



# Prevalence of brain MRI findings in children with nonacquired growth hormone deficiency: a systematic review and meta-analysis

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## Abstract

**Purpose** To verify and integrate the prevalence and phenotype of abnormalities in the sellar region in patients with growth hormone deficiency (GHD) using MRI data.

**Methods** We searched PubMed and EMBASE up to December 14, 2020. The inclusion criteria were as follows: (1) pediatric patients diagnosed with nonacquired GHD and (2) detailed data sufficient to assess the proportion of sellar and parasellar abnormalities on brain MRI scans. Finally, thirty-two studies with 39,060 children (mean or median age, 3.4–14.1 years) were included. The number and type of MRI findings from all included studies were pooled by two authors. The heterogeneity across studies was evaluated with the *Q* test or the inconsistency index (*I*<sup>2</sup>) statistic. Subgroup analyses were performed according to the type of GHD (isolated GHD [IGHD] vs. multiple pituitary hormone deficiency [MPHD]), MRI magnet, geographical region, and cutoff serum growth hormone (GH) level.

**Results** The pooled proportion of sellar and parasellar abnormalities was 58.0% (95% CI, 47.1–68.6%; *I*<sup>2</sup>, 98.2%). The MPHD group showed a higher proportion of sellar and parasellar abnormalities and pituitary stalk interruption syndrome than the IGHD group (91.4% vs. 40.1%, *P*<0.001; 65.3% vs. 20.1%, *P*<0.001). The patients in studies with low peak GH levels on stimulation tests were more associated with severe MR abnormalities (cutoff GH ≤ 5 μg/l vs. cutoff GH = 10 μg/l; 72.8% vs. 38.0%; *P*<0.001).

**Conclusion** The types and incidence of MRI abnormalities of the sellar region differ significantly between the IGHD and MPHD groups.

**Keywords** Growth hormone deficiency · Pediatric · Pituitary · Brain · MRI · Meta-analysis

## Introduction

Growth hormone deficiency (GHD) is a relatively common endocrine problem (1/3000~1/9000 in children [1]), which leads to short stature in childhood and could give rise to severe short stature in adulthood if there is no adequate supplemental hormone therapy.

GHD can be divided into acquired GHD and nonacquired (congenital) GHD according to its etiology. A clinical history of head trauma, central nervous system (CNS) infection, tumor, and cerebral irradiation are relatively common causes of acquired GHD. Though most of these causes of acquired GHD are easy to detect in imaging studies, the structural abnormalities in the vicinity of the pituitary gland of some nonacquired GHD cases may not be clearly revealed.

After the first study of pituitary stalk transection (interruption) using MRI was reported in 1987 [2], MRI has been regarded as the most superior and essential imaging modality for evaluating sellar and parasellar structural abnormalities in patients with GHD. In addition, in the initial evaluation of patients with GHD, it is important to use MRI to identify midline anomalies that may accompany nonacquired GHD, tumors, and other infiltrative diseases that may cause pituitary hormone abnormalities.

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Furthermore, MRI provides important information for predicting prognosis and determining the need for screening in patients with nonacquired GHD. According to previous studies, isolated GHD (IGHD) patients with pituitary abnormalities are known to have a higher rate of progression to multiple pituitary hormone deficiency (MPHD) at follow-up than IGHD patients without pituitary abnormalities [3]. In addition, it has been reported that patients with IGHD who had pituitary abnormalities had better GH replacement treatment results than IGHD patients who did not have these abnormalities [4–6].

There have been many studies using MRI for nonacquired GHD. However, most of the studies were conducted in relatively small study populations, and the reported incidence of sellar and parasellar structural MRI abnormalities between studies has varied greatly [7–22]. For example, the incidence of isolated pituitary hypoplasia in IGHD patients ranges from as little as 4% [8] to as much as 50% [23]. The largest recent population study was conducted by Magnie et al., published in 2013, on 15,043 children with nonacquired GHD in KIGS (Pfizer International Growth Database) from 1987 to 2011 [24]. This study was a highly valuable study that confirmed that there is an important association between the pituitary structure and function in a large study population of various countries. However, as a limitation of the study, the exact number of patients in the two groups, IGHD and MPHD, was not revealed, so the proportion of MRI abnormalities between the two groups was not clearly identified; furthermore, it was difficult to clarify the criteria for pituitary hypoplasia from the KIGS data, which was the most common MRI abnormal finding. Moreover, the influences of other variables, such as the imaging protocol, geographical region, and the cutoff serum GH level for the diagnosis of GHD, were not evaluated. These areas are worth further investigation in a large study population. From this point of view, we performed a systematic review and meta-analysis to verify and integrate the MRI phenotype of patients with GHD.

## Materials and methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [25].

### Search strategy and selection criteria

PubMed and EMBASE databases were searched up to December 14, 2020, using the following search terms: pituitary AND ((growth hormone deficiency) OR (GH deficiency)) AND ((MRI) OR (MR imaging) OR (magnetic resonance imaging)) AND ((idiopathic) OR (nonacquired) OR (acquired) OR (secondary) OR (congenital) OR

(pathologies) OR (structural abnormalities) OR (organic)) AND (children OR pediatric OR paediatric). The literature search was restricted to articles published in English. The literature search was performed by one reviewer (J.S.H.).

The inclusion criteria were as follows: (1) pediatric patients ( $\leq$  18 years old) diagnosed with nonacquired GHD [26] and (2) detailed data sufficient to assess the proportion of sellar and parasellar abnormalities on brain MRI scans. The exclusion criteria were as follows: (1) acquired GHD (craniopharyngioma, microadenoma, history of head trauma, cranial irradiation, or CNS infection) and complex syndromes [24, 26, 27]; (2) conference abstracts, review articles, letters, erratum, articles in press, case reports, or books; (3) adult patients; (4) insufficient data for evaluating outcomes; and (5) overlapping study populations and data. Studies with larger study populations were chosen in cases of overlapping patients and data.

### Data extraction and quality assessment

Data were extracted by two reviewers (J.S.H. and S.W.J.) using a standardized extraction form and disagreement was settled by consensus.

1. Study characteristics: authors, publication year, study period, institution, country, and study design
2. Patient characteristics: number of patients, age, sex, mean or median age, diagnostic method of GHD, and type of GHD (IGHD vs. MPHD)
3. MRI characteristics: MR imaging magnet, matrix size, field of view (FOV), slice thickness, contrast enhancement, and imaging criteria of sellar and parasellar abnormalities
4. MRI findings: proportion of total and specific sellar and parasellar abnormalities (isolated anterior pituitary hypoplasia (IAPH), empty sella, isolated stalk abnormality, isolated ectopic posterior pituitary (EPP), pituitary stalk interruption syndrome (PSIS), congenital mass), proportion of midline brain anomalies, and proportion of CNS abnormalities outside the pituitary area. PSIS was defined as triad of thin or interrupted pituitary stalk, aplasia or hypoplasia of the anterior pituitary, and absent or EPP [2, 28].

Two independent reviewers (J.S.H. and S.W.J., with 8 and 10 years of radiology experience, respectively) assessed the quality of each included study using the Risk of Bias Assessment tool for Nonrandomized Studies (RoBANS 2.0) with consensus [29]. The RoBANS tool is configured to evaluate the risk of bias in a total of 8 domains, including comparability of participants, selection of participants, confounding variables, intervention (exposure) measurement, blinding of outcome assessment, outcome evaluation, incomplete outcome data, and selective outcome reporting. The “comparability of participants” domain was not applicable in most of

the included studies and was excluded in the quality assessment. The risk of bias of all domains was classified into three categories: “low risk,” “high risk,” and “unclear risk.” Quality assessment results were presented using Revman 5.0 version (Cochrane Community, Oxford, UK).

### Statistical analysis

The primary outcome of this study was the pooled proportion of sellar and parasellar abnormalities, midline brain anomalies, and CNS abnormalities outside the pituitary area in patients with GHD. The statistical heterogeneity across studies was evaluated with the  $Q$  test or the inconsistency index ( $I^2$ ) statistic, and a  $P$ -value  $< 0.1$  in the  $Q$  test and  $I^2 \geq 50\%$  were considered to indicate significant heterogeneity [30]. Hartung-Knapp adjustment for the random-effects model for the meta-analysis of single proportions was performed [31]. Individual study weights were evaluated with the inverse variance method with the arcsine transformation [32]. In addition, we further investigated subgroup analyses according to the type of GHD (IGHD vs. MPHID), MRI magnet, geographical region, and cutoff serum GH level for the diagnosis of GHD (cutoff GH  $\leq 5$   $\mu\text{g/l}$  vs. cutoff GH = 10  $\mu\text{g/l}$ ) to explore the potential sources of heterogeneity.  $P$  values  $< 0.05$  were regarded as statistically significant [33]. In subgroup analysis according to cutoff serum GH level, sellar abnormalities were additionally divided into two groups by severity of the MR abnormalities (IAPH vs. isolated EPP or PSIS or any two out of the three abnormalities of anterior pituitary hypoplasia, stalk abnormality, and EPP) [3, 34]. Begg’s test was used to evaluate publication bias [35]. A funnel plot was visually assessed and  $P < 0.05$  of Begg’s test results represented the presence of publication bias. All statistical analyses were performed by an experienced professional statistician (J.S.L.) using the “meta” package in R software version 4.0.2 (R Foundation for Statistical Computing).

### Results

In total, 885 articles were initially identified by a systematic search. After a full-text review of 75 articles, 32 studies with 39,060 children were ultimately included (see the flow diagram in Fig. 1) [7–22, 24, 34, 36–49].

#### Characteristics of included studies and quality assessment

The study and patient characteristics are described in Table 1. In brief, 12 studies were retrospective, and one study was prospective in design. The number of patients ranged from 18 to 15,043, with mean or median ages of 3.4 to 14.1 years. The diagnosis of GHD was based on two pharmacologic stimulation tests in most studies (supplementary material 1).

Regarding peak GH levels of pharmacologic stimulation tests, 17 studies defined GHD when the peak GH was  $< 10$   $\mu\text{g/l}$ . In 6 studies, cutoffs for the peak GH level were  $\leq 5$   $\mu\text{g/l}$  [12, 16, 22, 39, 40, 44]. Twenty-four studies included both IGHD and MPHID patients. Two studies [8, 14] and one study [40] included only IGHD and only MPHID patients, respectively.

The imaging methods are described in Table 2. MR imaging was conducted by either 0.5T, 1T, 1.5T, or 3T magnets. In studies that reported imaging slice thickness, most studies used slice thicknesses of  $\leq 3$  mm, except for a few studies [15, 17]. In studies with available FOV data, varying FOVs were used from 11 to 23 cm. In 16 studies, contrast-enhanced MRI scans were performed. In 13 studies, use of contrast-enhanced MRI scans could not be assessed due to a lack of information. Imaging criteria for each sellar abnormality are provided in supplementary material 2.

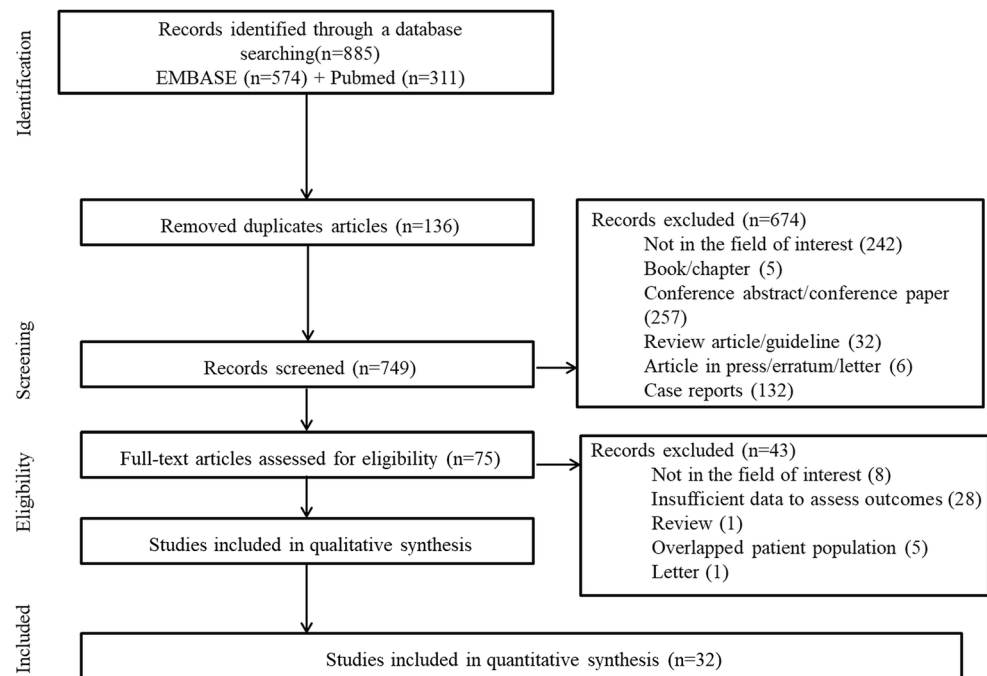
The quality of the included studies was generally acceptable, but the risk of bias caused by incomplete outcome data was relatively high (31.3%) (supplementary material 3). This is because there were studies with a relatively large proportion ( $> 20\%$ ) of GHD patients who did not undergo MRI. In the two domains of blinding of outcome assessment and outcome evaluation, the proportion of unclear risk of bias was high (59.4% and 34.4%, respectively). The reasons for unclear risk of bias were that the report did not specify whether blinding was performed regarding clinical information for MRI reviewers or the report did not specify the criteria for abnormal sellar and parasellar MRI findings, respectively.

#### Sellar and parasellar abnormalities

The proportion of sellar and parasellar abnormalities was acquired in 32 studies, composed of 17,540 patients, and ranged from 8.3 to 100% [7–22, 24, 34, 36–49]. The pooled proportion of sellar and parasellar abnormalities was 58.0% (95% CI, 47.1–68.6%) (Fig. 2). Significant heterogeneity was noted in the  $Q$  test ( $P < 0.001$ ) and Higgins  $I^2$  (98.2%). No publication bias existed ( $P = 0.94$  by Begg’s test), which was illustrated in the funnel plot analysis (supplementary material 4). The pooled estimates of each sellar and parasellar abnormality are summarized in Table 3. The most common type of abnormality was PSIS (34.5%; 95% CI, 20.8–49.6%). The etiologies of sellar and parasellar mass were hypothalamic hamartoma, arachnoid cyst, pituitary cyst, and Rathke cyst [24, 48].

#### Midline brain anomaly and CNS abnormalities outside the pituitary area

The proportion of midline brain anomalies was assessed in 29 studies, composed of 16,947 patients, and ranged from 0 to 45.7%. The pooled proportion of midline brain anomalies was 1.1% (95% CI, 0.1–3.0%) (Fig. 3). Significant heterogeneity was noted in the  $Q$  test ( $P < 0.001$ ) and Higgins  $I^2$  (89.3%).

**Fig. 1** Flow diagram of study selection

Publication bias was detected by Begg's funnel plot analysis ( $P = 0.037$ ) (supplementary material 5a). The adjusted pooled proportion of midline brain anomalies was 2.6% (95% CI, 0.9–5.1%) after applying a trim-and-fill method (supplementary material 5b). The etiologies of midline brain anomalies were hypoplasia of the optic nerve or optic chiasm, septo-optic dysplasia, corpus callosum dysgenesis, abnormality of the septum pellucidum, solitary central maxillary incisor syndrome, midline palate cleft syndrome, GHD with anophthalmia, nasal pyriform aperture stenosis, medially deviated carotid artery, complex anomaly of the hypothalamo-hypophyseal tract, sphenoidal meningocele, vermian agenesis, and craniopharyngeal canal in ten studies [11, 13, 17, 20, 24, 36, 44, 46, 48, 49]. The pooled proportion of CNS abnormalities outside the pituitary area was 0.4% (95% CI, 0.0–1.2%) (supplementary material 6a). Significant heterogeneity was noted in the  $Q$  test ( $P < 0.001$ ) and Higgins  $I^2$  (82.1%). Publication bias existed based on Begg's funnel plot analysis ( $P = 0.024$ ) (supplementary material 6b), and the adjusted pooled proportion of CNS abnormalities outside the pituitary area was 1.2% (95% CI, 0.4–2.3%) after applying the trim-and-fill method.

### Subgroup analysis

The results of subgroup analyses by type of GHD, geographical region, MRI magnet, and cutoff serum GH level for the diagnosis of GHD are summarized in Tables 4 and 5 and supplementary material 7–10. Patients with MPHHD showed a higher proportion of sellar and parasellar abnormalities than those with IGHD (91.4% vs. 40.1%,  $P < 0.001$ ). In the analysis

of specific sellar and parasellar abnormalities, the pooled proportion of PSIS was higher in patients with MPHHD than in those with IGHD (65.3% vs. 20.1%,  $P < 0.001$ ). The type of GHD did not influence heterogeneity in other specific sellar and parasellar abnormalities or midline brain anomalies ( $P \geq 0.103$ ). Geographical region, MRI magnet, and cutoff GH level for the diagnosis of GHD were not significant factors of heterogeneity regarding sellar and parasellar abnormalities ( $P = 0.668, 0.228, \text{ and } 0.101$ , respectively). When sellar abnormalities were divided into two groups by severity (isolated anterior PH vs. severe MR abnormalities [isolated EPP or PSIS or any two out of the three abnormalities of anterior pituitary hypoplasia, stalk abnormality, and EPP]), the pooled proportion of severe MR abnormalities was significantly higher in patients with studies with cutoff GH values  $\leq 5 \mu\text{g/l}$  compared to those with a cutoff value of GH = 10  $\mu\text{g/l}$  for provocation tests (72.8% vs. 38.0%;  $P < 0.001$ ) (supplementary material 11).

### Discussion

In our systematic review and meta-analysis, the pooled proportion of sellar and parasellar abnormalities was 58.0% in children diagnosed with GHD, and significant heterogeneity was noted among the studies. Approximately 1.1% (2.6% after adjustment) of patients with GHD showed midline brain anomalies. Patients with MPHHD showed a higher proportion of sellar and parasellar abnormalities compared with those with IGHD (91.4% vs. 40.1%). In the analysis of each sellar and parasellar abnormality, the pooled proportion of PSIS was

**Table 1** Study and patient characteristics

Study (year of publication)	Institution	Country	Study period	Study design	Patients (n)	Age (years), mean (SD)*/median (range) <sup>†</sup>	Male:female (n)	IGHD:MPHD (n)
Abrahams JJ et al. (1991) [7]	Yale University School of Medicine	USA	NA	NA	35	NA (0–15) <sup>†</sup>	26:9	15:20
Arends NJ et al. (2002) [36]	Sophia Children's Hospital/Erasmus University	Netherlands	NA	Retrospective	39	8.3 (3.5) for IGHD, 5.3 (3.4) for MHPD*	24:15	24:15
Argyropoulou M et al. (1992) [37]	Hospital des Enfants Malades	France	NA	NA	46	9 (1)*	29:17	20:26
Ariza Jimenez AB et al. (2020) [8]	Hospital Materno-Infantil	Spain	2002–2016	Retrospective	96	NA (0–14) <sup>†</sup>	66:30	96:0
Bordallo MAN et al. (2004) [38]	Pedro Ernesto University Hospital	Brazil	1996–2003	Retrospective	37	NA	NA	10:27
Bressani N et al. (1990) [9]	University of Milan	Italy	NA	NA	57	10 (3.7)*	41:16	36:21
Duttia P et al. (2010) [10]	Postgraduate Institute of Medical Education & Research, Chandigarh	India	NA	NA	31	10.5 (4.2)*	23:8	8:23
Hamilton J et al. (1998) [11]	Hospital for Sick Children	Canada	1993–1996	NA	35	NA (2–17) <sup>†</sup>	27:8	20:15
Hanew K et al. (2006) [12]	Multicenter study	Japan	1986–1998	NA	44	8.7 (0.4)* for severe cases	NA	12:32
Kalina MA et al. (2012) [13]	Medical University of Silesia	Poland	NA	NA	85	14.1 (7.3–18.7) <sup>†</sup>	59:29	76:9
Kara O et al. (2018) [14]	Ankara Child Disease Hematology Oncology Training and Research Hospital	Turkey	2009–2012	Retrospective	183	10.01 (3.25)*	78:105	183:0
Kemp SF et al. (2002) [39]	Multicenter study (National Cooperative Growth Study Substudy 8)	USA	1996–2000	Prospective	21,738 (482 with GHD who underwent MRI)	8.6 (NA)*	NA	NA
Li G et al. (2010) [40]	Shandong Provincial Hospital	China	1999–2008	NA	125	13.24 (4.62)*	63:13	0:125
Liotta A et al. (1999) [15]	University of Palermo	Italy	NA	NA	24	6.22 (4.21)*	16:8	15:9
Longui CA et al. (2004) [41]	Santa Casa de S Paulo	Brazil	NA	NA	31	10.6 (2.9) in the normal group, 10.2 (4.0) in the MR abnormality group*	23:8	18:13
Maghnie M et al. (2013) [24]	Multicenter	NA	1987–2011	NA	15,043	NA	NA	NA
Maghnie M et al. (1999) [42]	IRCCS Policlinico S. Matteo di Pavia	Italy	NA	NA	35	9.0 (2.5)*	23:12	23:12
Mészáros F et al. (2000) [16]	University of Vienna, District Hospital Sahy	Austria and Slovakia	NA	NA	37	7.8 (4.6)*	10:27	17:20
Naderi F et al. (2015) [43]	Bahrami Pediatrics Hospital	Iran	2010–2011	Retrospective	40	8.01 (3.34)*	21:19	NA
Nagel BHP et al. (1997) [17]	University of Tubingen	Germany	NA	NA	56	10 (1.2) for MPHD, 9.5 (3.8) for severe IGHD, 7.3 (3.8) for partial IGHD*	NA	43:13
Otto AP et al. (2015) [44]	Hospital das Clinicas	Brazil	1979–2013	Retrospective	83	8.7 (4.1)*	44:39	44:39



**Table 1** (continued)

Study (year of publication)	Institution	Country	Study period	Study design	Patients (n)	Age (years), mean (SD)*; median (range)†	Male:female (n)	IGHD:MPHD (n)
Pampanini V et al. (2015) [45]	Tor Vergata University Hospital and Bambino Gesù Children's Hospital	Italy	1998–2012	Retrospective	68	3.37 (0.29)*	43:25	42:37 (developed MPHD)
Pinto G et al. (1999) [46]	Necker-Enfants Malades hospital	Paris	NA	NA	48	4.8 (0.7)*	26:22	NA
Secco A et al. (2009) [18]	University of Genova	Italy	NA	NA	40	4.2 (IQR:3.5–5.0)	30:18	32:16
Stawerska R et al. (2007) [19]	Polish Mother's Memorial Hospital – Research Institute	Poland	NA	NA	47	11.05 (3.5)*	35:12	39:8
Tillmann V et al. (2000) [34]	Royal Manchester Children's Hospital	UK	NA	Retrospective	82	9.6 (5.1)*	NA	63:19
Tsai SL et al. (2012) [20]	Children's Hospital of Eastern Ontario Multicenter	Ireland	1998–2010	Retrospective	52	NA	NA	37:15
Van Iersel L et al. (2018) [47]	Ospedale Infantile Regina Margherita	Netherlands	2001–2011	Retrospective	456	NA (0.17–16.11)†	308:148	213:96
Vannelli S et al. (1993) [21]	Ospedale Infantile Regina Margherita	Italy	NA	Retrospective	18	NA (6.6–16.4)†	4:14	11:7
Walvoord EC et al. (2004) [48]	Riley Hospital for Children	USA	1990–2000	Retrospective	236	9.0 (4.5)*	177:59	NA
Zenaty D et al. (2003) [49]	Robert DebrHospital	France	NA	NA	69	4.1 (2.6)*	50:19	44:25
Zimmermann A et al. (2007) [22]	Ruprecht-Karls University Heidelberg	Germany	1984–2004	NA	44	9.7 (4.1)*	34:10	27:17

IGHD, isolated growth hormone deficiency; MPHD, multiple pituitary hormone deficiency; NA, not available

**Table 2** Technical MRI features of included studies

Study (year of publication)	MR imaging magnet	FOV	Slice thickness	Matrix size	Contrast enhancement
Abrahams JJ et al. (1991)	1.5T	NA	NA	NA	CE
Arends NJ et al. (2002)	0.5T	18 cm	3 mm	205 × 256	NE
Argyropoulou M et al. (1992)	0.5T	25 cm	3 mm	256 × 256 or 256 × 192	M
Ariza Jimenez AB et al. (2020)	3T	NA	NA	NA	CE
Bordallo MAN et al. (2004)	1.5T	NA	2 mm	NA	CE
Bressani N et al. (1990)	1.5T	NA	3 mm	NA	NA
Dutta P et al. (2010)	1.5T	NA	2 mm	NA	NA
Hamilton J et al. (1998)	1.5T	NA	3 mm	NA	CE
Hanew K et al. (2006)	NA	NA	NA	NA	NA
Kalina MA et al. (2012)	1T	23 cm	3 mm	256 × 256	CE
Kara O et al. (2018)	1.5T	16–20 cm	2–3 mm	256 × 256	CE
Kemp SF et al. (2002)	NA	NA	NA	NA	NA
Li G et al. (2010)	1.5T	NA	3 mm	NA	M
Liotta A et al. (1999)	NA	NA	2 mm	NA	CE
Longui CA et al. (2004)	1T	NA	2 mm	NA	CE
Maghnie M et al. (2013)	NA	NA	NA	NA	NA
Mészáros F et al. (2000)	1.5T	23 cm	3 mm	256 × 256	NE
Naderi F et al. (2015)	1.5T	NA	2.5 mm	256 × 224	CE
Nagel BHP et al. (1997)	0.5–1.5T	NA	3–4 mm	NA	NE
Otto AP et al. (2015)	1.5T	NA	3 mm	NA	CE
Pampanini V et al. (2015)	1.5T	11 cm	0.75 mm	512 × 512	CE
Pinto G et al. (1999)	NA	NA	NA	NA	NA
Secco A et al. (2009)	NA	NA	2–3 mm	NA	NA
Stawerska R et al. (2007)	NA	NA	NA	NA	CE
Tillmann V et al. (2000)	0.5T	20 cm	1.75 mm	NA	NA
Tsai SL et al. (2012)	1.5T	NA	2 mm	256 × 192 to 512	CE
Van Iersel L et al. (2018)	NA	NA	NA	NA	NA
Vannelli S et al. (1993)	0.5T	NA	3 mm	NA	NA
Walvoord EC et al. (2004)	NA	NA	NA	NA	NA
Zenaty D et al. (2003)	0.5T	NA	NA	NA	NA
Zimmermann A et al. (2007)	0.5T	NA	2–2.5 mm	NA	CE
Maghnie M et al. (1999)	1.5T	20 cm	3 mm	256 × 256	NA

NA, not available; CE, contrast-enhanced MRI; NE, noncontrast-enhanced MRI; M, mixed population of CE and NE

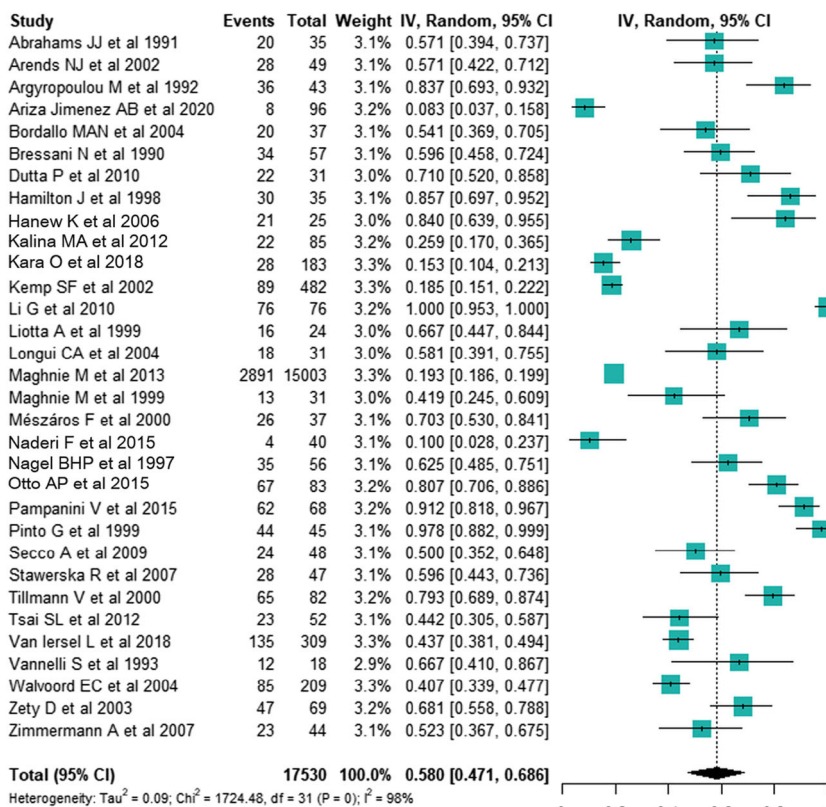
higher in patients with MPHD than in those with IGHD (65.3% vs. 20.1%). Other variables of geographical region, MRI magnet, and cutoff GH level for the diagnosis of GHD did not influence heterogeneity.

The consensus guideline published by the Growth Hormone Research Society recommended performing brain imaging for all children diagnosed with GHD [50]. Despite the increasing use of brain MRI for children with GHD, the real-world incidence of abnormal pituitary anatomy in this population is not well known due to variability in the diagnostic criteria, the lack of a united reference standard of pituitary size, and different opinions on the role of MRI in the diagnosis of GHD [51, 52]. To our knowledge, this is the first systematic review and meta-analysis to report the proportion

of sellar and parasellar abnormalities on MRI, and the pooled estimate was 58.0% in children with GHD.

Previous studies have identified a relationship between pituitary abnormality phenotype and endocrine profile in children with GHD; a patient with normal MRI findings or anterior pituitary hypoplasia is more likely to have IGHD, whereas PSIS is associated with MPHD [51]. In children with MPHD, normal pituitary anatomy is uncommon [51]. This study also confirmed via meta-analysis that the pooled proportion of sellar and parasellar abnormalities was as high as 91.4% in the MPHD group and was significantly higher than that in the IGHD group (40.1%). Moreover, we performed a meta-analysis to confirm the pituitary phenotype-endocrine profile correlation. The pooled estimate of PSIS incidence was

**Fig. 2** Forest plot of proportions for total sellar and parasellar abnormalities on brain MRI scans in patients diagnosed with growth hormone deficiency. The green box represents the point estimate, and its area represents the weight given to the study. A horizontal line indicates the 95% CI, and diamonds represent the overall pooled proportions



significantly higher in patients with MPPH (65.3%). In addition, patients with MPPH showed a higher proportion of EPP and complex sellar abnormalities (i.e., any two out of the three abnormalities of anterior pituitary hypoplasia, stalk abnormality, and EPP); conversely, patients with IGHD showed a higher proportion of IAPH, although the differences were of borderline significance ( $P=0.109, 0.103$ ).

The anterior and posterior pituitary, the hypothalamus, the optic nerves, and the forebrain have a common origin—the anterior neural plate—in the developing embryo [53]. Midline developmental anomalies are regarded as a spectrum disorder with variable clinical phenotypes from mild to severe forms [54]. In this study, various midline brain anomalies were identified in children with GHD and the pooled proportion was

**Table 3** Summary of the meta-analytic pooled proportions for sellar/parasellar abnormalities

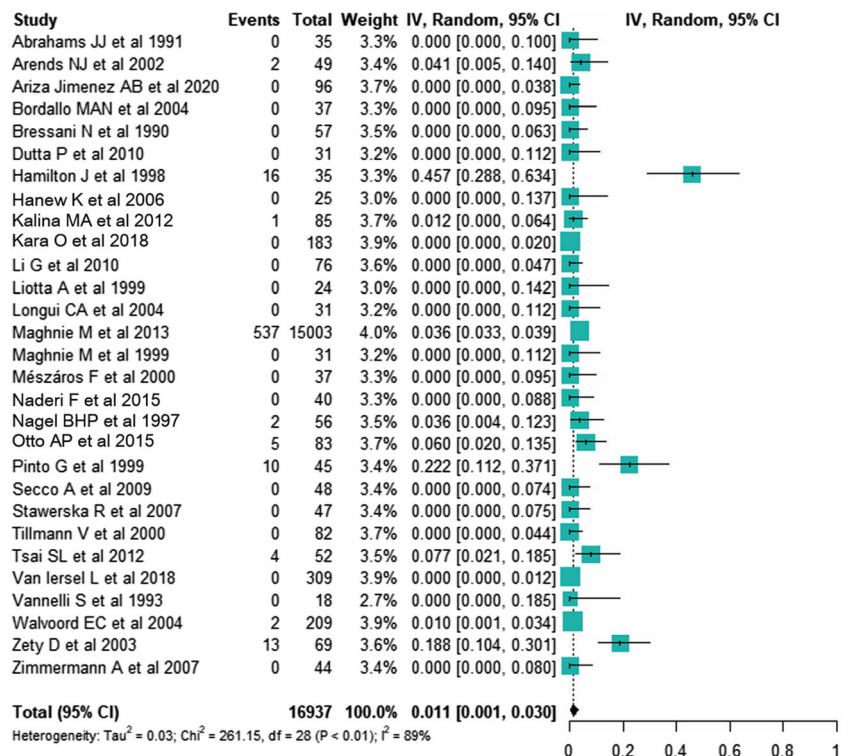
Outcome	No. of studies	Proportion (95% CI)	Quantifying heterogeneity	
			I <sup>2</sup> (95% CI)	P-value of heterogeneity test
Total sellar/parasellar abnormality	32	0.580 (0.471–0.686)	98.2% (97.9–98.5%)	<.0001
Type of sellar/parasellar abnormalities				
Isolated anterior pituitary hypoplasia	24	0.094 (0.051–0.148)	90.2% (86.7–92.7%)	<0.001
Empty sella	26	0.012 (0.000–0.039)	88.9% (85.0–91.8%)	<0.001
Isolated stalk abnormality	22	0.0005 (0.000–0.003)	32.1% (0.0–59.6%)	0.075
Isolated ectopic posterior pituitary	24	0.009 (0.000–0.031)	89.4% (85.5–92.2%)	<0.001
Any two out of three abnormalities <sup>a</sup>	22	0.037 (0.008–0.086)	95.1% (93.7–96.2%)	<0.001
PSIS <sup>b</sup>	21	0.345 (0.208–0.496)	97.9% (97.5–98.3%)	<0.001
Mass	31	0.001 (0.000–0.003)	56.6% (35.2–70.9%)	<0.001

<sup>a</sup> Any two out of the three abnormalities of anterior pituitary hypoplasia, stalk abnormality, and ectopic posterior pituitary

<sup>b</sup> PSIS, pituitary stalk interruption syndrome. PSIS was defined as a triad of thin or interrupted pituitary stalk, aplasia or hypoplasia of the anterior pituitary, and absent or ectopic posterior pituitary



**Fig. 3** Forest plot of proportions for midline brain anomalies on brain MRI scans in patients diagnosed with growth hormone deficiency. The green box represents the point estimate, and its area represents the weight given to the study. A horizontal line indicates the 95% CI, and diamonds represent the overall pooled proportions



1.1% (2.6% after adjustment). There was no significant difference in the pooled estimates between the IGHD and MPHD groups. This result might be limited because only a few included studies ( $n=10$ ) reported cases with concomitant midline brain anomalies and there might be a possibility of underestimation of the incidence. Although the prevalence seems rare, all radiologists and researchers involved in the diagnosis and management of children with GHD should have good knowledge of the association between the pituitary gland and other midline brain defects. The interpretation of brain MRI data should be performed by neuroimaging experts who are familiar with midline brain anomalies.

Previous studies have demonstrated conflicting results regarding the association between the severity of GHD and brain MRI abnormalities. According to Acharya et al. [55] and Frindik et al. [52], severe GHD with a low peak GH level on stimulation tests was more associated with pituitary abnormalities on MRI, compared to mild GHD. In contrast, a recent paper by Alba et al. demonstrated that the severity of GHD did not predict pituitary abnormalities, and they concluded that brain MRI should be performed in all children with GHD regardless of the severity of the deficiency [56]. In our subgroup analysis, the pooled proportion of sellar and parasellar abnormalities was not significantly different between subgroups defined by the cutoff GH level on stimulation tests. However, patients in studies with low peak GH levels on stimulation tests were more associated with severe MR abnormalities than those in studies with peak GH levels of 10  $\mu\text{g/l}$ . This result could be limited, because we categorized the

studies by a cutoff GH level of “10  $\mu\text{g/l}$ ” rather than using a constraint of “5 to 10  $\mu\text{g/l}$ ” due to insufficient data, and patients in the subgroup could have a wide range of peak GH levels on stimulation tests.

There are limitations in our study. First, the diagnostic criteria of abnormal MRI were variable among the included studies, and the prevalence of pituitary abnormalities in each study could be influenced by the different criteria. In most of the included studies, the diagnosis of pituitary hypoplasia was based on pituitary height. However, the diagnostic criteria used for pituitary hypoplasia were not consistent, evaluating height based on the normal population (below 2 standard deviations) or using an absolute value (e.g., 2 mm or 3 mm). Worldwide normative morphological data using artificial intelligence algorithms or volumetric measurements using three-dimensional MRI might improve the quality of pituitary assessment in future studies [57]. Second, gene defects are increasingly recognized as factors of abnormal pituitary development; however, we could not perform subgroup analysis due to insufficient data. Third, the diagnostic method of GHD by the GH stimulation test was not uniform in the included studies. Therefore, we conducted subgroup analysis according to the peak GH cutoff values.

In conclusion, this systematic review and meta-analysis demonstrated that sellar and parasellar abnormalities were common in children diagnosed with GHD. The patients with GHD rarely had concomitant midline brain anomalies. Patients with MPHD showed more frequent and more complex sellar and parasellar abnormalities than patients with IGHD. In addition,

**Table 4** Subgroup analyses of MIR findings by type of growth hormone deficiency (isolated growth hormone deficiency vs. multiple growth hormone deficiency)

Outcome	IGHD <sup>a</sup>			MPHD <sup>b</sup>			P-value by test for subgroup differences*
	Proportion (95% CI)	Quantifying heterogeneity		Proportion (95% CI)	Quantifying heterogeneity		
		I <sup>2</sup> (95% CI)	P-value of heterogeneity test		I <sup>2</sup> (95% CI)	P-value of heterogeneity test	
Total sellar/parasellar abnormality	0.401 (0.339–0.552)	91.0% (89.5–93.9%)	<0.001	0.914 (0.861–0.956)	77.8% (67.9–84.6%)	<0.001	<0.001
Isolated anterior pituitary hypoplasia	0.099 (0.039–0.183)	90.7% (87.0–93.3%)	<0.001	0.034 (0.004–0.093)	77.0% (63.9–85.3%)	<0.001	0.103
Empty sella	0.004 (0.000–0.016)	62.0% (39.8–76.1%)	<0.001	0.013 (0.000–0.064)	84.6% (77.5–89.5%)	<0.001	0.476
Isolated stalk abnormality	0.0008 (0.000–0.0043)	18.2% (0.0–51.7%)	0.224	0.0003 (0.000–0.0033)	0.0% (0.0–0.0%)	0.969	0.685
Isolated EPP <sup>c</sup>	0.009 (0.001–0.027)	65.0% (44.5–78.0%)	<0.001	0.017 (0.000–0.083)	81.6% (71.9–87.9%)	<0.001	0.652
Any two out of three abnormalities <sup>d</sup>	0.009 (0.000–0.029)	70.0% (50.8–81.7%)	<0.001	0.049 (0.004–0.138)	80.3% (67.9–88.0%)	<0.001	0.109
PSIS <sup>e</sup>	0.201 (0.084–0.352)	91.4% (87.4–94.1%)	<0.001	0.653 (0.476–0.811)	81.6% (70.7–88.4%)	<0.001	<0.001
Mass	0.0001 (0.000–0.0004)	0.0% (0.0–0.0%)	1.000	0.000 (0.000–0.000)	0.0% (0.0–0.0%)	1.000	1.000
Midline brain anomaly	0.005 (0.000–0.022)	69.2% (52.3–80.1%)	<0.001	0.005 (0.000–0.019)	46.2% (10.3–67.7%)	0.011	0.979

<sup>a</sup> IGH, isolated growth hormone deficiency<sup>b</sup> MPHD, multiple growth hormone deficiency<sup>c</sup> EPP, ectopic posterior pituitary<sup>d</sup> Any two out of the three abnormalities of anterior pituitary hypoplasia, stalk abnormality, and ectopic posterior pituitary<sup>e</sup> PSIS, pituitary stalk interruption syndrome

\*P values &lt; 0.05 were regarded as statistically relevant

**Table 5** Subgroup analyses of sellar and parasellar MR abnormalities by geographical region, MRI magnet, and cutoff serum growth hormone level for a diagnosis of growth hormone deficiency

Outcome	No. of studies	Proportion (95% CI)	Quantifying heterogeneity		P-value by test for subgroup differences*
			I <sup>2</sup> (95% CI)	P-value of heterogeneity test	
<b>Geographical region</b>					
Europe	20	0.578 (0.451–0.699)	95.8% (94.5–96.7%)	< 0.001	0.668
Asia	5	0.721 (0.034–1.000)	98.2% (97.0–98.9%)	< 0.001	
North America	4	0.481 (0.000–1.000)	97.9% (96.0–98.9%)	< 0.001	
South America	3	0.710 (0.000–1.000)	82.3% (25.3–95.8%)	0.018	
<b>MRI magnet</b>					
0.5T	6	0.687 (0.549–0.810)	72.2% (35.9–88.0%)	0.0029	0.228
1.5T	12	0.571 (0.387–0.745)	96.1% (94.5–97.2%)	< 0.001	
<b>Cutoff GH<sup>a</sup> level</b>					
Cutoff ≤ 5 µg/l	6	0.769 (0.434–0.977)	98.1% (97.2–98.7%)	<0.001	0.101
Cutoff = 10 µg/l	17	0.533 (0.386–0.677)	96.5% (95.5–97.4%)	<0.001	

\*P values < 0.05 were regarded as statistically relevant

<sup>a</sup> GH, growth hormone

this study confirmed a significant correlation between the frequency of severe MR abnormalities and low cutoff serum GH levels on stimulation tests in a large population of nonacquired GHD. The observed anatomic abnormality-endocrine profile correlation supports that brain MRI is essential to identify congenital structural abnormalities of the sellar and parasellar regions in children with nonacquired GHD.

**Abbreviations** GH, Growth hormone; GHD, Growth hormone deficiency; CNS, Central nervous system; IGHD, Isolated growth hormone deficiency; MPHD, Multiple pituitary hormone deficiency; IAPH, Isolated anterior pituitary hypoplasia; EPP, Isolated ectopic posterior pituitary; PSIS, Pituitary stalk interruption syndrome

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## Declarations

**Conflict of interest** We declare that we have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants performed by any of the authors.

**Informed consent** Statement of informed consent was not applicable since the manuscript does not contain any patient data

**Consent to participate** Statement of informed consent was not applicable since the manuscript does not contain any patient data

**Consent for publication** All of the authors gave consent for publication of the article.

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