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Neuroimaging findings and severity of hypopituitarism in a cohort of 78 children

Abstract

Objectives: To evaluate neuroimaging abnormalities in children with hypopituitarism and correlate with the number of pituitary hormone deficiencies, age at diagnosis, severity of growth hormone deficiency and response in the first year of treatment with recombinant human growth hormone.

Material and methods: It was a cross-sectional descriptive study. Children with hypopituitarism followed at a pediatric university hospital over a 10-year period were included. All neuroimaging were reviewed by the researcher and classified as: normal, with hypoplastic adenohypophysis, absent pituitary stalk, ectopic neurohypophysis or empty sella. The Fisher-exact and the Mann-Whitney tests were applied for categorical and numerical data, respectively. The distribution of numerical variables was assessed by Shapiro-Wilks test. The significance level adopted was 5%.

Results: Seventy-eight patients aged between 0.5 and 17.82 years were included in the study. We found male predominance. Only 29.5% of patients had normal magnetic imaging resonance, with hypoplastic adenohypophysis being the most frequent abnormality. Half of the patients had neonatal complications history. The same proportion of isolated growth hormone deficiency and multiple pituitary hormones deficiencies were found. Severe growth hormone deficiency was found in 82% of patients with neuroimaging abnormalities. Appropriate response to therapy was observed in 76.6% of patients, being more prevalent in those with multiple pituitary hormones deficiencies.

Conclusions: The presence of neuroimaging abnormalities was related to multiple pituitary hormones deficiencies, severe growth hormone deficiency and neonatal abnormalities, without however having relation to early-onset of disease.

Keywords: magnetic resonance imaging, children, congenital abnormalities, hypoplastic adenohypophysis, growth hormone deficiency, treatment

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Introduction

Hypopituitarism is characterized by partial or total failure in pituitary hormones secretion. The causes and clinical presentation vary with age, and depends on the affected cell group, severity of hormone deficiency and disease onset velocity. Most children with hypopituitarism are diagnosed early in life by the presence of midline defects or neonatal problems such as hypoglycemia, prolonged jaundice, micropenis and cryptorchidism.[1]

Diagnosis is based on clinical, laboratory and radiological parameters. Magnetic resonance imaging (MRI) is the neuroimaging method of choice.[2] The most frequently findings in MRI of children with hypopituitarism are: hypoplastic adenohypophysis (HA), absent pituitary stalk (APS), ectopic neurohypophysis (EN) and empty sella (ES).[3]

Growth hormone deficiency (GHD) is the most common endocrine deficiency in these patients.[4,5] Growth hormone (GH) values seems to be related to pituitary size, however, no correlation between size and severity of pituitary disorders has been demonstrated yet.[6] Patients with GHD and MRI abnormalities differ from those with normal neuroimaging regarding anthropometrics parameters.[7]

The aim of this study was to evaluate neuroimaging abnormalities in children with hypopituitarism and correlate with the number of pituitary hormone deficiencies, age at diagnosis of GHD, severity of GHD and growth response in the first year of treatment with recombinant human growth hormone (rhGH).

Material and methods

It was a cross-sectional descriptive study. The medical records of all patients with hypopituitarism accompanied in a period of 10 years at Endocrinology Unit of Pediatrics Institute of Federal University of Rio de Janeiro, Brazil were reviewed. Seventy-eight children were selected. The following data were collected: date of birth, sex, weight and length at birth, type of delivery and presentation, gestational age and classification for gestational age, neonatal complications, consanguinity, family history of hypopituitarism, weight, height, age at diagnosis of each hormone deficiency, response to stimulation test and method used, associated diseases, medications in use and doses, latest laboratory results, growth velocity and height standard deviation score (SDS) immediately before and after one year of treatment with rhGH.

GHD was characterized by short stature [height <3rd percentile or -2SDS for age and sex] and decreased growth velocity (<10th percentile for age and sex), associated with GH peak in two stimulation tests <5ng/mL (Immunochemiluminometric assay). In case of neuroimaging abnormalities only one test was sufficient

for the diagnosis.[2,4] Severe GHD was characterized by GH peak in stimulation test <3ng/mL. The age at onset of GHD was considered early or late when initiated before or after 3 years old, respectively.[4]

Adrenocorticotropic deficiency (ACTH) was defined as cortisol peak after provocative test with insulin or glucagon <18ng/mL in the presence of hypoglycemia.[5,8]

Central hypothyroidism was defined by thyroid-stimulating hormone (TSH) normal or below and free thyroxine (fT4) below the reference value for age and sex.[5,9,10]

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) deficiencies were presumed in the absence of pubertal signs in girls and boys older than 13 and 14 years old respectively associated with prepubertal gonadotropin values.[5,11]

Antidiuretic hormone (ADH) deficiency was characterized by polyuria and polydipsia associated with plasma sodium >145mmol/L, serum osmolality >300mOsm/kg and urine osmolality <300mOsm/kg.[5]

We compared the growth velocity and height SDS just before and one year after the beginning of replacement therapy with rhGH. Appropriate response was seen in those who doubled growth velocity or increased at least one SDS.[2,5]

All MRI were reviewed by the researcher, blindly, and classified as: normal, with HA, APS, EN or ES.

Δ growth velocity was calculated by the formula: Δ growth velocity (%)=(growth velocity in the first year of therapy - pretreatment growth velocity) / pretreatment growth velocity X 100.

The response to treatment was compared to the five groups of radiological changes and with isolated GHD and multiple pituitary hormones deficiencies (MPHD).

The adenohypophysis size and number of pituitary hormones deficiencies were expressed as median and interquartile range (IQR) and compared using the Mann-Whitney test. The Fisher-Exact and Mann-Whitney tests were applied for categorical and numerical data, respectively. The distribution of numerical variables was assessed by Shapiro-Wilks test. The significance level adopted was 5%. Statistical analysis was performed with the statistical software SAS® System, version 6.11 (SAS Institute, Inc., Cary, North Carolina).

The study was approved by the Research Ethics Committee of institution.

Results

Ninety-two patients were eligible to participate in the study, 14 of which were excluded: one due to hypopituitarism of tumor origin (postoperative period for craniopharyngioma), 5 by association with dysmorphic features (1 Turner syndrome, 2 Cornelia de Lange syndrome and 2 Aarskog syndrome), 2 had responsive stimulus test, 4 did not perform imaging of the hypothalamus-pituitary region and 2 for loss to follow-up.

Seventy-eight children with hypopituitarism between 0.5 and 17.82 (6.64±4.93) years underwent the study. Forty-eight were prepubertal (Tanner stage I) at diagnosis.[5] We found male predominance, of 2.1 boys for every girl. Family history of hypopituitarism was seen in 3.8% (n=3) of patients and consanguinity in 2.6% (n=2). Breech delivery was observed in only 3.8% (n=3) of patients. The birth weight ranged from 1360-4800 (3081.54±634.63) grams and length of birth from 38.5-55 (48.15±3.09) centimeters.

Only 23 patients (29.5%) had normal MRI, while 55 (70.5%) showed abnormalities. HA was the most frequent abnormality seen in these patients (36/46.2%), followed by EN (25/32.1%), APS (23/29.5%) and ES (16/20.5%). The adenohypophysis size was similar in boys and girls, ranging from 2.0-6.82 (3.91±0.86) millimeters. Four patients had sept-optic-dysplasia associated with other hypothalamic-pituitary abnormalities.

Nearly half of the patients had neonatal complications (48.7%), including hypoglycemia (17/21.8%), jaundice (17/21.8%), cryptorchidism [10 of 53 (18.9%)], micropenis [7 of 53 (13.2%)], asphyxia (7/9%) and ambiguous genitalia (3/3.8%). Table 1 shows the relationship between neuroimaging abnormalities and neonatal complications.

Table 1 Neuroimaging abnormalities and neonatal complications

MRI findings		Present N (%)	Absent N (%)	*p value*
Normal	Yes	07 (18.4)	16 (40.0)	**0.036**
	No	31 (**81.6**)	24 (**60.0**)	
HA	Yes	19 (50.0)	17 (42.5)	0.51
	No	19 (50.0)	23 (57.5)	
APS	Yes	13 (34.2)	10 (25.0)	0.37
	No	25 (65.8)	30 (75.0)	
EN	Yes	15 (39.5)	10 (25.0)	0.17
	No	23 (60.5)	30 (75.0)	
ES	Yes	10 (26.3)	06 (15.0)	0.22
	No	28 (73.7)	34 (85.0)	
Pituitary size (mm)	Median IQR	3.47 (3.20-4.64)	3.94 (3.44-4.54)	0.29

MRI, magnetic resonance imaging; HA, hypoplastic adenohypophysis; APS, absent pituitary stalk; EN, ectopic neurohypophysis; ES, empty sella; mm, milimiters; IQR, Interquartile range (Q1 - Q3)

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The same proportion of isolated GHD and MPHD were found. GHD wasn't present in only one patient. TSH was the most prevalent deficiency apart from GHD, followed by ACTH, FSH, LH and ADH deficiencies, which was seen in only one patient. Table 2 shows the relationship between neuroimaging abnormalities and the prevalence of pituitary hormones deficiencies.

Table 2 Neuroimaging abnormalities and pituitary hormones deficiencies

MRI findings		Isolated GHD N (%)	MPHD N (%)	*p value*
Normal	Yes	19 (**48.7**)	**04** (**10.3**)	**0.0002**
	No	20 (51.3)	35 (89.7)	
HA	Yes	13 (**33.3**)	23 (**59.0**)	**0.020**
	No	26 (66.7)	16 (41.0)	
APS	Yes	07 (**17.9**)	16 (**41.0**)	**0.022**
	No	32 (82.1)	23 (59.0)	
EN	Yes	07 (17.9)	18 (**46.2**)	**0.007**
	No	32 (82.1)	21 (53.8)	
ES	Yes	05 (**12.8**)	11 (**28.2**)	0.079
	No	34 (87.2)	28 (71.8)	
Pituitary size (mm)	Median IQR	4.01 (3.48–4.82)	3.42 (3.06–4.00)	**0.005**

MRI, magnetic resonance imaging; GHD, growth hormone deficiency; MPHD, multiple pituitary hormones; HA, hypoplastic adenohypophysis; APS, absent pituitary stalk; EN, ectopic neurohypophysis; ES, empty sella; mm, milimiters; IQR, Interquartile range (Q1 - Q3)

The provocative tests used for the diagnosis of GHD were: insulin (n=72, being one of these with sex steroids priming); clonidine (n=33); glucagon (n=15); exercise (n=6); pyridostigmine (n=3) and taquitest (n=2). The peak GH response in these provocative tests ranged from 0.05 to 4.9 (1.96±1.62) ng/mL (Immunochemiluminometric assay).

Severe GHD was found in 50 patients (64.9%). Of these 50 patients, 41 (82%) had MRI abnormalities (p=0.06). APS and ES had significant association with severe GHD (p=0.028).

The age at diagnosis of GHD ranged from 1.33 to 18.41 (8.09±3.82) years, and was considered early-onset in 11 patients (14.3%) and late-onset in 66 patients (85.7%). We haven't found significant association between MRI abnormalities and early-onset of GHD.

Of the 39 patients with isolated GHD, 3 had early-onset (7.7%) and 36 late-onset (92.3%) of GHD respectively. On the other hand, of the 38 patients with MPHD including GHD, 8 had early-onset (21.1%) and 30 late-onset (78.9%) of GHD respectively (p=0.094).

The mean dose of rhGH used for the treatment of GHD was 0.27±0.04mg/kg/wk. The increase in growth velocity ranged from 0 to 1425% (189.2±237.1) and height SDS ranged from –0.4 to +3.41 with an average of 0.95. Based on these results, 59 patients were classified as having a good response (76.6%) and 18 patients (23.4%) poor response to therapy.

Of the 39 patients with isolated GHD, 26 had good response (66.7%) and 13 (33.3%) poor response to rhGH. On the other hand, of the 38 patients with MPHD including GHD, 33 had good response (86.8%), while 5 (13.2%) had poor response to rhGH (p=0.036). Table 3 shows the relationship between neuroimaging abnormalities and growth response in the first year of rhGH use.

Table 3 Neuroimaging abnormalities and response to rhGH treatment

		Response to rhGH		
MRI findings		**Good N (%)**	**Poor N (%)**	***p value***
Normal	Yes	15 (25.4)	07 (38.9)	0.21
	No	44 (74.6)	11 (61.1)	
HA	Yes	30 (50.8)	06 (33.3)	0.15
	No	29 (49.2)	12 (66.7)	
APS	Yes	20 (33.9)	03 (16.7)	0.12
	No	39 (66.1)	15 (83.3)	
EN	Yes	23 (**39.0**)	02 (**11.1**)	**0.023**
	No	36 (61.0)	16 (88.9)	

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Table Continued...

		Response to rhGH		
MRI findings		**Good N (%)**	**Poor N (%)**	***p value***
ES	Yes	12 (20.3)	04 (22.2)	0.55
	No	47 (79.7)	14 (77.8)	
Pituitary size (mm)	Median IQR	3.90 (3.19–4.53)	3.53 (3.29–4.83)	0.76

MRI, magnetic resonance imaging; HA, hypoplastic adenohypophysis; APS, absent pituitary stalk; EN, ectopic neurohypophysis; ES, empty sella; mm, milimiters; IQR, Interquartile range (Q1 - Q3)

Discussion

Only a minority of cases of GHD has a clear etiology and most of them remain as idiopathic.[12] Genetic and environmental factors seem to be involved.[13] Male predominance is described in the ratio of approximately 2 boys for every girl.[12,14-16] as we also found in our study (2,1 boys for every girl). Although family history of hypopituitarism is seen in 5-30% of cases.,[13,15,17] we found less than 4.0%. This lower incidence can be explained by the lack of studies in the Brazilian population and the large number of consanguineous marriages in the Indian population where most studies are concentrated. Acharya et al. observed consanguinity in 29.5% of patients[18] while we observed in few cases. Patients with family history of hypopituitarism, consanguinity or dysmorphic features should do genetic studies.[12]

Neuroimaging abnormalities are reported in 50-70% of patients with hypopituitarism.[19] In our study these abnormalities were found at a rate slightly higher, with HA corresponding to almost half of the cases, followed by EN, APS and SV. The adenohypophysis size was similar in boys and girls, with maximum height corresponding to 5.62±0.8 millimeters in boys and 6.82±0.99 millimeters in girls. In other studies, although different populations were evaluated, similar findings were observed.[20-23]

The prevalence of neonatal complications was seen in nearly half of our patients, being slightly higher than that reported in general population (15-30%), but slightly lower than that described in GHD patients (69.2%). We don't know if perinatal changes affect the pituitary stalk causing hypopituitarism or if structural and functional defects of the hypothalamic-pituitary axis increase the prevalence of these complications.[24]

Most children with GHD have isolated GHD. MPHD can happen over time as complex genetic programming controls the pituitary development.[12] We found the same prevalence of isolated GHD and MPHD, what can be explained by our population be part of a tertiary care center where the cases referred often are more complex.

Craft et al. reported high frequency of perinatal insults and neuroimaging abnormalities in children with idiopathic hypopituitarism.[25] Our study showed significant association between neuroimaging abnormalities and neonatal complications in general (p=0.036), and also with hypoglycemia (p=0.016) and jaundice (p=0.012) specifically. However, we haven't found significant association with asphyxia, micropenis, cryptorchidism or ambiguous genitalia.

The presence of HA, APS and EN were associated with MPHD. The gravity of stalk interruption can determine the number and magnitude of pituitary hormone deficiencies.[26] Wang et al. showed that EN was highly predictive and specific of GHD.[27] Arends et al. compared neuroimaging abnormalities in patients with hypopituitarism and controls and found pituitary abnormalities in 58.0% of patients with isolated GHD and 87.0% of patients with MPHD, without finding abnormalities in the control group.[28] Arslanoglu et al. found differences in pituitary height and volume between patients with isolated GHD and controls.[29]

Although it seems to be a higher prevalence of radiological abnormalities in patients with severe GHD, the relationship between neuroimaging and severity of hormonal dysfunction hasn't been fully established.[16] Jagtap et al. showed higher frequency of MRI abnormalities, particularly EN in patients with severe GHD, regardless of the number of pituitary hormone deficiencies.[30] We showed a higher prevalence of radiological changes, such as APS and ES in patients with severe GHD. However, this association hasn't been proven in those with HA and EN.

Coutant et al. demonstrated that children with GHD and MRI abnormalities were lower and younger at diagnosis.[7] Tauber et al. found that children with HA and EN had earlier symptoms of GHD.[31] However, in our study, we haven't found significant association between MRI abnormalities and early-onset of GHD, or between early-onset of GHD and MPHD (p=0.094).

Some patients with GHD diagnosed in childhood will not remain deficient in adulthood.[12] Predictors of permanent GHD are severity of GHD, other hormonal deficiencies, low levels of Insulin Growth Factor 1 (IGF1) and neuroimaging abnormalities. The MRI may be the most important criterion to retest patients during the transition phase.[32] In our study we didn't compared MRI changes to transient or permanent GHD, because of the young age of our patients and the fact that many of them haven't reached final height what could compromise data analysis.

There was a higher prevalence of EN (p=0.023) in patients with adequate response than in those with inadequate response to rhGH. The implications of neurohypophysis location are still unknown. There are reports that in patients in which the neurohypophysis is along the stalk, GH secretion is greater in adulthood. Although we found no significant association between pituitary size and response to treatment, Arends et al. suggested that pituitary hypoplasia would be related to better response to treatment with rhGH. In our study we showed better response in the first year of treatment in patients with severe GHD (p=0.036), as shown in other studies.[15,33]

We concluded that the presence of neuroimaging abnormalities was related to MPHD, severe GHD and neonatal abnormalities, without having relation to early-onset of GHD.

Further studies are needed to determine which patients will progress from isolated GHD to MPHD and which patients diagnosed with GHD in childhood will continue deficient in adulthood.

Although we haven't performed genetic evaluation, we believe that the precise definition of neuroimaging abnormalities should become even more important as genetic studies advance and new genes that cause isolated GHD and MPHD are identified.

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Conflicts of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study. There are no prior publications or submissions with any overlapping information, including studies and patients. All authors listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

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