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Original Article

Physical development of pituitary and pituitary hypoplasia in children from neonate to adolescent: MRI assessment and comparison

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Abstract: The aim of this study was to provide reference ranges of pituitary diameter and volume in children of different age and sex and analyze anatomical features of pituitary in children with growth hormone deficiency (GHD). 1031 MR images of Chinese children aged from 1 to 18 were reviewed. We measured the width, length, height, axial maximal area and volume of pituitary, and the length and diameters of pituitary stalk. The diameters and volume of pituitary in children with GHD were significantly smaller than that in normal children, but such difference was not found in pituitary stalk. There was a correlation between pituitary volume and GHD occurrence. Also, diameters, axial maximal areas, and volume of pituitary in normal children increase with age. For the above parameters, no significant difference was found between males and females. Importantly, MRI is recommended in providing clinical and biochemical evidence of pituitary hormone dysfunction. We provided reference range to standardize the diagnosis of pituitary GHD. Further, pituitary volume indicates the severity of GHD.

Keywords: Growth hormone deficiency, pituitary hypoplasia, mri, pituitary development

Introduction

Magnetic resonance imaging (MRI) has a rapid development, with fast sequences and increasing image resolution allowing accurate visualization of even small structures [1]. Owing to the excellent contrast resolution and high spatial resolution, MRI is proved to be an essential tool of examining pituitary gland in children with neurological and endocrine disorders [2]. The diameters and volume of the pituitary gland are various in Children with different age, sex, and hormonal environment [3]. Pituitary MRI is advocated as a part of the baseline investigations to be performed on children with poor growth or suspected endocrinopathy [4]. Sellar imaging is often recommended when there is a suspicion of pituitary disease [5]. However, previous radiological reports of pituitary gland are frequently based upon clinicians' subjective judgments, and there is a lack of evaluation criterion in image.

Previous neuroimaging studies have noted that pituitary diameters of children and adolescents increase with age [6]. Several authors have reported the diameters or volume of pituitary gland measured by MR images [7, 8], Sebahattin provided normative data of pituitary diameters in pediatric population [9]. Argyropoulou measured the height of normal pituitary and its correlation with age [10]. To the best of our knowledge, there is few study provided both diameters and volume of pituitary of children or adolescents. Furthermore, most MRI data about the diameters or shape of normal pituitary gland were measured in a single plane (usually gland height). Some studies provided the data of pituitary of children with GHD compared with normal children, Argyropoulou reported the pituitary height of patients with idiopathic growth hormone deficiency in MRI [11]. Bozzola measured the height of pituitary and provided its role in the diagnosis and prognosis of growth hormone deficiency [12]. Based on these work, we hope to assess the hypoplastic pituitary comprehensively by providing more data and information of pituitary.

Therefore, the aim of our study was to provide a normal reference range of pituitary diameters

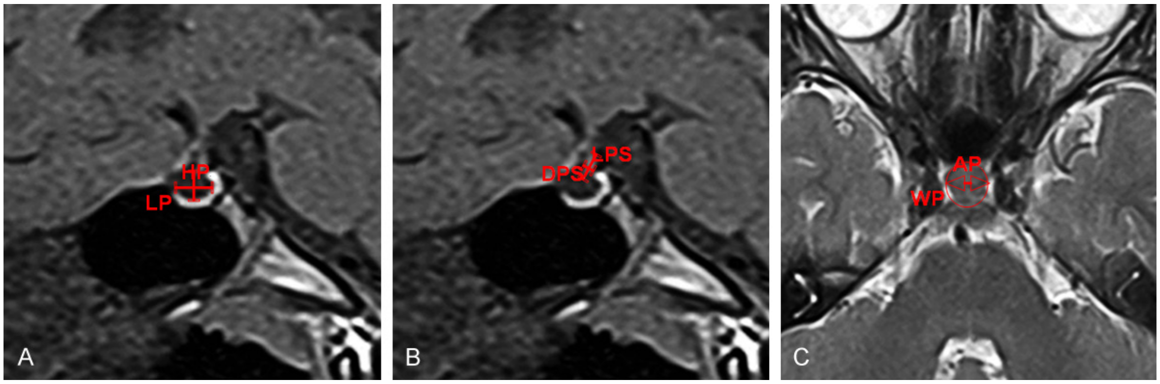

Figure 1. Diameters and axial maximal area of pituitary gland and the length and diameters of pituitary stalk. A: LP: The maximal length of the pituitary; HP: The maximal height of the pituitary. B: LPS: The length of pituitary stalk; DPS: The diameters of pituitary stalk. C: WP: The maximal width of the pituitary; AP: The maximal area of the pituitary, measuring at the horizontal plane.

and volume of Chinese children of different sex and age. We established multiple parameters to evaluate the shape of pituitary, which could provide more comprehensive data for clinicians. We also measured the diameters and volume of pituitary of children with GHD and compared it with normal children. Our data would be helpful to diagnose and examine GHD and analyze its severity.

Materials and methods

Ethic statement and patient selections

The experiments were carried out in agreement with the Declaration of Helsinki of World Medical Association. The radiological data were obtained from the electronic record system maintained at the workstation of the Radiology Department of the First Hospital of Jilin University. The data from the individuals were analyzed anonymously, and the study protocol was approved by the Ethnic Committee of First Hospital of Jilin University. Patient records/information was anonymized and de-identified prior to analysis. Among 15,945 cranial, sellar, or pituitary MRI scans performed from 01-01-2005 to 12-31-2015 in our center, 1031 MR images from 1031 Chinese children aged 1-18 were acquired. In the group of children with normal growth hormone level (normal children for short), the main exclusion criteria are: (1) history of hypophysical hormone level abnormity; (2) positive medical history for meningitis, malignancy, endocrine abnormality, genetic syndrome, (3) preterm delivery at less than 35 week gestation, birth asphyxia, hospitalization for head injury, craniospinal irradiation, or abnormal MRI of the brain, (4) severe mental illness (e.g. autism, schizophrenia) or mental retardation. We recruited 780 individuals in group of normal children meeting with the above criteria. In the group of children with GHD, the main inclusion criteria are: (1) Clinical diagnosis is pituitary hypoplasia; (2) Short stature causes of endocrine disorders: less than the mean stature of normal children with same age and sex for 2 standard deviation (SD); growth rate is less than 4 cm/y; skeletal development retardation of 2 years or more; growth hormone deficiency: GH medicine (insulin and levodopa) challenge test: GH peak <10 ng/ml [13-15]; Hypophysoma, hypophysitis and other pituitary destructive diseases were excluded from above recruitments, we recruited 251 children in the group of pituitary hypoplasia. TSH, ACTH, PRL and GH were measured by automated chemiluminescent immunoassay systems or kits from Bayer Ltd.

Imaging techniques

MRI data were acquired at Trio-Tim 3.0 T super conduct MRI system (SIEMENS) using the product head coil and foam cushions to minimize head movement. A standard 3D inversion recovery prepped T1-weighted spoiled gradient echo (GE) sequence (echo time [TE]/repetition time [TR]=20/2000 ms; field of view [FOV] of 220 mm, 1.8 mm isotropic resolution) was acquired for anatomical localization and a CSF-nulled T2-weighted FLAIR sequence (TE/TR=80/3000 ms, FOV 220 mm, slice thickness of 5 mm, 256*512 matrix) was acquired to

Table 1. The definition of variables of pituitary gland and stalk

Variable	Definition
WP▲	The maximal width of the pituitary
LP△	The maximal length of the pituitary
HP△	The maximal height of the pituitary
AP▲	The maximal area of the pituitary, measuring at the horizontal plane
VP	The volume of pituitary: VP=[13]
LPS◆	The length of pituitary stalk
DPS◆	The diameters of pituitary stalk

△shown in **Figure 1A**; ◆shown in **Figure 1B**; ▲shown in **Figure 1C**. The formula of VP can be derived from the formula of spheroidicity volume if considering the pituitary as a half of spheroidicity [13].

Table 2. The group of normal children and children with pituitary hypoplasia

	Age	n	Boys (%)	Girls (%)
Group I	0-4 years	164	84 (51.2)	80 (48.8)
Group II	5-9 years	179	91 (50.8)	88 (49.2)
Group III	10-14 years	190	96 (50.5)	94 (49.5)
Group IV	15-18 years	247	127 (51.4)	120 (48.6)
Group i	0-4 years	45	22 (48.9)	23 (51.1)
Group ii	5-9 years	47	26 (55.3)	21 (44.7)
Group iii	10-14 years	63	34 (54.0)	29 (46.0)
Group iv	15-18 years	96	46 (47.9)	50 (52.1)

Group I-IV: normal children; group i-iv children with pituitary hypoplasia.

identify pituitary. Each individual was test for 657 s without gap scanning.

MRI measurements

All the measurements were performed independently by two neuro-radiologists who are professional in the diagnosis of pituitary disease. Before performing the measurements, we selected 20 patients for a pilot study. 50 randomly selected patients were evaluated by all doctors to determine interclass correlation coefficient as an inter-observer reliability measure. The definition of variables (**Figure 1**) are listed in **Table 1**. All the measurements were same both in group 1 (normal children) and group 2 (children with GHD).

Statistical analysis

Statistical analyses were performed by SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA) and results visualized by Microsoft Office Excel program (Microsoft Corp, Redmond, WA, USA). Mean and standard errors calculated for each groups of different sex and age. The results are presented as Mean ± SD. Independent samples student's t-test was used after the demonstration of homogeneity of variance with an F test to compare variables between matching different age and sex groups. One-way ANOVA was used to compare the differences between several groups. Correlations between groups were assessed by One-Sample Kolmogorov-Smirnov test. A *p*-value <0.05 was considered statistically significant.

Results

Patient evaluation

Among the 1031 MR images, 780 pituitary MRI scans from 780 children were recruited in the group of children with normal growth hormone level (Group 1: 63.73%), with 398 boys and 382 girls. 251 MRI scans from 251 individuals were recruited in group of children with growth hormone deficiency (Group 2: 20.51%), with 128 males and 123 females. Both Group 1 and Group 2 were divided into 4 subgroups based on different age stage (**Table 2**). The basic information including height, weight, and hormone level of normal and child with GHD was shown (**Tables 3**, **4**).

Diameter line of pituitary

The pituitary diameters as HP, LP, and WP were measured in all subjects, including both group 1 and group 2. HP, LP, and WP in same age group were analyzed separately with the method of two independent sample t-test. All the pituitary diameters of children with pituitary hypoplasia, including males and females, were smaller than normal children (**Figure 2**, Supplementary Table 1).

Pituitary diameters of normal children were also analyzed statistically by age. The pituitary diameters increase with age in both males and females (one-way ANOVA) (**Figure 3**, Supplementary Table 2).

Due to different findings between males and females, the results were given separately by sex. The results were applied comparative t-test to perform statistical analysis. No significant differences of pituitary diameters between

Table 3. The basic information of children (female) with or without GHD

	Group I	Group II	Group III	Group IV	Group i	Group ii	Group iii	Group iv
Height (cm)	94.0±2.0	118.1±2.4	149.1±2.5	156.5±2.6	85.8±2.5	99.9±2.1	128.3±3.0	138.2±2.4
Weight (Kg)	13.6±1.2	20.9±1.8	38.7±2.5	48.2±2.2	11.1±1.4	15.0±1.4	28.6±2.0	37.6±2.1
GH peak (ng/ml)△	-	-	-	-	7.1±1.8	5.9±1.4	4.4±1.6	6.2±1.7
TSH (mIU/L)	6.9±0.9	6.1±2.0	7.2±2.3	5.5±1.1	6.0±1.1	6.3±1.7	6.9±2.0	5.9±1.9
8:00 am ACTH (ng/L)	22.7±1.9	18.5±4.0	25.9±2.8	30.0±3.9	21.9±2.5	19.8±3.1	22.0±3.5	21.9±3.3
PRL (ng/ml)	12.6±3.4	11.5±2.5	11.1±2.9	19.8±3.6	12.0±2.7	12.9±3.2	13.1±3.9	21.6±2.8

△the peak growth hormone levels after insulin stimulation of normal children were not shown.

Table 4. The basic information of children (male) with or without GHD

	Group I	Group II	Group III	Group IV	Group i	Group ii	Group iii	Group iv
Height (cm)	95.1±2.2	119.1±2.6	149.8±2.4	167.2±2.7	83.3±2.7	101.1±2.5	130.4±2.7	144.2±3.0
Weight (Kg)	14.2±1.1	22.1±1.9	40.6±2.8	56.1±2.3	10.9±1.2	15.9±1.6	30.8±1.9	41.8±2.3
GH peak (ng/ml)△	-	-	-	-	7.8±2.1	6.8±2.4	6.5±1.9	7.6±2.1
TSH (mIU/L)	5.8±2.0	5.2±1.9	6.7±2.1	4.9±1.2	5.5±1.5	5.9±2.0	6.6±1.9	5.3±2.2
8:00 am ACTH (ng/L)	25.5±2.1	22.3±2.1	28.8±3.3	29.1±2.8	20.2±3.1	22.9±3.3	21.2±2.0	28.2±3.0
PRL (ng/ml)	13.4±2.0	12.9±1.8	13.2±1.6	15.9±2.4	12.8±1.7	13.2±2.2	13.9±3.1	16.6±3.8

△the peak growth hormone levels after insulin stimulation of normal children were not shown.

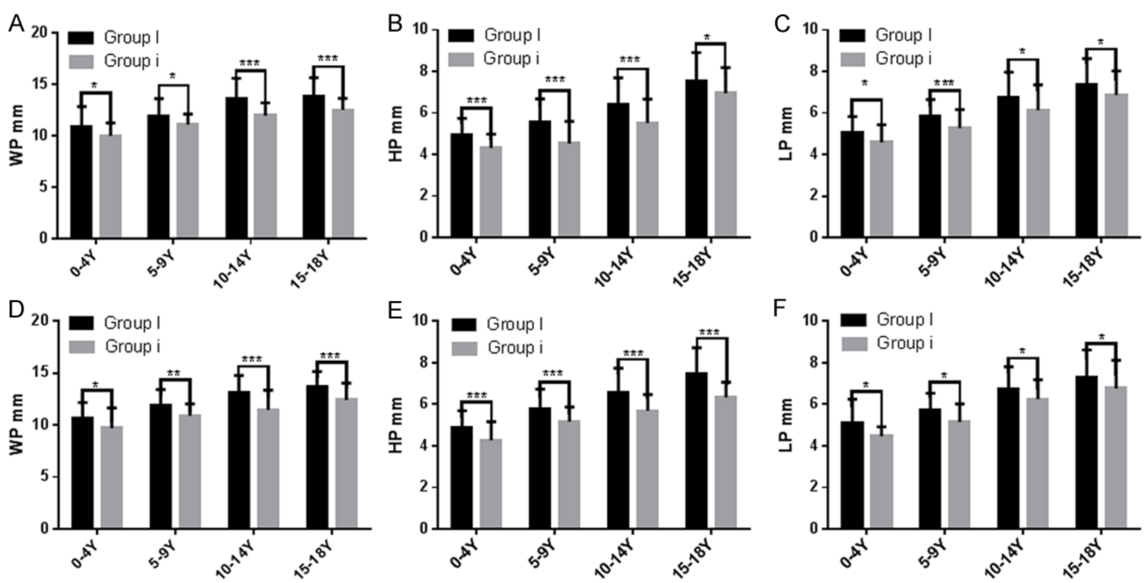

Figure 2. Pituitary diameters in children with or without pituitary hypoplasia. Pituitary diameters in same age group of children with or without pituitary hypoplasia were analyzed separately with the method of two independent sample t-test. A-C: Statistical results of HP, LP, and WP in females with or without pituitary hypoplasia; D-F: Statistical results of HP, LP, and WP in males with or without pituitary hypoplasia. The statistical analysis method was two-tailed student's t-test, *P<0.05, **P<0.01, ***P<0.001.

males and females in same age group was found.

Axial maximal area and volume of pituitary

The AP and VP were measured in most of individuals excluding 21 children with indefinitely maximum area in MRI. The volume of pituitary was calculated with the HP, LP, and WP. AP and VP in same age group were analyzed separately with the method of two independent sample t-test. AP and VP of children with pituitary hypoplasia were smaller than that of normal children (**Figure 4**, Supplementary Table 3).

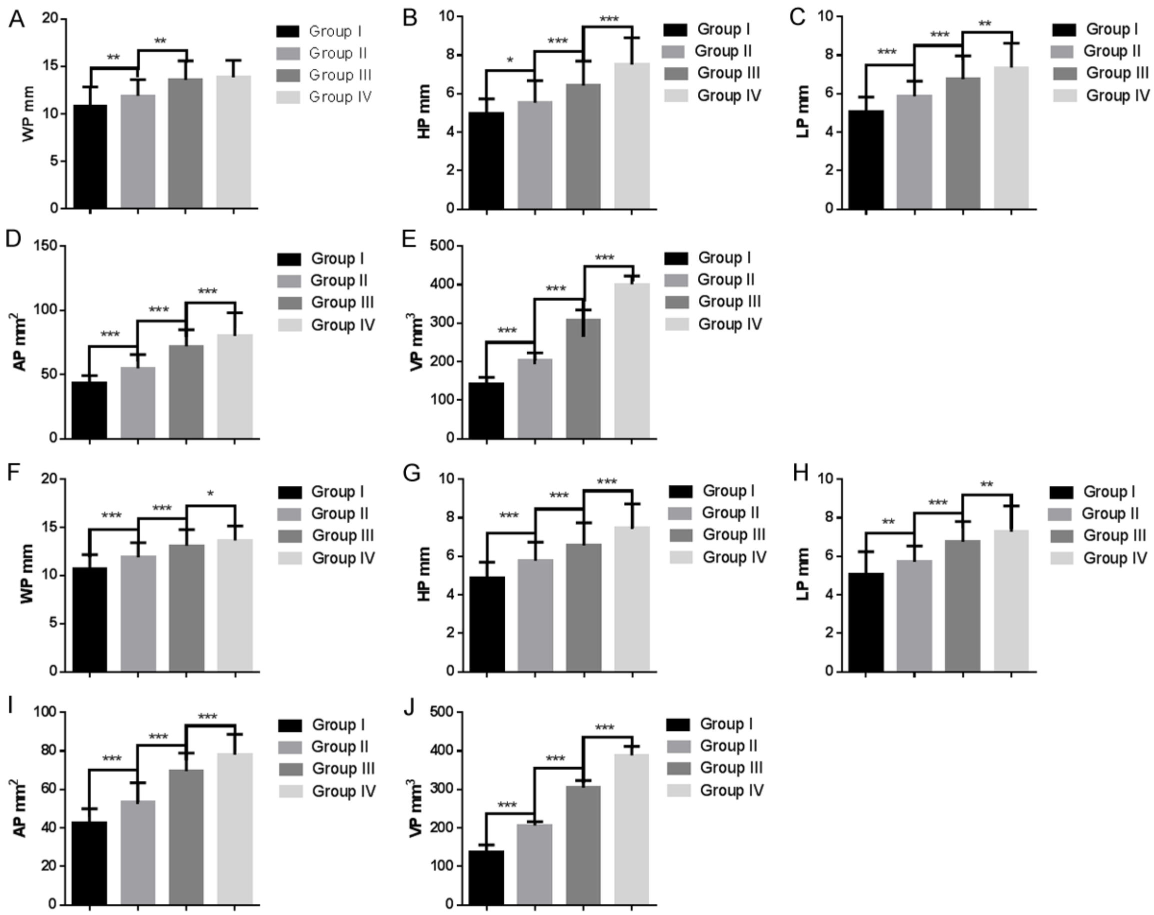

Figure 3. Diameters, axial maximal area and volume of pituitary between different age groups in normal males and females. A-E: The statistical results of diameters, axial maximal area and volume of pituitary between different age groups in normal females; F-J: The statistical results of diameters, axial maximal area and volume of pituitary between different age groups in normal males. The statistical analysis method was one-way ANOVA, *P<0.05, **P<0.01, ***P<0.001.

In the group of normal children, AP and VP were significantly different between any two age groups (one-way ANOVA). However, no significant difference between males and females was found.

Measurement of pituitary stalk

The length and diameter of pituitary stalk were measured excluding 34 children with indefinitely pituitary stalk in MRI. However, there were no significant difference between normal children and children with GHD (Two independent sample t-test) (**Figure 5**, Supplementary Table 4).

Discussion

In this study, we reported anatomical data of pituitary gland and pituitary stalk of children from neonate to adolescent with or without GHD. By analyzing several parameters as the pituitary diameters, axial maximum area and volume, we could get more information about normal pituitary and pituitary hypoplasia.

In our study, we calculated pituitary volume based on pituitary diameters [13]. The formula of VP can be derived from the formula of spheroidicity volume if considering the pituitary as a half of spheroidicity. Koichi Takano reported the pituitary volume measuring with a technique called overcontiguous sections (OS), which can provide a more exact and direct data of pituitary volume [14]. Compared with OS, MRI is more prevalent and convenient. Our data provides a diagnose criteria for normal pituitary based on the approximate estimation of pituitary volume on MRI. In addition, this simple formula was suggested to be used to estimate the

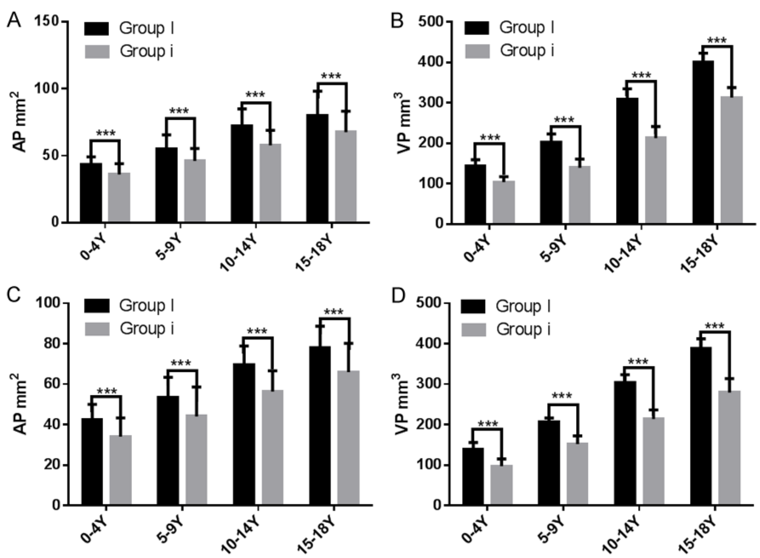

Figure 4. The statistical results of axial maximal area and volume of pituitary in normal children and children with pituitary hypoplasia. A, B: Statistical results of axial maximal area and volume of pituitary in females with or without pituitary hypoplasia; C, D: Statistical results of axial maximal area and volume of pituitary in males with or without pituitary hypoplasia. The statistical analysis method was two-tailed student's t-test, *P<0.05, **P<0.01, ***P<0.001.

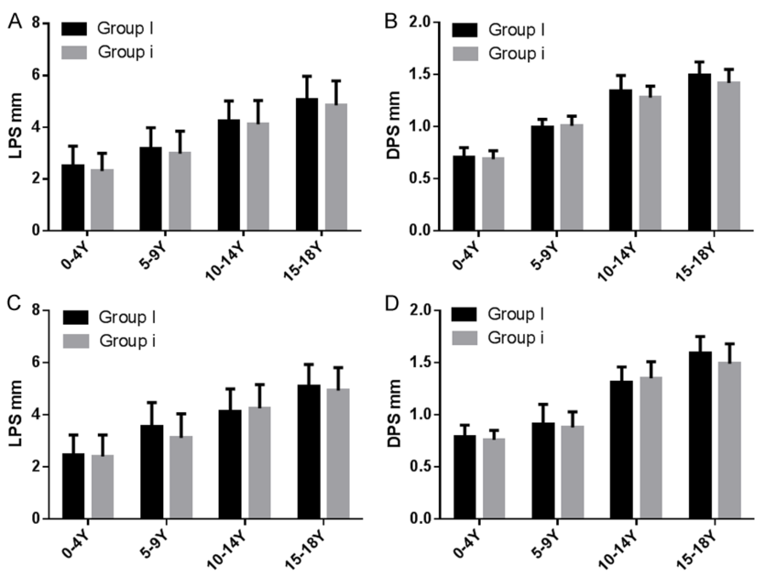

Figure 5. The statistical results of diameters and length of pituitary stalk in children with or without pituitary hypoplasia. A, B: Statistical results of diameters and length of pituitary stalk in normal girls and girls with pituitary hypoplasia; C, D: Statistical results of diameters and length of pituitary stalk in males with or without pituitary hypoplasia. The statistical analysis method was two-tailed student's t-test.

pituitary volume to predict the pituitary disease [9].

Pituitary matures and develops in a variable rates, with a burst in puberty. During the puberty, growth hormone, gonadotropin, thyroid-stimulating hormone etc. increase to stimulate physical growth and sexual maturity [3]. According to our results, all of pituitary diameters, axial maximal areas, and volume increase with age, the difference between two age groups was significant. These findings were in agreement with the result of A.M. Fink [13].

Considering the different physical changes in males and females during the period from neonate to adolescent, we compared the diameters and volume of pituitary between males and females in order to ensure if the data standard we provided was applicable to both males and females. In group of normal pituitary, the result showed that males did not have significantly larger or smaller pituitary gland size and volume than females, even in the age of adolescent. The finding of pituitary volume is in agreement with the result of Lurie [15]. However, we are not in agreement with previous reports that the female's pituitary volume is larger than male's during the period of adolescent. The variability is caused by different ethnic compositions of the study populations. In addition, the growth bursts of males and females during adolescent are both included in the age group IV, therefore, there is no difference in pituitary size and volume between males and females.

Pituitary develops and changes with age, which brings difficulties in diagnosing a younger pituitary or a delay-developed pituitary when assessing a small pituitary in MRI. So one of the major purposes of our study was to determine the size and volume of pituitary in children with pituitary hypoplasia. Based on our inclusion criteria, the size and volume of pituitary in children with pituitary hypoplasia was smaller compared to normal children. In addition, the measurement of hypogenetic pituitary can provide a diagnostic criteria of pituitary hypoplasia. We also measured the length and diameter of pituitary stalk in order to find the relationship between pituitary stalk and the pituitary hypoplasia [16]. As a result, the length and diameter of pituitary stalk were not correlated with pituitary hypoplasia. However, during our study, we found that the unclear pituitary stalk (67%) always belong to the children with pituitary hypoplasia (data not shown).

The comparison between hypogenetic pituitaries with normal pituitaries showed that children with GH deficiency had smaller pituitaries. Furthermore, we found that there was a significant correlation between pituitary volumes and growth hormone deficiencies. The lower the GH, the smaller the volumes of pituitary, which is in agreement with the result of Li [17]. FaribaNaderi also believed that abnormal MRI results were associated with GH level [18]. Thus, we believed that the volume of pituitary measured by MRI could be used to assess the severity of pituitary hypoplasia.

Additionally, MRI is considered to be essential in the assessment of patients with suspected hypothalamo-pituitary pathology [19]. Physicians involved in the care of such patients have, in MRI, a valuable tool that can help them determine the pathogenesis of their patients' underlying pituitary conditions [20]. Indeed, the use of MRI has led to an enormous increase in our knowledge of pituitary morphology, improving, in particular, the diagnosis of hypopituitarism [21]. Recently, high-resolution, heavily T2-weighted sagittal images/T2-DRIVE [18], or fast imaging employing steady state acquisition sequence obtained at submillimetre thickness, provide an excellent visualization of the suprasellar region and are especially suited to the assessment of the pituitary stalk without using contrast medium [18]. They would provide us more information on the diagnosis of pituitary abnormalities.

MRI appeared to be largely used as a diagnostic tool for screening pituitary abnormalities in children with pituitary hypoplasia by endocrinologists in daily clinical practice [22]. There is a constant debate about which investigations, anthropometrical, biochemical, imaging or genetic, are required to firmly establish the diagnosis of pituitary hypoplasia, particularly permanent GHD, in childhood and adolescence [23]. The existence of MRI abnormalities can be a good indicator to the severity of the hormonal deficiency, combining with the changes of biochemical index and hormone level, we can diagnose the pituitary hypoplasia. There is a recognized need for more normative data on pituitary size in the pediatric population [24].

Comparing the pituitary diameters and volume of children with suspicious pituitary hypoplasia to normal children's at the same age, we can assess the target pituitary's developmental state. The data can not only help diagnosing but also screening the early pituitary hypoplasia. In addition, our data can reflect the severity and progress of pituitary hypoplasia, which is helpful to the treatment. Furthermore, considering the follow-up of pituitary hypoplasia, this comparison is necessary. In conclusion, pituitary MRI is advocated as a part of the essential investigations to be performed in children with pituitary hypoplasia, and the follow up. The standardization of pituitary diameters are considered necessary. Our results of the pituitary gland and stalk in healthy children and children with pituitary hypoplasia provide data to support this standardization.

In conclusion, MRI is recommended in providing clinical and biochemical evidence of pituitary hormone dysfunction. We provided reference range to standardize the diagnosis of pituitary GHD. Further, pituitary volume indicates the severity of GHD.

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Disclosure of conflict of interest

None.

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Supplementary Datas

The exact t, F, or *p* values of statistical analysis

Supplementary Table 1. The t and *p* values of **Figure 2**

	0-4 Y	5-9 Y	10-14 Y	15-18 Y
WP (female)	t=2.08879	t=2.08855	t=4.08497	t=4.81162
	p=0.0392411	p=0.0391208	p=7.956997e-005	p=3.314061e-006
HP (female)	t=3.61435	t=3.69344	t=3.37972	t=2.4472
	p=0.000471511	p=0.000350316	p=0.00097714	p=0.0154266
LP (female)	t=2.41808	t=2.97239	t=2.34063	t=2.33285
	p=0.0173941	p=0.00365056	p=0.0208877	p=0.0208414
WP (male)	t=2.52754	t=3.12929	t=4.72933	t=4.72583
	p=0.012991	p=0.00222103	p=5.856262e-006	p=4.763588e-006
HP (male)	t=3.0048	t=2.98935	t=4.04141	t=5.69602
	p=0.00333045	p=0.00341948	p=9.110859e-005	p=5.249557e-008
LP (male)	t=2.42936	t=3.0913	t=2.47129	t=2.1773
	p=0.0168395	p=0.00250051	p=0.014777	p=0.0308285

Supplementary Table 2. The F and *p* values of **Figure 3**

	F	*P*
WP (female)	51.68	<0.0001
HP (female)	85.41	<0.0001
LP (female)	85.49	<0.0001
AP (female)	147.5	<0.0001
VP (female)	2729	<0.0001
WP (male)	72.39	<0.0001
HP (male)	104.7	<0.0001
LP (male)	77.22	<0.0001
AP (male)	278.3	<0.0001
VP (male)	3587	<0.0001

Supplementary Table 3. The t and *p* values of **Figure 4**

	0-4 Y	5-9 Y	10-14 Y	15-18 Y
AP (female)	t=4.71693	t=3.50984	t=5.36309	t=4.24865
	p=7.702151e-006	p=0.000657351	p=3.987931e-007	p=33.555495e-005
VP (female)	t=10.5765	t=12.8885	t=16.6296	t=23.0053
	p=4.830013e-018	p=1.656873e-023	p=4.815146e-033	p=0.000000e+000
AP (male)	t=4.58436	t=3.79711	t=6.88499	t=6.01079
	p=1.272567e-005	p=0.000235409	p=2.322997e-010	p=1.084642e-008
VP (male)	t=9.84807	t=18.7148	t=22.9603	t=23.7688
	p=1.470940e-016	p=1.070360e-036	p=0.000000e+000	p=0.000000e+000

Supplementary Table 4. The t and *p* values of **Figure 5**

	0-4 Y	5-9 Y	10-14 Y	15-18 Y
LPS (female)	t=1.20375	t=0.893418	t=0.632038	t=1.51006
	p=0.231498	p=0.373638	p=0.528554	p=0.132907
DPS (female)	t=0.377306	t=2.16913	t=0.688633	t=1.25088
	p=0.706715	p=0.0521314	p=0.4923	p=0.212685
LPS (male)	t=0.961476	t=1.00474	t=1.99267	t=1.19894
	p=0.338609	p=0.317287	p=0.0585482	p=0.164894
DPS (male)	t=1.17877	t=0.741032	t=1.31309	t=1.45049
	p=0.24118	p=0.460184	p=0.191503	p=0.1704906