CLINICAL STUDY

Magnetic resonance imaging of CNS in 15 043 children with GH deficiency in KIGS (Pfizer International Growth Database)

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Abstract

Objectives: Neuroimaging has become an essential part of the diagnostic process in children with GH deficiency (GHD). The aim of the study was to document the frequency of neuroanatomical abnormalities in a very large cohort of children with GHD and to relate these findings to patient clinical characteristics.

Design and methods: Results of magnetic resonance imaging (MRI) were reported in 15 043 of 43 725 children with non-acquired GHD (idiopathic, neurosecretory dysfunction (NSD) and known congenital cause) who were enrolled in KIGS (Pfizer International Growth Database) between 1987 and 2011. Clinical characteristics of patients before GH treatment with normal MRI (idiopathic GHD (IGHD) and NSD) were compared with those of patients with abnormal pituitaries (hypoplasia, empty sella (ES), HME (hypoplastic anterior pituitary, missing pituitary stalk and ectopic posterior pituitary)).

Results: Abnormal MRIs were found in 4032 (26.8%) children, within which ES ($n = 1178$ (7.8%)) and HME ($n = 1019$ (6.8%)) were the most frequent findings. In 2361 children diagnosed as IGHD or NSD before MRI examination, anatomical abnormalities ((pituitary hypoplasia: $n = 974$); (HME: $n = 459$)) were documented. Patients with anatomical abnormalities had more severe characteristics of GHD: normal MRI < pituitary hypoplasia < ES < HME.

Conclusions: GHD is associated with a great variety of neuroanatomical abnormalities as identified by MRI. The investigation and evaluation of MRI need to be conducted in a structured mode. There is an association between anatomical and functional abnormalities of the pituitary.

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Introduction

GH deficiency (GHD) in children is defined as a reduced secretion of GH in accordance with age- and gender-specific normative values, which is causal to an impairment of growth. GHD can be both congenital and acquired. In the case of acquired GHD, hypothalamic–pituitary structures are affected/destroyed and can be identified by neuroimaging. However, the causes of congenitally diminished GH secretion are very different and anatomical abnormalities in the pituitary region may or may not be present or identifiable.

In fact, the neuroimaging findings in GHD mainly include the following: first, normal or hypoplastic pituitary gland/empty sella (ES) without anatomical abnormalities of the hypothalamus or pituitary stalk and secondly, moderate-to-severe (pituitary height ≤ 3 mm) hypoplastic pituitary gland with ectopic posterior pituitary located anywhere from the median eminence to the distal stalk (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25). Isolated GHD is more commonly observed in the first

category while multiple pituitary hormone deficiencies (MPHD) occur more frequently in the second. An ES occurs in 10% of idiopathic GHD (IGHD) (12). MPHD may be associated with a variety of cerebral malformations such as Arnold-Chiari I and II, agenesis of the septum pellucidum, septo-optic dysplasia, vermis dysplasia, syringomyelia, absence of the internal carotid artery, dysgenesis of the corpus callosum, arachnoid cysts and tentorium anomalies with basilar impression (11, 20, 22, 25). The frequency of these radiological findings and their endocrine spectrum is variable. In particular, MPHD is more frequently associated with ectopic posterior pituitary and anterior pituitary hypoplasia than isolated GHD (2, 3, 5, 13, 14, 15, 17, 18, 20, 21, 22, 23, 24, 25). The variability between different studies can be ascribed to the degree of restriction in the studies' diagnostic criteria, to the diagnostic limits of GHD itself (transitory deficits, recovery, false positives, etc.) and/or to the lack of a convincing standard for a normal size of the pituitary gland among the pre-pubertal paediatric population. Idiopathic MPHD, except for a few genetic conditions of

hypopituitarism (25), has been reported less frequently in association with anterior pituitary hypoplasia and normal posterior pituitary and pituitary stalk.

When KIGS (Pfizer International Growth Database) was established in 1987, many of the modern developments that nowadays are essential for the aetiological definition of GHD, such as molecular genetics and neuroimaging by means of magnetic resonance imaging (MRI), were not available. Today, an MRI of the CNS is considered a well-recognized diagnostic procedure in every child with proven impaired GH secretion. MRI is not invasive, the methodology is standardized and the inconvenience caused to the patient is continuously being reduced by shortening the time of imaging with modern scanning equipment. Nevertheless, MRI is expensive and often requires sedation of the child. Furthermore, the evaluation of findings in the CNS is challenging as it requires highly specialized expertise and thus often does not provide the desired high-quality representation of all anatomical details. In addition, some existing structural findings may remain difficult to verify due to technical limitations (e.g. resolution and impaired quality of images caused by patient movement) and developmental changes (e.g. size of pituitary gland). Moreover, structural lesions identified in MRI may not be reflected by pituitary function, i.e. hormonal abnormalities. All these aspects need to be considered when evaluating the results of CNS MRIs reported within KIGS. The aim of this first analysis of MRIs in KIGS patients is to document the frequency of neuroanatomical abnormalities as reported in daily clinical practice and to relate these findings to patient clinical characteristics.

Materials and methods

Patient data were retrieved from the KIGS database (26). KIGS was established in 1987 as a worldwide observational registry to monitor outcomes and safety of Genotropin (somatropin, Pfizer, Inc., Strängnäs, Sweden) treatment in children with short stature. KIGS is conducted in accordance with the Declaration of Helsinki (27).

All patients observed in KIGS are classified according to the primary cause of short stature (primary diagnosis) as standardized in the KIGS Aetiology Classification List (28). Patients with non-acquired GHD, classified as 'IGHD' (KIGS codes 1.1), 'neuro-secretory dysfunction (NSD)' (KIGS code 1.2) or 'GHD of known and congenital origin' (KIGS codes 2.1.ff), were included in this analysis (Fig. 1). The latter category included aetiologies such as genetic causes of GHD, central malformations, complex syndromes with congenital GHD, prenatal infections, bio-inactive GH syndrome and functional GHD.

Additionally, MRI reported in patients with short stature but normal GH secretion was reviewed. Those

Figure 1 Flow chart showing the distribution of patients analysed.

patients were diagnosed by KIGS investigators as idiopathic short stature (ISS) (KIGS codes 3.1.ff) and small for gestational age (SGA) (KIGS code 3.4.ff, 3.5.ff). Results of MRI investigations reported until January 2011 were analysed. All diagnostic procedures were performed at KIGS centres in accordance with local clinical practice. The final diagnoses, as reported to KIGS, were established by a local KIGS investigator. The extent of pituitary deficits was established and reported by the investigators without giving details of methodology of testing.

No specific study requirements governing either MRI techniques or radiological interpretation were provided by the KIGS guidelines. In other words, MRIs reported in KIGS were performed according to the clinical standards at each KIGS centre. More than 85% of MRIs were performed before starting GH treatment.

The MRI findings, as reported in KIGS, were subsequently reviewed by one author (M B Ranke) and verified (based on) or (with reference to) reported primary diagnosis (KIGS code). In the case of discrepancy, a relevant KIGS code was applied where possible or anatomical diagnosis was assigned based on the reported MRI finding.

The MRI findings included i) normal or hypoplastic pituitary gland without anatomical abnormalities of the hypothalamus or pituitary stalk and ii) moderate-to-severe (vertical height ≤ 3 mm) hypoplastic pituitary gland with ectopic posterior pituitary located anywhere from the median eminence to the distal stalk (25).

In order to investigate whether groups of patients with typical MRI findings were distinguished by auxological or biochemical characteristics, an analysis of the characteristics was carried out according to the principles common for KIGS data (29). The data analysis was descriptive. Group comparisons were undertaken by Student's *t*-test when applicable, accepting differences at the 1% level as significant. Additionally, characteristics of patients with various diagnostic

Table 1 Reclassification of children with presumed congenital GHD within KIGS.

Diagnosis	Patients with or without MRI Frequency (n; %)	Patients after MRI review Frequency (n; %)	Patients reported as IGHD or NSD reclassified according to MRI results Frequency (n; %)
Idiopathic GHD (classical form; IGHD)	37.792 (86.4)	10.378 (68.9)	—
Neurosecretory dysfunction (NSD)	2.100 (4.8)	593 (3.9)	—
GHD of known and congenital origin	3.833 (8.8)	4.032 (26.8)	2.338 (99.0)
Total	43.725 (100)	15.043 (100.0) ^a	2.361 (100) ^a
GHD of known and congenital origin			
Central malformations (not restricted to the pituitary area)			
Septo-optic dysplasia	776 (1.8)	363 (2.4)	1
Missing (hypoplastic) corpus callosum	—	22	6
Abnormality of septum pellucidum	—	4	1
Solitary central maxillary incisor syndrome	27	2	—
Midline palate cleft syndrome	117	22	1
GHD with anophthalmia	—	1	—
Other (not specified)	515 (1.2)	123 (0.8)	48
Total	1.435 (3.3)	537 (3.6)	57 (2.4)
Complex syndromes with GHD			
Fanconi pancytopenia	34	4	—
Rieger syndrome	1	1	—
Ectrodactyly-ectodermal dysplasia-clefting (EEC)	5	—	—
Others (not specified)	104	14	—
Total	144	19	—
Abnormalities within/near the pituitary area			
Empty sella ^b	805 (1.8)	449 (3.0)	96
Partial empty sella	—	73	41
Pituitary hypoplasia	—	1.178 (7.8)	974
HME ^c	268 (0.6)	1.019 (6.8)	459
Pituitary – non-functioning – microadenoma	—	76	73
Thickening of pituitary stalk	—	9	7
Duplication of pituitary	—	1	1
Abnormal pituitary infundibulum	—	6	4
Arachnoid cyst	74	82	40
Hypothalamic hamartoma	—	7	5
Cyst in anterior pituitary	—	9	9
Cyst in pars intermedia	—	11	10
Rathke cyst	—	31	25
Other cyst/benign structure in/near pituitary	—	17	13
Total	1.147 (2.6)	2.968 (19.7)	1.757 (74.4)
CNS abnormalities outside the pituitary area			
Congenital hydrocephalus	90	33	12
Chiari I malformation	—	59	42
Other Chiari malformation	—	2	2
Dandy–Walker malformation	—	3	2
Leucomalacia	—	11	10
Syringomyelia	—	3	3
Pachygyria	—	1	—
Pineal cyst	—	36	34
Cavum septi pellucidi	—	5	1
Cyst other part brain (not arachnoidea)	—	15	12
Cyst outside brain's structures	—	5	5
Vessel anomalies in cerebrum	—	10	8
Other brain structure anomalies (not specified)	—	95	77
Total	90 (0.2)	278 (1.8)	208 (8.8)
Prenatal infections, bio-inactive GH, functional GHD, genetic causes of GHD, malformations outside neurocranium	1.017	230	21
Other acquired GHD and short stature		40 ^a	23 ^a
Total	1.017 (2.3)	270 (1.8)	44 (1.9)
Total	43.725 (100)	15.043 (100.0)	2.361 (100)

^aThese patients were reclassified as acquired GHD or other short stature according to the KIGS Classification List.^bEmpty sella (including pituitary aplasia; pituitary aplasia is well-defined life-threatening condition of neonatal onset).^cHypoplastic anterior pituitary, missing stalk and ectopic posterior pituitary.

groups were tested with ANOVA and *post hoc* testing, as applicable.

Results

Patients with presumed congenital GHD, as classified by the KIGS Aetiology Classification System (28), are presented in Table 1. Of the 43 725 children with KIGS codes 1.1, 1.2 and 2.1.ff, 37 792 (86.4%) were diagnosed by the KIGS investigators as 'IGHD', 2100 (4.8%) as having GHD associated with NSD and 3833 (8.8%) as having known and congenital GHD resulting from different causes. The performance of MRI was not taken into consideration in this classification.

MRI investigations were performed in 15 043 children, of which 12 434 (82.66%) were diagnosed as IGHD, 662 (4.40%) as NSD and 1947 (12.94%) as GHD due to known and congenital causes. When the reported MRI findings were considered, the number of patients with IGHD reduced to 10 378 (68.89%), the number of NSD reduced to 593 (3.94%), while the number of children with anatomical anomalies in the MRI increased to 4032 (26.80%). In many instances, the KIGS Aetiology Classification System did not include a specific code for the respective anatomical abnormality. In particular, there was no specific code for hypoplasia of the pituitary (HP) with no other structural anomaly of the brain, although this was the largest single reported anomaly within the group of known disorders ($n=1.178$; (7.83%)). There was, however, a great variety of findings indicating abnormalities both within and outside the hypothalamic-pituitary region. MRI abnormalities were observed in 2361 children primarily classified as IGHD or NSD. Of these children, the most frequent MRI findings were pituitary hypoplasia ($n=974$) and HME ($n=459$). The analysis of MRI findings in patients classified as ISS and SGA for a total of 1844 patients showed that 151 subjects (8.2%) displayed abnormalities that were restricted to the pituitary area, with pituitary hypoplasia ($n=86$) and HME ($n=20$) being the most common ones.

The background and clinical characteristics of patient groups, stratified by major aetiological classifications as based on the results of MRIs performed before and at the start of GH treatment, are presented in Table 2. The groups analysed were as follows: i) IGHD (code 1.1) without pathological images; ii) NSD (code 1.2) without pathological images; iii) HP (no KIGS code available); iv) ES (code 2.1.2.2); and v) HME (code 2.1.2.7). In comparison with IGHD and NSD, patients with ES and HME had more severe GHD, showed a higher frequency of MPHD, had a lesser reduction of birth weight, were more often born in breech position, had less short parents and were younger and shorter at the start of GH treatment. Patients with HP demonstrated characteristics that were in-between those of the patients with IGHD and NSD and the patients with ES and HME. The gender distribution was the same in all groups.

Table 2 Characteristics of patients with various diagnoses based on MRI findings before and at the start of GH.

Diagnosis KIGS code	NSD normal MRI (A) 1.2 Median (10/90. Perc)	IGHD normal MRI (B) 1.1 Median (10/90. Perc)	Pituitary hypoplasia (C) 2.1.2.8 Median (10/90. Perc)	Empty sella (D) 2.1.2.2 Median (10/90. Perc)	HME (E) 2.1.2.7 Median (10/90. Perc)	No differences between groups (A-E) $P>0.01$
Parameter (n)	593	10 378	1 178	449	1 018	
Sex male (%)	66.7	67.9	67.3	65.5	69.1	All
Birth weight (SDS)	-0.84 (-2.22/0.52)	-0.69 (-2.15/0.78)	-0.54 (-2.11/0.95)	-0.39 (-1.99/1.18)	-0.39 (-1.82/1.08)	CD, DE
Birth by breech (%)	0.8	2.2	4.2	3.8	7.5	CD
maxGH ($\mu\text{g/l}$)	13.8 (7.9/30.2)	6.6 (2.2/10.7)	4.9 (0.6/10.9)	3.1 (0.3/9.0)	3.1 (0.5/9.3)	BC, DE
MPHD (%)	11.8	11.1	25.0	52.1	49.8	AB, DE
At GH start						
Age (years)	10.9 (5.7/14.4)	11.0 (5.0/14.7)	9.7 (3.5/15.1)	8.2 (1.2/14.7)	6.2 (1.4/14.1)	AB
Height (SDS)	-2.72 (-3.80/-1.83)	-2.70 (-3.97/-1.64)	-3.16 (-5.04/-1.86)	-3.13 (-5.40/-1.50)	-3.26 (-4.98/-1.38)	AB, CD, DE
Ht - MPH (SDS)	-1.72 (3.29/-0.12)	-1.55 (-3.25/-0.08)	-2.12 (-4.49/-0.44)	-2.34 (-4.67/-0.43)	-2.71 (-4.46/-0.65)	AB, CD

The groups with no differences in patient characteristics are presented in Table 2. Interestingly, comparisons between patients with HP and ES showed no differences in birth weight SDS, proportion of birth by breech, height SDS at GH start and distance to midparental height SDS.

Discussion

We aimed to define the neuroimaging phenotype in a very large database of GHD children. In addition, we sought to identify indications for pituitary imaging and the prevalence of hypothalamic–pituitary and CNS abnormalities associated with hypopituitarism.

Notably, different aetiologies are diagnosed by MRI parameters alone or by a combination of endocrine values and neuroimaging (25, 28); in particular, some specific abnormalities, such as posterior pituitary ectopia and pituitary stalk agenesis, associated with IGHD are identified by imaging of hypothalamic–pituitary anatomy. Indeed, the first report about the latter MRI findings in children with GHD was published in 1987 (1), and since then, MRI has become a standard diagnostic technique used to identify anatomical causes of GHD, which was previously diagnosed by anthropometrical and biochemical methods alone (20, 22, 25).

Ideally, the best scanning techniques to obtain an optimal amount of information are those that provide 2–3 mm thick, high-resolution T1- and T2-weighted MRI images (Fig. 2) in the coronal and sagittal planes (22, 30, 31). Coronal scans allow for the visualization of the pituitary gland, stalk, chiasm and parasellar regions while sagittal images are best suited for the evaluation of the midline plane. Recently, high-resolution, heavily T2-weighted sagittal images/T2-DRIVE (25), or fast imaging employing steady state acquisition sequence obtained at sub-millimetre thickness, provide an

excellent visualization of the suprasellar region and are especially suited to the assessment of the pituitary stalk without using contrast medium. Axial T2-weighted fluid attenuation inversion recovery images covering the entire brain are recommended in order to screen for additional abnormalities (25). The main limitation of our study is related to a lack of MRI standardization as there are neither KIGS guidelines regarding the way MRIs are performed (e.g. technical requirements, timing of examination and patient selection) nor how they are evaluated and classified. However, we believe that as our study is based on a very large patient cohort, this limitation is outweighed.

As shown by the KIGS database, MRI appeared to be largely used as a diagnostic tool for screening pituitary abnormalities in children with GHD by paediatric endocrinologists in daily clinical practice. From this, 73.2% of patients were identified as having a normal pituitary gland, 7.8% as having pituitary hypoplasia, 3.0% as having ES and 6.8% as having HME. It is worth noting, on the one hand, that it is not known within KIGS how ‘hypoplasia’ of the pituitary was defined in each patient and, on the other, that there are particular difficulties in measuring and establishing the size of the anterior pituitary, which varies with age, sex, pubertal status and shape (7, 8, 22, 25, 32). As ES represents an ‘epiphenomenon’ of pituitary hypoplasia (3), the latter finding appears very likely to be the most common MRI abnormality in GHD in our study.

Overall, the prevalence of pituitary abnormalities in the paediatric population undergoing neuroimaging for reasons other than pituitary disease is lacking and data are not available on pituitary incidentalomas (33). Indeed, previous studies have reported the prevalence of ES to be about 5–9% for all ages, with an increase in prevalence with age (34, 35). Most frequently, this anomaly is an incidental finding of little or no clinical

Figure 2 Normal sellar region. (A) Sagittal T1-weighted image. The posterior pituitary lobe (PPL), physiologically bright on T1-weighted image, anterior pituitary lobe (APL), pituitary stalk (PS), median eminence (ME), optic chiasm (OC), tuber cinereum (TC), and mammillary bodies (MB) are clearly visible. (B) Anterior pituitary hypoplasia. Small anterior pituitary lobe housed within a small pituitary fossa (arrow). Normal posterior lobe (arrowhead) and pituitary stalk (double arrowheads). (C) Hypoplastic anterior lobe (arrow). Small and ectopic posterior lobe, located at the level of the median eminence (arrowhead). The pituitary stalk is not visible (double arrowheads).

importance, the only exception being pseudotumour cerebri in which clinical symptoms and additional MRI findings may confirm the diagnosis (36). Additionally, the large study published by Jordan *et al.* (37) identified 63 (6.6%) children with 68 incidental intracranial MRI findings in the total cohort of 953 children with sickle cell anaemia screened with MRI of the brain for the Silent Infarct Transfusion Trial. Among the children with abnormalities was one child in whom intrasellar Rathke cleft cyst was detected and no other abnormalities of hypothalamus/pituitary region.

Indeed, among our 1844 patients with ISS and SGA, 151 displayed pituitary abnormalities, and pituitary hypoplasia was the most common. Surprisingly, HME was documented in 20 of them and equally distributed between ISS and SGA patients. This raises the question about the misclassification bias based on GH response to stimulation tests where false-negative results have been recently reported in patients with structural hypothalamic–pituitary abnormalities (38).

Due to the small size of the pituitary structures and in the absence of systematic use of contrast medium enhancement (13, 25), it may not always be possible to obtain a complete image of the pituitary stalk, particularly at the given resolution of the images and even in the presence of small moving artefacts. Thus, the diagnoses of ES and HME are not always absolutely certain. This observation is strengthened by the fact that the frequency of MPHD among patients with ES was not dissimilar to that of patients with HME. Certainly, ectopic posterior pituitary and pituitary stalk agenesis are more commonly associated with severe pituitary hormone defects compared with those with either pituitary hypoplasia or ES who had a more preserved hypothalamic–pituitary region and function (3, 12, 13, 14, 17, 18, 22). In addition, the higher frequency of breech presentation in patients with HME is in line with what has been previously reported in the presence of structural hypothalamic–pituitary abnormalities (1, 3, 10, 11).

There is no doubt that MRI investigations play a major role in the diagnostic process of GHD. However, anatomical and functional findings *a priori* do not always mirror each other. Biochemical investigations to define partial pituitary deficits are probably even less standardized than MRI. Consequently, there is a constant debate about which investigations, be they anthropometrical, biochemical, imaging or genetic, are required to firmly establish the diagnosis of GHD, particularly permanent GHD, in childhood and adolescence (39). Although genetic analyses may in the future help define an aetiological diagnosis when anatomical abnormalities in the CNS are observed (40, 41, 42), it is probably the case that all investigations complement each other and need to be done in a standardized manner according to the best available techniques and with the greatest possible expertise.

Declaration of interest

M Maghnie has no conflict of interest to declare. M-K Häggström and A Lindberg are full-time employees of Pfizer Health AB. M B Ranke is a member of the International KIGS Board and received lecture fees from Pfizer, Eli Lilly, Novo Nordisk and Ipsen.

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