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Progression from isolated growth hormone deficiency to a combined pituitary hormone deficiency in a cohort of paediatrics patients with pituitary morphology abnormalities on MRI

Cristina Aguilar-Riera[1,5*], Diego Yeste[1,4,5], Núria González-Llorens[1], Eduard Mogas[1], Ariadna Campos-Martorell[1,5], Paula Fernandez-Alvarez[2], Elida Vázquez[3] and María Clemente[1,4,5]

Abstract

Objective To evaluate the baseline and follow-up clinical and radiological characteristics of a paediatric cohort initially diagnosed with isolated congenital growth hormone deficiency (IGHD) and pituitary morphology abnormality in MRI.

Patients and methods Observational, ambispective and longitudinal review of paediatric patients with an initial diagnosis of growth hormone deficiency with pituitary morphology abnormality in MRI followed-up in a single tertiary hospital.

Results After mean 11.3 (±3.5DS) years of follow-up, the thirty patients (20 males) were classified into two groups: (1) isolated congenital growth hormone deficiency (IGHD) with 24 patients (9.5 years median follow up), and (2) combined pituitary hormone deficiencies (CPHD) with 6 patients (13.5 years median follow up). Median age at diagnosis was IGHD 3.0 [2.0–4.0] and CPHD 3.0 [1.5–5.2] years. Regarding the cerebral MRI scan results, 2 patients had septo-optic dysplasia (CPHD), 5 had pituitary stalk interruption syndrome (3 IGHD), one had ectopic posterior pituitary (IGHD), 16 had anterior pituitary hypoplasia (15 IGHD) and 6 had the latter two conditions combined (5 IGHD). In genetic studies, 1 of 25 patients had positive NGS panel results and it was in the IGHD group. The target gene detected was *GLI2*. Clinical exome sequencing was performed with six patients, yielding inconclusive results (1 in the IGHD group and 5 in the CPHD group). Array CGH was performed with eight patients (4 in the IGHD group and 4 in the CPHD group) and was negative in all patients. In the CPHD group, associated deficiencies begin to appear after 5 years [4.0–6.0] median follow-up, with thyrotropin being the most frequent (80%), followed by gonadotropin deficiency. ACTH and AVP deficiencies were less frequent.

*Correspondence:
Cristina Aguilar-Riera
cristina.aguilar@vallhebron.cat

Full list of author information is available at the end of the article

Conclusions Multiple hormone deficiencies were diagnosed during this cohort's follow-up evaluation, whose first presentation was isolated growth hormone deficiency and pituitary morphology abnormality in MRI. Pathogenic gene variant involved in congenital hypopituitarism (*GLI2*) was found in one patient. Regular follow up of pituitary hormonal function in such patients is advisable due to the risk of new added deficiencies.

Keywords Growth hormone deficiency, Hypopituitarism, Genetic tests, Pituitary magnetic resonance image

Background

Congenital hypopituitarism (CH) is defined as the deficiency of one or more pituitary hormones resulting from events during fetal development [1]. This may be the result of genetic mutation, antenatal insult, or as is commonly the case, be idiopathic [1] The estimated incidence is 1 per 3,000–10,000 live births [2, 3]. This condition can present as a single hormonal deficiency with the most common manifestation being insufficient growth hormone (IGHD); or as a combined hormonal deficiency with two or more pituitary deficiencies (CPHD) [2-8].

During embryogenesis, hypothalamic-pituitary (H-P) development is controlled by a complex sequence of crosstalk with spatiotemporal activation and inactivation of transcription factors and signalling molecules between the hypothalamus, Rathke's pouch, and the anterior pituitary primordium [4, 7-9]. Described genes involved in the early stages of hypothalamic-pituitary development are: *HESX1*, *SOX 1/2/3*, *PITX1*, *PITX2*, *OTX2*, *RAX*, *LHX3*, *LHX4*, *GLI2*, *ARNT2*, *PAX6*, *BMP4*, *FGFR1*, *FGFR8*, *PROKR2*, *ROBO*, *WNT*, *CDON*, *IGSF1*, *CHD7*, *NFKB2*, *FOXA2*, *TCF7L1*, *MAGEL2*, *L1CAM*, *EIF2S3*, *PNPLA6*, *GLI3*, *SHH*, *ALMS* [1-3, 8-10]. Pathogenic variants in the above genes usually give rise to syndromic manifestations of hypopituitarism. They usually present with malformations or affections in other systems of the body such as immune-level abnormalities, skeletal, ophthalmic, or auditory malformations [1-4, 9, 10]. In addition, they may display midline abnormalities in the cerebral imaging studies: pituitary stalk interruption syndrome (PSIS) [11, 12] septo-optic dysplasia (SOD), and holoprosencephaly (HPE) [1-4, 9, 10, 13].

Alterations in genes involved in the later stages of hypothalamic pituitary formation, namely *POUFU1*, *PROP1*, *KCNQ1*, *IFT172*, *GH1*, *GHRHR*, *RNPC3*, *TBX19*, *PCSK1*, *POMC*, *TBL1X*, *TRH*, *TRHR*, give rise to isolated or combined deficiencies depending on the timing of each gene's expression [1, 4, 9]. They generally occur without extracerebral involvement and patients may show anatomical alterations focused on the pituitary region, mainly in the form of pituitary hypoplasia (APH) [2-4, 9, 10, 14].

In these patients a great variability in the genotype-phenotype relationship is observed, depending on the type of pathogenic variant and its penetrance [4, 6]. In addition, the aetiology remains unknown in most patients and the causative mutations are identified in only a small proportion (10–20%) of cases. This suggests that other genes and/or environmental or epigenetic factors may play a key role in the pathogenesis of the disease [2, 3, 5, 9, 15, 16].

Close monitoring of pituitary function is required because in patients with initially a single deficiency, other hormonal deficiencies may develop over the years [2, 3, 14, 17]. The risk of progression from IGHD to CPHD varies depending on the aetiology [17-19]. In children with congenital idiopathic IGHD the most frequently observed additional deficiency is thyroid stimulating hormone (TSH) followed by luteinizing (LH) and follicle-stimulating (FSH) hormones, while the least frequent hormone deficiency in the majority of cases is arginine vasopressin (AVP) [17-19]. Adrenocorticotropic hormone (ACTH) deficiency may gradually evolve at any time during follow up in the presence of H-P abnormalities and/or TSH deficiency [17-19].

Given the paucity of the knowledge about the aetiology of these conditions, the aim of the present study is to describe the clinical and genetic characteristics, the hypothalamic-pituitary radiological involvement and the follow-up of a series of patients first diagnosed with congenital isolated growth hormone deficiency (GHD).

Patients and methods

An ambispective, observational, and longitudinal review was conducted of paediatric patients with GH deficiency and pituitary morphology abnormality in a tertitary hospital. This study was approved by the Ethics Committee of Vall d'Hebrón Institut de Recerca. Informed consent was obtained from all subjects and/or their parents or legal tutors.

Patients

Children and adolescents primarily diagnosed with hormone growth deficiency were recruited from the paediatric endocrinology department.

Inclusion criteria were: 1)short stature (<-2SDS) due to GHD. GHD was defined as: altered dynamic function test of GH secretion (< 7.4ng/mL; Siemens Immulite 2500 [20]), glucagon test (< 5 years of age) or L-DOPA (≥ 5 years of age), low insulin-like growth factor 1 (≤ 2SDS) and good response to recombinant human growth hormone (rhGH) treatment (HtSDS + 0.5 in 2 years); and 2) pituitary morphology abnormality in MRI defined as: anterior pituitary hypoplasia (APH) -2SDS according to tables adjusted for sex and height [21], ectopic posterior

pituitary (EPP), holoprosencephaly (HPE), pituitary stalk interruption syndrome (PSIS) with a specific tirade (hypoplastic or absent anterior pituitary gland, thin or absent infundibulum and ectopic neurohypophysis location) or septo-optic dysplasia (SOD) presenting at least two of following: optic nerve hypoplasia (ONH), pituitary hypoplasia, or midline abnormalities such as agenesis of the corpus callosum (ACC) or absence septum pellucidum [2, 3, 11, 13, 21].

The exclusion criteria were: (1) pituitary hormonal deficits secondary to infiltrative/oncological processes, trauma, or intracranial surgery, (2) GH deficiency not confirmed; (3) MRI focused on the hypothalamic-pituitary region not performed; and (4) history of adverse perinatal events including birth asphyxia or breech delivery.

Methods: demographics and clinical

All data from patients was collected by reviewing the relevant digital medical records of the hospital system.

Demographic variables were: sex and current age. The diagnostic chronology variables were: age at diagnosis of GH deficiency and in the case of CPHD, age at diagnosis of each other deficiency, gestational age, whether patients had been small for gestational age (SGA), anthropometry, and Tanner stage at diagnosis of the first deficiency.

Clinical variables included were: clinical description of the symptoms upon diagnosis of each hormonal deficiency, phenotypic extrapituitary findings and neurological development; hormonal status (prior to GHD diagnosis, at diagnosis of GHD and during follow-up with IGF1 ng/mL and SDS, TSH mU/L, T4L ng/dL, cortisol ug/dL, ACTH pg/mL, prolactin ng/mL, LH/FSH Ul/L testosterone ng/dL, estradiol pg/mL, inhibin B pg/mL and AMH ng/mL), HtSDS, growth velocity z score and bone age in years (at the diagnosis of GHD, at the start of GH treatment and at 2 years of treatment), pituitary imaging MRI, genetic study and treatment of hormonal deficiencies and dose of rhGH.

Methods: investigation

Patients who later developed other pituitary deficiencies in addition to that of the growth hormone were classified as combined pituitary hormone deficiencies (CPHD).

During follow-up, annual morning basal cortisol, TSH and FT4 determinations were performed on all patients. The diagnosis of the other hormonal deficiencies were reached in the following manner: (1) TSH deficiency was diagnosed based on serum free T4 levels below the reference range and serum TSH < 8 mU/L; (2) ACTH deficiency was diagnosed with ACTH stimulation based on pick serum cortisol < 18ug/dL after a low-dose Synacthen® or after an insulin tolerance test all with low ACTH level. The tests were conducted in the patients with suggestive clinical findings or low morning basal cortisol (< 5.27ug/dl) [22-24]; (3) FSH/LH deficiency was diagnosed in boys when they did not present a testicular enlargement (testicular volume of 4 ml) by 14 years of age and in girls when there was an absence of breast development or menarche at 13- or 15-years old respectively, and then was confirmed by low basal and stimulated FSH/LH values. Neonatal FSH/LH deficiency was ruled out in boys if there was no history of cryptorchidism or microphallus [25]; (4) AVP deficiency was diagnosed with a water deprivation test and/or arginine-stimulated copeptin test conducted in patients with suggestive clinical symptoms [26, 27].

Following an analysis of their clinical description data, patients were classified into two groups: IGHD and CPHD. Calculation of HtSDS and growth velocity z score were based on the Barcelona Longitudinal Growth-Study 1995–2017 [28] for all patients. Bone age was determined by of Greulich & Pyle's method [29].

Methods: genetic tests

One or more of the following genetic studies was used for each patient: 1) *NGS-panel* (capture and sequencing of the exonic and intronic regions flanking the *HESX1*, *IGSF1*, *LHX3*, *LHX4*, *OTX2*, *PAX6*, *POU1F1*, *PROK2*, *PROKR2*, *PROP1*, *ROBO1*, *FGF8*, *FGFR1*, *GLI2*, *GLI3*, *SOX3*, genes involved in congenital hypopituitarism and *GH1*, *GHR*, *GHRHR*, *GHSR* genes involved in growth hormone deficiency, using the methodology Cell3 Target Custom Panel tier 2 (NONACUS) on Illumina's NextSeq platform, with bioinformatic analysis of the obtained sequences and alignment using IMEGEN's Data Genomics platform2) *array CGH* (Aligent CytoGenomics v2.0, with the ADM-2 algorithm and a minimum of 3 consecutive probes to detect an abnormality with EasyArray v3.0 interpretation software); 3) *clinical exome NGS* (Next Generation Sequencing, using the XGen Exome Panel v2.0 (IDT) kit).

For patients with isolated deficits, the initial genetic study was the NGS-panel (Next-Generation Sequencing) described above. If neurological delay was detected, an additional array CGH (Comparative Genomic Hybridization) was performed. Furthermore, array CGH was also utilized in patients with isolated deficits if specific phenotypic traits were present, suggesting the possibility of an underlying genetic abnormality.

For patients with combined deficits, the NGS panel was ideally performed first; however, due to the limited number of genes included in the panel, clinical exome sequencing was directly pursued in certain cases when a broader genetic investigation was required. In cases where patients presented additional malformations or multiple deficits, direct clinical exome sequencing was

used, either initially or following array CGH, depending on the clinical context.

In our center, both the NGS genetic panels and exomes are regularly reviewed every two years to ensure that the most up-to-date and comprehensive panels are utilized in clinical practice.

Statistical analysis

The mean with standard deviation or median with first and third quartiles [Q1-Q3] of the quantitative variables and percentages in the qualitative variables were calculated. When performing comparisons between 2 groups the Mann-Whitney U test for quantitative variables and Chi-Square test for qualitative variables were used. Two-sided P values < 0.05 were considered statistically significant. All analyses were performed using Excel procedures (version16.84, Microsoft 365).

Results

This study included 30 patients with GH deficiency and pituitary morphology abnormality after 19 others were excluded. There was a predominance in male sex (67%) with a current mean age of 13.3 ± 3 years and a mean age at diagnosis of 3.5 ± 2.9 years (Table 1 and supplementary table). The mean gestational age was 36.1 ± 4.8 weeks with nine preterm patients and three SGA (10%). The mean birth weight of the patients was 2642.2 ± 971.2 g. Regarding breech presentation, there were 21 cases of cephalic presentation and 9 cases of breech presentation. The anthropometry at the first appointment showed a mean HtSDS of -2.8 ± 1.2 (Table 1). The pituitary MRI findings were: sixteen APH, one EPP, six APH with EPP, two SOD and five PSIS (Table 1 and supplementary table). According to the presence of additional pituitary deficiencies, patients were divided into two groups: (1)

Table 1 Clinical characteristics, hypothalamic-pituitary MRI findings of IGHD and CPHD groups and comparison between them

		All *N* = 30	IGHD *n* = 24 (80%)	CPHD *n* = 6 (20%)	*p*-value
Age at growth disorder initial follow up (mean ± SD) or (median and IQR) years		3.5 ± 2.9	3.0 [2.0–4.0]	3.0 [1.5–5.2]	0.37
Current age (mean ± SD) or (median and IQR) years		13.3 ± 3.0	13.0 [11.0–15.0]	15.0 [13.0–16.0]	0.07
Sex		Males 20 (67%) Females 10 (33%)	Males 17 (71%) Females 7 (29%)	Males 3 (50%) Females 3 (50%)	NA
Gestational age (mean ± SD) or (median and IQR) weeks		36.1 ± 4.8	37 [37–39]	37.5 [26–40]	0.47
SGA		3 (10%)	3 (12.5%)	0	NA
HtSDS at first visit (mean ± SD) or (median and IQR)		-2.8 ± 1.2	-2.6 [-3.4, -2.2]	-2.8 [-4.7, -0.8]	**0.0001**
Tanner first visit		1	1	1	NA
Clinical (number of patients and %)	**Phenotype dysmorphology**		7 subjects (29.1%)	6 subjects (100%)	NA
	Neurodevelopment delay		1 subject (4%)	3 subjects (50%)	
Cerebral MRI	**APH**	16	15/24	1/6	NA
	EPP	1	1**/24	0/6	
	APH + EPP	6	5/24	1/6	
	PSIS	5	3/24	2/6	
	SOD	2	0/24	2/6	
rhGH treatment	**Age at initiation (median and IQR) years**		5.0 [4.0-9.2]	6.0 [4.0–7.0]*	0.47
	HtSDS at initiation (median and IQR)		-2.5 [-3.5, -2.4]	-3.8 [-4.8, -3.6]	**0.01**
	Velocity z score at initiation (median and IQR)		-2.5 [-3.4, -2.0]	-3.2 [-4.2, -2.0]	0.64
	Bone age (chronological age years)		-1.0 [-1.0-, -2.0]	-2.0 [-2.0-, -3.0]	**0.003**
	rhGH doses mcg/kg/d (median and IQR)		30.0 [27–30]	29.0 [28–32]	0.38
rhGH after 2 years treatment	**HtSDS (median and IQR)**		-1.5 [-2.2, -0.7]	-1.6 [-2.6, -0.9]	0.33
	Δ HtSDS at 2 years treatment (median and IQR)		1.4 [1.0-1.8]	2.2 [2.2–2.3]	**0.02**
Follow up (median and IQR) years			9.5 [7.5–11.2]	13.5 [9.2–14.7]	0.11
Current Tanner			12 Tanner V 12 Tanner I	3 Tanner V 3 under pubertal induction	NA

*One patient without rhGH treatment (family decision)

**This subject also has agenesis septum pellucidum

NA, not applicable; IGHD, isolated congenital growth hormone deficiency; CPHD, combined pituitary hormone deficiencies; SGA, small for gestational age; HtSDS, height z scores; Δ HtSDS, height z score increase; APH, anterior pituitary hypoplasia; EPP, ectopic posterior pituitary; PSIS, pituitary stalk interruption syndrome; SOD, septo-optic dysplasia

IGHD group with 24 (80%) subjects and (2) CPHD with 6 subjects (20%).

IGHD group characteristics

In this group of 24 patients there was a predominance of the male sex (71%) with a median current age of 13.0 [11.0–15.0] years. The median gestational age was 37 [37–39] weeks with five preterm patients. The median age at initial follow-up was 3.0 [2.0–4.0] years. The reason for consulting the paediatric endocrinology specialist for all of them was growth retardation, with three patients (12%) having been SGA. The median birth weight of the patients was 3029.5 [2662.5-3288.7] g. Regarding breech presentation, there were 15 cases of cephalic presentation and 7 cases of breech presentation. The *anthropometry* in the first visit showed a median HtSDS of − 2.6 [-3.4, -2.2] with Tanner stage 1 in all patients. In relation to the phenotypic characteristics, 29.1% of the subjects presented some dysmorphic trait. The most common were prominent and wide forehead with low scalp implantation, wide nasal root, high-arched palate, and some tooth deficiencies. In addition, two patients presented Chiari malformation type 1, one patient was obese (BMI z score + 2SD), and one patient had neurodevelopmental delay and congenital hearing loss (Table 1). The median peak of GH was 2.6 ng/mL [1.8–4.7] recorded at the median age of 5.0 [4.0-9.2] years.

In relation to *rhGH treatment*, the median age at the onset was 5.0 [4.0-9.2] years with a median HtSDS of -2.5 [-3.5, -2.4], median growth velocity z scores of -2.5 [-3.4, -2.0] and median bone age delay 1.0 [1.0–2.0] year. Two years after treatment, all patients presented an adequate response to rhGH with a median HtSDS of -1.5 [-2.2, -0.7] and a median HtSDS increase of 1.4 [1.0-1.8] (Table 1).

The *median follow-up time* was 9.5 [7.5–11.2] years. Twelve of these patients underwent puberty spontaneously and in the remaining 12 patients pubertal development had not yet started (with the three oldest aged 12–13 years). The rest of the pituitary axes evaluated in the baseline analyses and throughout the evolution were normal and patients did not present symptoms suggestive of other hormonal deficiencies (Table 1).

The *pituitary MRI* findings were: fifteen patients with APH (one with hypothalamic hamartoma and pars intermedia cyst), one patient with EPP (located at infundibular region) and septum pellucidum agenesis, five patients with APH and EPP (located at infundibular region), and three patients with PSIS (EPP located in the hypothalamic level in one, in the median eminence in the second and in the infundibular region in the third) (Table 1 and supplementary table).

Regarding the *genetic studies* carried out, five array CGH were performed (20.8%): four with normal results and one with the presence of a familial balanced chromosomal translocation t(2;6) (q31;q15) with a hypopituitarism NGS panel without pathogenic findings. A total of 23 hypopituitarism NGS panels (95.8%) were performed, one with likely pathogenic variant: ***GLI2*** heterozygosity NM_001374353.1:c.2515del p.(Asp839Thrfs*56) (likely pathogenic). Finally, a clinical exome was performed on one subject without conclusive pathogenic findings (Supplementary table).

CPHD group characteristics

In this group of 6 patients there was equal prevalence of the male and female sex with a current median age of 15.0 [13–16] years. The median gestational age was 37.5 [26–40] weeks with 4 preterm. The median birth weight of the patients was 2507.5 [1281.2–1281.2] g. Regarding the presentation at birth, there were 4 cases of cephalic presentation and 2 cases of breech presentation. The average age at first visit of CPHD was 3.0 [1.5–5.2] years. Diagnosis in all patients was due to growth restriction (none with SGA) and two were also blind. *Anthropometry* at the first appointment showed a median HtSDS of -2.8 [-4.7, -0.8] with a Tanner stage 1 in all.

The *pituitary MRI* findings were: one patient with APH with absence of olfactory bulbs and interhypothalamic adhesion, one patient with APH and EPP (located at median eminence), two patients with SOD (two patients with ONH), and two patients with PSIS (EPP located at median eminence) (Table 1 and supplementary table).

Phenotypic abnormalities were observed in all patients, of which the most frequent were prominent forehead, wide nasal root, high-arched palate, syndactyly or other alterations in fingers, tooth deficiencies, low set ears, macrocephaly or microcephaly. Other comorbidities observed were arthrogryposis and neurodevelopmental delay in one patient with PSIS, while Hirschsprung disease, brachydactyly, interventricular septal defect, and Brown syndrome were observed in another patient with APH. Other comorbidities observed were arthrogryposis and neurodevelopmental delay in one patient with PSIS, Hirschsprung disease, brachydactyly, interventricular septal defect, and Brown syndrome in another patient with APH. One patient with SOD presented neurodevelopmental delay, epilepsy, hypothalamic obesity (BMI 37.7 + 3.7 kg/m^2 SD and hyperphagia), sensorineural hearing loss, visual impairment, and scoliosis with congenital torticollis. The other two patients (one with APH and EPP, and the other with PSIS) only presented neurodevelopmental delay, and the one with SOD also presented with blindness (Table 1 and supplementary table).

Genetic studies were performed with inconclusive findings. Array CGH were performed with 4 patients (two patients with PSIS, one with APH and EPP, and one patient with APH) with no interpreted losses or gains of

Table 2 Onset of additional pituitary deficiencies of CPHD group

Patient	Gender	1st Deficit (age)	2nd Deficit (age)	3rd Deficit (age)	4th Deficit (age)
1	Boy	GH (7 yrs)	TSH & ACTH (8 yrs)	LH/FSH (14 yrs)	NA
2	Girl	GH (1 yrs)	TSH (5 yrs)	AVP (8 yrs)	LH/FSH (13 yrs)
3	Boy	GH (6 yrs)	TSH (12 yrs)	NA	NA
4	Boy	GH (1 yrs)	LH/FSH (14 yrs)	NA	NA
5	Girl	GH (3 yrs)	TSH (9 yrs)	ACTH (11 yrs)	NA
6	Girl	GH (3 yrs)	TSH (7 yrs)	NA	NA

NA, not applicable; GH, growth hormone; TSH, thyroid stimulating hormone; ACTH, adrenocorticotropic hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; AVP, arginine vasopressin hormone

genetic material being detected as pathogenic. The NGS panel was negative in the two patients in whom it was performed (one patient with PSIS and neurodevelopmental delay and one patient with APH and EPP). Finally, five clinical exomes were performed with the two patients with SOD, the two patients with PSIS and the patient with APH with inconclusive results.

Regarding *GH deficiency*, the median peak of GH was 1.3 ng/mL [0.9–2.3] recorded at median age of 3.0 [1.5–5.3] years. The median age at onset of rhGH treatment was 6.0 [4–7] years, with a median HtSDS of -3.8 [-4.8,-3.6] and a median growth velocity z score of -3.2 [-4.2, -2], and a median bone age delay of 2.0 [2.0–3.0] years. Two years after the start of treatment, all patients presented a good response with a median HtSDS of -1.6 [-2.6, -0.9], a median HtSDS increase of 2.2 [2.2–2.3]. It should be noted that one patient did not undergo treatment with rhGH due to a family decision. Four patients are being treated with rhGH at adult doses (Table 1).

Additional pituitary deficiencies observed after growth hormone deficiency

Gonadotropin deficiency was diagnosed due to delayed puberty, corticotrophin and thyrotropin deficiencies due to asthenia or analytical control, and arginine-vasopressin deficiency for clinical symptoms of nocturnal enuresis with polydipsia or/with polyuria.

Patients were followed for a median of 13.5 [9.2–14.7] years. Thyrotropin was the most frequently observed deficiency (5 patients) diagnosed at a median age of 9 years [5–11]. Half of the group developed gonadotropin deficiency (3 patients) and two patients developed corticotrophin deficiency at eight and eleven years of age. The least frequent deficiency was arginine vasopressin which was found in one patient at 8 years old (Table 2).

The three patients presenting with LH/FSH deficiency (one female) were diagnosed due to delayed puberty and low basal and stimulated FSH/LH values. Subsequently, pubertal induction was started at a median age of 14 years [13.5–14]. The female patient's puberty was induced with 17β estradiol patches. One male is currently receiving HCG and rFSH treatment and in the other male patient pubertal induction was performed with IM testosterone (Table 1).

Reviewing the order of development of additional pituitary deficiencies, *thyrotropin* deficiency was the second deficiency manifested in all patients. *Corticotrophin* combined with TSH was the second deficiency in one patient and the third in another. Gonadotropin deficiency, clearly manifested in three patients at the onset of puberty, developed as the second, third and fourth deficiency. Finally, *arginine vasopressin* deficiency developed third in one patient (Table 2). The median time of appearance of the second deficiency was 5.0 [4–6] years after the IGHD diagnosis; the third, after 8.0 [7.5-8] years; and the fourth, after 12 years (only one patient) (Table 2).

Discussion

CH is a condition with wide clinical, cerebral MRI and genetic heterogeneity. The most frequent deficiency is GH, which can present by itself or combined with others. In this paper the follow-up of paediatric patients who were initially diagnosed with isolated GH deficiency as well as pituitary morphology abnormality on MRI is described. Six patients manifested other pituitary hormonal deficiencies during follow-up so according to the presence of additional pituitary deficiencies, patients were divided into two groups: isolated congenital growth hormone deficiency (IGHD) and combined pituitary hormone deficiencies (CPHD) respectively. The clinical features, anthropometry, pituitary MRI, response to rhGH treatment and genetics tests are presented and compared between the two groups (IGHD andCPHD).

Notably in this study of 30 patients, males predominated, as was also observed in reviews by Cerbone et al. and studies by Child et al. [1, 11]. In general, patients with GH deficiency and pituitary morphology abnormality on MRI are diagnosed at an earlier age than other patients with GH deficiency, probably due to greater impairment in the pituitary gland. Accordingly, the mean age at diagnoses of our cohort was 3 years.

CPHD had significantly more affected HtSDS at first visit and at rhGH initiation (p-value 0.0001 and 0.01 respectively). Patients in both groups had all presented growth impairment during the first year after birth, although no patient presented hypoglycaemia during the neonatal period. Furthermore, there was a clear predominance of neurodevelopmental impairment and phenotype dysmorphology in the CPHD group, which was also

observed in other reviews by Cerbone et al. Child et al. and Blum et al. [17-19].

In general, the median ages of initiation of rhGH were similar in patients with IGHD and the others who subsequently developed other pituitary deficiencies. However, patients with CPHD had significantly more delayed bone age (p-value 0.003). The GH response was very good in both groups, although the increase in HtSDS at two years was significantly better in the CPHD group (p-value 0.02). These data are consistent with the review by Cerbone et al. and study by Blum et al. [17, 19] which point out there is a greater risk of developing combined pituitary deficiencies in patients with a single growth hormone deficiency with more severe growth restriction, although this does not exclude milder forms from evolving to CPHD.

A total of 2.5% positive results in the different genetic tests were observed. This low results in genetic tests suggest there may be other genes involved, neither studied with our panel (only includes 20 genes) nor yet described. In addition, no genetic causes may be involved in the etiology of CH [13] Variability in the pathogenic variants' penetrance and also in the phenotypes of the genes that intervene in the hypothalamic-pituitary development makes it difficult to interpret the results obtained and to describe new genes, as previously reported [5, 9, 17, 30]. In addition, the sample was small, and the number of subjects would have to be increased to have more accurate data. To remark on our sample of patients with initial diagnoses of IGHD with MRI abnormalities we did not find any pathogenic variations on *PROP1* and *POU1F1* genes despite these being the most frequently described genes in patients with congenital hypopituitarism [16]. This may be due, as mentioned before, to the small sample of subjects or to the inclusion criteria of patients with initial diagnoses of IGHD deficiency. While not detailed in this manuscript, unpublished data from our clinical practice indicate that the diagnostic yield increases to approximately 16% with clinical exome sequencing and up to 20% when array-CGH is additionally performed.

Only one patient in the IGHD group presented positive findings in the genetic tests. The patient with *GLI2* likely pathogenic variants had no dysmorphological trait and presented APH with EPP in MRI. The MRI cerebral abnormality reported in the literature as being associated with this gene correlate with the one identified in our patient [2, 3, 17]. However, the clinical phenotype most frequently described as linked to this gene was not present in the patient, suggesting a variable penetrance (*GLI2* with polydactyly and midface abnormalities/central incisor) [1-3, 17].

The IGHD patients did not present any other phenotypic abnormalities except for the MRI alterations that were restricted to the hypothalamic-pituitary region. In addition, the proportion of patients with PSIS was notably smaller in this group compared with the CPHD group (3/24 vs. 2/6). The three patients with IGHD and PSIS did not have positive results in the genetic NGS panel, which includes the most frequent genes associated with PSIS (*HESX1*, *LHX4*, *SOX3*, *OTX2*, *ROBO1* and *PROKR2*). According to Cerbone et al., Child et al. and Gregory et al. [9, 17, 18] the presence of midline defects (optic nerve hypoplasia or alteration of the corpus callosum and septum pellucidum) together with alterations in the H-P axis or an interruption of the pituitary stalk and localization of EPP or APH (depending on the degree and the presence of empty sella turcica) confer a greater risk of progression to other pituitary deficiencies [9, 17-19]. Therefore, some patients in this group will require closer monitoring of hormonal status depending on their MRI findings.

It should be noted that no positive results were found in the CPHD group with the selected genetic tests including the non-conclusive CES. Jee et al. [31] report that congenital sporadic hypopituitarism has a more complex aetiology than is associated with a simple monogenic disorder with complete penetrance and that an oligogenic or digenic inheritance may be present as has also been suggested by Hamdi-Rozé et al. and Gregory et al. [30, 32]. In addition, sporadic cases could be caused by environmental factors such as drug and alcohol abuse during pregnancy, among others [13]. As mentioned previously, the small number of patients and the limited genes analysed could have contributed to the negative results observed in this cohort.

In our series, thyrotropin deficiency was the most prevalent hormonal pituitary deficiency and the least frequent was arginine-vasopressin, in keeping with the results presented in the review by Cebrone et al. and the studies of Child et al. and Blum et al. [17-19]. The median time until the appearance of additional deficiencies was 5 years for the second, and 8 years for the third deficiency, in line with previous reports [17]. Nevertheless, among the various studies reviewed by Cebrone et al. [17] presentation time of second deficiencies varied. In our cohort, TSH was the second deficiency in all but one patient. All patients with central hypothyroidism required increasing doses of levothyroxine during follow-up to maintain FT4 levels in the mid-upper half of the normal range according to recommendations [3, 33] supporting the diagnosis of TSH deficiency.

The average follow up of patients with CPHD was 4.4 years longer than that of those with IGHD. Considering this and the fact that 12 of the latter patients had not yet reached the age of puberty, it is probable that with longer follow-up other deficiencies might appear in these patients. Therefore, it should be taken into account that there is a possibility that with longer follow-up, some of

the IGDH patients may develop other deficiencies. Additionally, it remains uncertain whether IGHD may persist or resolve during adulthood. Some patients may no longer require rhGH treatment, and this should be reassessed at that time.

Study limitations

The limitations of our study include the retrospective nature of the study, and the limited number of patients included.

Conclusion

In patients with IGHD and pituitary abnormalities it is advisable to follow up their pituitary hormonal function over the years due to the risk of manifestation of new added deficiencies. Although, it is difficult to establish risk factors for the appearance of other deficiencies. In our series, patients who developed CPHD presented more height impairment at diagnoses, more delayed bone age and a greater response to rhGH treatment. Furthermore, in these cases dysmorphic phenotypic features, delayed neurodevelopment, and malformations in other organs were usually associated with more severe findings in the brain MRI. Finally, the genetic study was positive in only one patient (*GLI2*) probably related to the inclusion criteria.

Abbreviations

IGHD	Isolated congenital growth hormone deficiency
CPHD	Combined pituitary hormone deficiencies
CH	Congenital hypopituitarism
PSIS	Pituitary stalk interruption syndrome
SOD	Septo-optic dysplasia
HPE	Holoprosencephaly
APH	Pituitary hypoplasia
H-P	Hypothalamic-pituitary
TSH	Thyroid stimulating hormone
LH	Luteinizing hormone
FSH	Follicle-stimulating hormone
AVP	Arginine vasopressin
ACTH	Adrenocorticotropic hormone
GH	Growth hormone
rhGH	Recombinant human growth hormone
EPP	Ectopic posterior pituitary
ONH	Optic nerve hypoplasia
ACC	Corpus callosum
SGA	Small for gestational age
MRI	Magnetic resonance

Supplementary Information

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Supplementary Material 1

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Author contributions

CA organized the data collection and drafted the initial and final manuscript. DY conceptualized and designed the review and drafted the first and final manuscript. NG reviewed the manuscript and approved the final manuscript. EM reviewed the manuscript and approved the final manuscript. AC reviewed the manuscript and approved the final manuscript. AF reviewed the manuscript and approved the final manuscript. PF reviewed the manuscript and approved the final manuscript. EV reviewed the manuscript and approved the final manuscript. MC conceptualized and designed the review and drafted the first and final manuscript. All authors were involved in writing the manuscript and approved the final version.

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Data availability

Data availability: The datasets analyzed during the current study are available in the ClinVar repository https://www.ncbi.nlm.nih.gov/clinvar/. Accession number: SCV006080850, SCV006080849, SCV006080848.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee for Research with Medicines (Comité de Ética de Investigación con Medicamentos) of the Vall d'Hebron University Hospital, affiliated with the Vall d'Hebron Institute of Research **(CAI-VHIR) PR(AMI)319/2023**. Consent was obtained from all individual participants or their legal surrogates for the use of their data. In the case of participants under the age of 16, informed consent to participate was obtained from their parents or legal guardians. The Ethics Committee approved the study based on the use of anonymous data and the absence of any intervention. The research was conducted in accordance with the Declaration of Helsinki and relevant national ethical guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

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Author details

[1]Paediatric Endocrinology Service, Hospital Universitari Vall d'Hebron, Barcelona, Spain
[2]Molecular Genetics Laboratory. Hospital Universitari, Vall d'Hebron, Barcelona, Spain
[3]Paediatric Radiology Service, Hospital Universitari, Vall d'Hebron, Barcelona, Spain
[4]CIBER Enfermedades Raras, Instituto Carlos III, Madrid, Spain
[5]Universitat Autònoma de Barcelona, Barcelona, Spain

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