neural progenitor proliferation, oligodendrocyte lineage development, and myelination, processes that contribute to neurogenesis and white-matter maturation[12, 13]. In addition to its indirect actions through IGF-1, growth hormone can also act directly within the brain through growth hormone receptors expressed on neurons and glial cells, where it influences cellular survival and glial activity[15]. Experimental studies further suggest that GH and IGF-1 contribute to neural cell genesis and structural plasticity within the central nervous system [12, 13, 20]. Despite the volumetric gains observed in the present study, splenial volume remained smaller than in controls, suggesting that early disruption of GH–IGF-1 signalling may partly limit the potential for complete structural catch-up even after hormone replacement therapy.

Several corpus callosum subregions, including the mid-posterior isthmus, mid-anterior body, central body, and anterior genu, together with both thalami, were larger in IGHD compared with controls at baseline, with medium to large effect sizes. These findings differ from previous neuroimaging studies in growth hormone deficiency, which have more commonly reported reduced volumes of the splenium of the corpus callosum and thalamus[16, 19]. Notably, Low et al. (2023) reported a larger mean corpus callosum volume and smaller thalamic volumes in IGHD subjects compared with controls, however this study was limited by a small sample size of 8 subjects [2]. A possible biological explanation for this paradoxical enlargement relates to recent evidence of altered myelination patterns in pediatric GHD. A synthetic MRI study comparing 50 children with GHD and 50 typically developing children reported a widespread pattern of increased myelin volume fraction in the GHD group, including within the genu of the corpus callosum, among other white matter tracts[18]. The authors speculated that this increase may reflect elimination of synapses or compensatory fibre connections arising from impaired cortical and subcortical connectivity, although this mechanism remains unconfirmed. Increased myelin content within callosal fibres could plausibly contribute to the larger corpus callosum subregion volumes observed in the present cohort, particularly given the overlap with the genu. This hypothesis would require direct evaluation using quantitative myelin-sensitive imaging techniques to confirm whether the volumetric findings in the present study reflect genuine alterations in myelin content.

In contrast to the corpus callosum findings described above, the hippocampus, amygdala, putamen, and globus pallidus volumes in our IGHD cohort were comparable to those of healthy controls at baseline. This observation suggests that not all brain regions with a high density of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) receptors are equally susceptible to the effects of GH deficiency. Following rhGH therapy, the hippocampus and amygdala demonstrated significant volumetric increases, whereas the putamen and globus pallidus remained largely unchanged. Differences in structural response across brain regions may reflect variable sensitivity to GH–IGF-1 signalling and its interaction with other endocrine and metabolic regulators. The GH–IGF-1 axis is known to interact with thyroid hormones, nutritional status, and insulin-like growth factor binding proteins, particularly IGFBP-3, which influence IGF-1 bioavailability and tissue-specific signalling efficiency [21-23]. In addition, variability across studies may reflect methodological differences in MRI segmentation pipelines, parcellation schemes, and volumetric normalisation approaches, as well as cohort heterogeneity related to age at diagnosis and clinical characteristics[24, 25]. Taken together, these findings suggest that the structural effects of GH deficiency and the response to rhGH therapy may vary across brain regions, underscoring the importance of region-specific interpretation when evaluating neuroimaging changes in IGHD.

The findings of this study highlight MRI-based volumetry as a promising avenue for characterising structural brain changes associated with IGHD and its response to rhGH therapy. The marked baseline pituitary volume deficit, its partial normalisation following treatment, and the region-specific volumetric changes observed across multiple brain structures demonstrate that structural neuroimaging captures biologically meaningful, treatment-responsive changes that extend beyond auxological outcomes alone. These findings position MRI-based volumetry as a valuable complementary measure for evaluating the neurobiological impact of rhGH therapy, offering a window into treatment response that conventional clinical and biochemical monitoring cannot provide. Building on this foundation, future studies correlating volumetric changes with functional and cognitive outcomes, establishing normative paediatric reference ranges, and confirming reproducibility in larger prospective cohorts would help translate these findings toward routine clinical application, positioning MRI-based volumetry as a strong candidate for a non-invasive biomarker of treatment response in IGHD.

This study has several limitations. Although an ambi-directional design was employed, the use of separate control groups for baseline and follow-up comparisons may introduce cohort-related or measurement bias despite standardised post-processing procedures. Volumetric measurements were not normalised to total intracranial volume (TIV), which may have introduced variability related to differences in overall head size between subjects. However, IGHD and control groups were matched for age, sex, height, and weight,

which likely reduced the magnitude of this potential confound. Future studies incorporating TIV-adjusted or proportionally normalised volumes would strengthen between-group comparisons. Although Tanner staging was performed as part of standard endocrine assessment for the IGHD subjects, it was not incorporated as a covariate in the volumetric analyses, and pubertal staging was not assessed in the control group; this warrants acknowledgement given that pubertal maturation can influence brain structure via sex steroid-mediated effects. However, a subset of IGHD subjects received concurrent GnRH analogue therapy, which suppresses sex steroids to prepubertal levels, and the similar age and sex distributions across the remaining IGHD subjects and controls support a broadly comparable pubertal stage; the contribution of pubertal hormonal changes to the observed findings is therefore likely attenuated. Future studies incorporating pubertal stage as a formal covariate for both groups would further strengthen interpretation of these volumetric changes. Finally, neurocognitive and functional outcomes were not assessed in this study. Future studies incorporating cognitive, behavioural, and functional assessments alongside neuroimaging would provide a more comprehensive understanding of the clinical significance of the observed structural changes.

CONCLUSION

This study demonstrates that MRI-based volumetric analysis can provide objective insights into central nervous system structural involvement in children with isolated growth hormone deficiency. Distinct baseline structural alterations and region-specific longitudinal changes following rhGH therapy were identified, several of which may not be apparent through clinical or biochemical assessment alone. The observed patterns of pituitary growth, limbic and thalamic volumetric increases, and partial normalization of corpus callosum abnormalities highlight the potential neurobiological effects of growth hormone replacement. These findings support the potential role of MRI as a complementary tool in the evaluation of paediatric IGHD and provide further insight into the structural brain changes associated with growth hormone deficiency and its treatment.

Declarations

DATA AVAILABILITY

The de-identified dataset generated and analysed during the current study is available from the corresponding author upon request. The dataset contains the data necessary to support the findings of this study. Access to the data will be subject to applicable institutional and ethical requirements to ensure the confidentiality and privacy of the paediatric participants.

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AUTHOR CONTRIBUTIONS

S.M., N.F.M.G. and N.R. conceived and designed the study. S.M., A.A.Z. and M.Y.J. recruited patients and collected clinical data. S.M. performed the MRI segmentation and data analysis. M.Z.A. and T.L.K. performed the statistical analysis. S.M. and N.F.M.G. drafted the manuscript. N.F.M.G., K.R., A.A.Z., M.Y.J. and N.R. supervised the project and critically reviewed the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

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Figures

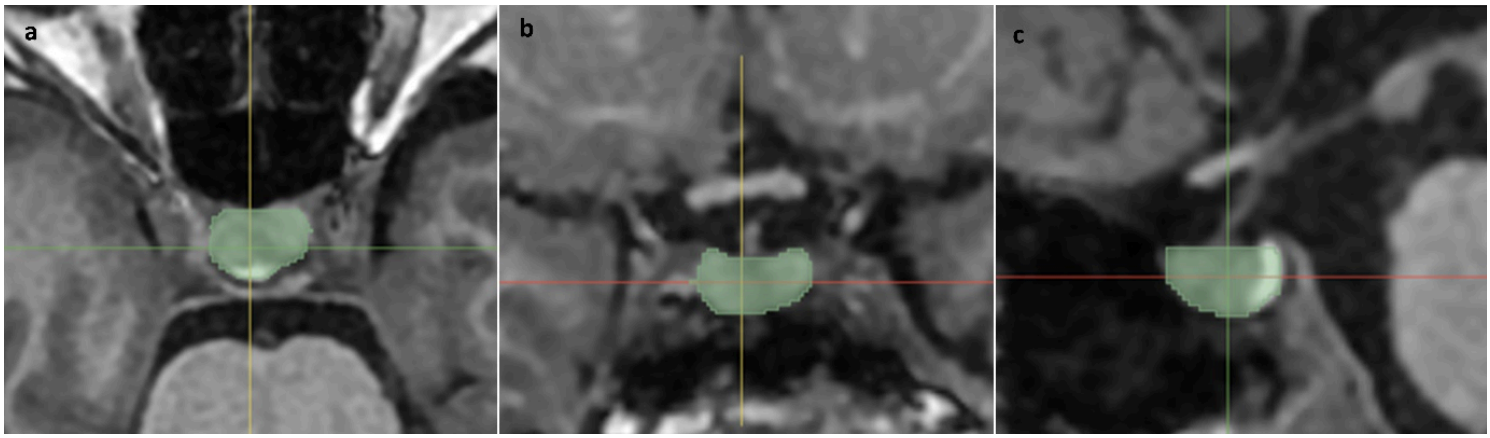


Figure 1

Manual segmentation of the pituitary gland. Representative T1-weighted MRI images showing manual segmentation of the pituitary gland (green overlay) performed using 3D Slicer, displayed in (a) axial, (b) coronal, and (c) sagittal planes. Crosshairs indicate the corresponding anatomical location across the three orthogonal planes.

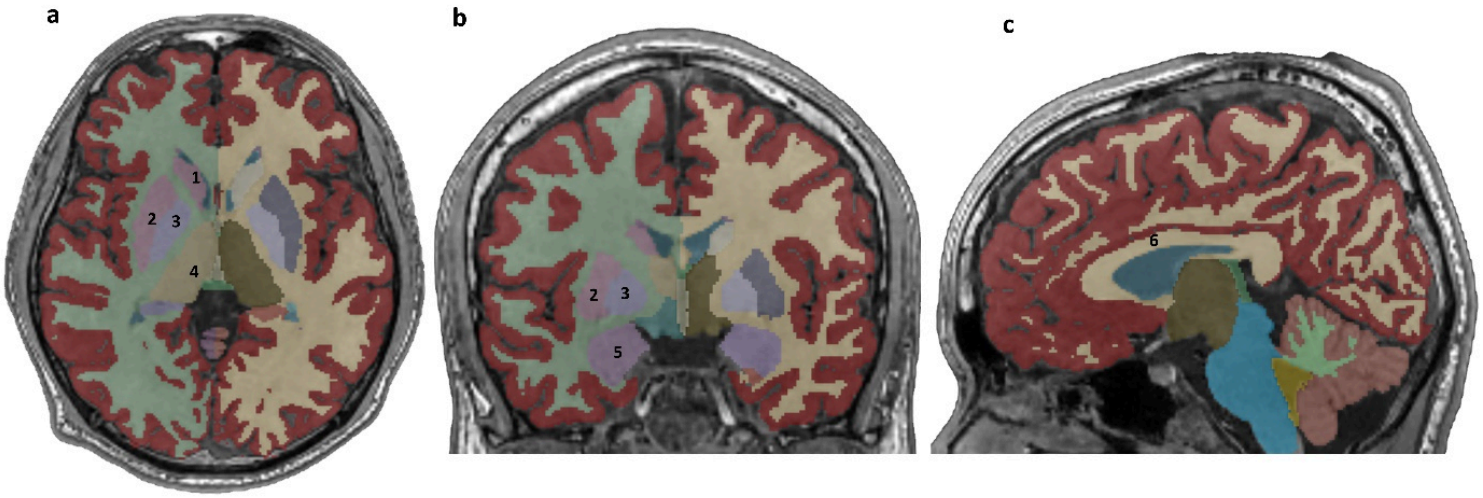


Figure 2

Automated segmentation of subcortical brain structures using FastSurfer. Representative T1-weighted MRI images showing colour-coded automated segmentation of subcortical structures, displayed in (a) axial, (b) coronal, and (c) sagittal planes. Numbered labels indicate: (1)caudate nucleus, (2)putamen; (3)globus pallidus; (4)thalamus; (5)amygdala; (6) corpus callosum.

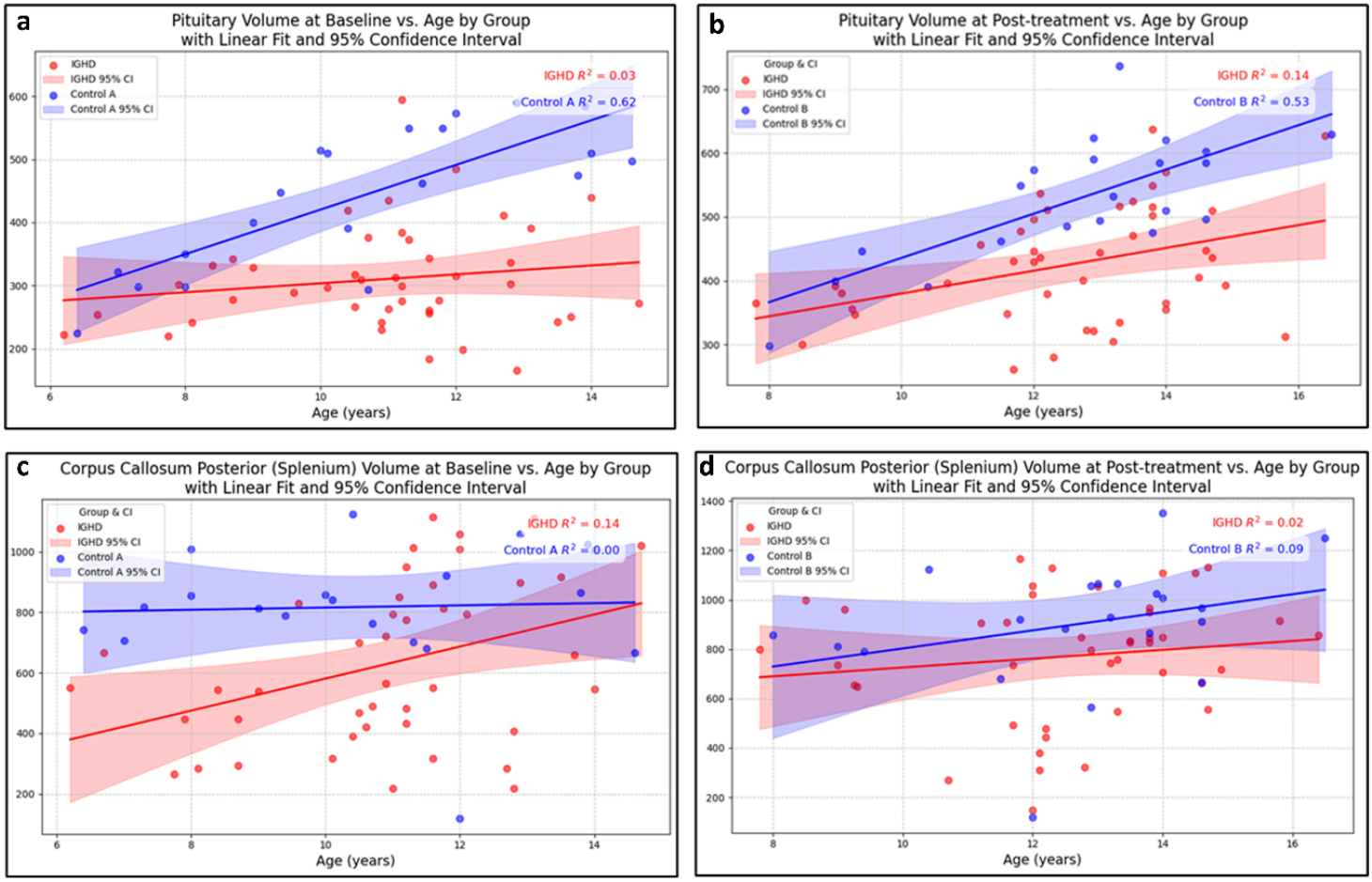


Figure 3

Age-related scatter plots of pituitary and splenium volumes that were reduced in the IGHD group compared with controls at baseline. Individual data points are shown with linear regression lines and 95% confidence intervals for IGHD and control groups. (a) Pituitary volume versus age at baseline comparing IGHD with Control A, showing smaller pituitary volumes in IGHD and a weaker age–volume relationship (IGHD R^2 = 0.03; Control A R^2 = 0.62). (b) Pituitary volume versus age at reassessment compared with Control B, demonstrating increased pituitary volumes in IGHD after rhGH therapy (IGHD R^2 = 0.14; Control B R^2 = 0.53). (c) Posterior corpus callosum (splenium) volume versus age at baseline showing smaller splenial volumes in IGHD (IGHD R^2 = 0.14; Control A R^2 = 0.00). (d) Splenium volume versus age at reassessment demonstrating increased splenial volumes in IGHD with reduced group differences (IGHD R^2 = 0.02; Control B R^2 = 0.09).

Supplementary Files

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