SHORT COMMUNICATION

Pituitary Hyperplasia in Children with Short Stature and Primary Hypothyroidism

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We present eight cases with short stature, pituitary hyperplasia, and hypothyroidism. Pituitary hyperplasia due to primary hypothyroidism was diagnosed on the basis of clinical manifestations, endocrine examination and MRI. After 2 to 6 months of L-thyroxine replacement therapy, the signs of hypothyroidism disappeared; free triiodothyronine, free thyroxine, thyrotropin and prolactin became normal; and pituitary enlargement regressed. In two children, the growth rate remained low when treated with L-thyroxine, but with additional recombinant human growth hormone (rhGH), the height increased by 11 cm per year. No recurrence of lesions was found on follow-up.

Key words: *Child, China, Growth hormone, Pituitary hyperplasia, Primary hypothyroidism, Short stature.*

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Pituitary enlargement secondary to primary hypothyroidism (PH) is a known but uncommon occurrence, and is also difficult to distinguish on CT and MRI from primary pituitary tumors(1). Following adequate hormone replacement with L-thyroxine, both symptoms and pituitary hyperplasia are reported to regress within a few months(2). It is important to recognize this condition so as to avoid unnecessary surgery. Previous reports have mainly focussed on CT and MRI identifying pituitary hyperplasia in children with primary hypothyroidism, whereas only a few reports focus on plasma GH levels(3,4). This study was conducted to observe the therapeutic effect of thyroxine on growth, and GH levels in these children.

METHODS

This study was conducted from 2002 to 2005 in the pediatric department of the Affiliated Hospital, Qingdao Medical College, China. Ethical approval and verbal consent were obtained. During this period, we encountered 8 patients who displayed a decreased growth rate, without typical clinical features of hypothyroidism. Hormonal analyses – which included GH stimulation tests (arginine, insulin), free triiodothyronine(FT_3), free thyroxine (FT_4), thyrotropin (TSH) (RIA assay) and thyroid antibody and prolactin (PRL), was conducted. ^{99} Tc-pertechnetate thyroid scan and MRI scan of the pituitary were undertaken. To assess for Turner syndrome, cytogenetic studies were conducted on every female subject. Based on the MRI findings and clinical signs and symptoms; endocrinological examinations were diagnostic for pituitary enlargement due to PH in a given child. The patients had a trial of T_4 hormone replacement (levothyroxine sodium 5-10μg/kg/d) and continued until serum TSH level was normalized. FT_3, FT_4 and TSH levels were taken as a guideline to adjust the dose of the drug. Clinical and biochemical evaluations, MRI and the

GH stimulation test were repeated bimonthly, 3 months and 6 months, respectively. Diagnostic criteria and guidelines for treatment were on the basis of relevant literature(5,6).

RESULTS

Initial endocrinological work-up revealed abnormal GH provocative tests, low levels of thyroid hormones and markedly elevated TSH and PRL (***Table* I** and **II)**. Thyroxine binding globulin and antithyroid peroxidase (anti-TPO) antibodies were positive in three children. Cytogenetic studies ruled out Turner syndrome in all female children. Pituitary MRIs revealed symmetrical enlargement of the pituitary gland, measuring 12-31 mm in size. The mean follow-up period was 22.8 ± 4.7 months. Following adequate hormone replacement with L-thyroxine symptoms, thyroid function and prolactin were normalized over 2-6 months. MRI demonstrated a marked decrease in the size of the pituitary mass within the sella turcica after 3 months of treatment and showed normal dimensions after 6 months of treatment. The height increased by 11.6 ± 1.7cm/year in six children; while in the other two, it was 4.9 cm/year and 5.2 cm/year, respectively (Patient 2 and 5, ***Table* II**). GH stimulation tests of these 2 patients remained abnormal. Thereafter, they were treated with daily injections of recombinant human growth hormone (rhGH) 0.1 IU/kg/d, in addition to L-thyroxine; resulting in a growth gain rate of approximately 11cm/year.

DISCUSSION

With long-standing hypothyroidism, thyrotroph hyperplasia can result in the expansion of the sella turcica and the enlargement of the pituitary gland(7). Khawaja, *et al*.(6) report that pituitary enlargement on MRI is found in 70% patients with primary hypothyrodism. The pituitary mass may extend outside the sella turcica and produce clinical symptoms(8). Radiana, *et al*.(9) suggest that the greatly increased number of TSH-cells in methimazole-induced-hypothyroidism is due, at least partially, to the transdifferentiation of somatotroph into thyrotroph cells and a role for TRH stimulation in the transdifferentiation process. Key transcription factors, such as Pit-1 and Gata 2 are known to be involved in pituitary endocrine cell differentiation(10). Depending on demand, somatotrophs can reversibly transform into thyrotrophs.

In adults, pituitary hyperplasia with hypothyroidism generally exhibit in various forms like features of hypothyroidism, amenorrhea; galactorrhea; visual abnormalities and headaches(5). While short stature or decreasing growth is a frequent reason for pediatric consultations, clinical features of hypothyroidism are subtle and missed. All over patients consulted for growth arrest but their clinical signs of hypothyroidism were mild and their intellectual development was normal. We found that these patients were hypothyroid and had pituitary enlargement upto 12-31 mm in size. A common cause of hypothyroidism is autoimmune destruction of the thyroid gland(11). Hashimoto's thyroiditis was the likely main cause in our patients; because antithyroid antibodies were positive and radionuclide thyroid scans showed an asymmetrical thyroid gland with irregular distribution of 99mTc. The other reason was congenital hypothyroidism, which was caused by thyroid hypoplasia or dyshormonogenesis. Although neonatal screening has been carried out for years, hypothyroidism, and consequently pituitary hyperplasia, continues to occur in our country.

The recommended and appropriate replacement therapy for hypothyroidism is levothyroxine sodium. After 6-12 months, all patients' pituitary hyperplasia regressed with adequate levothyroxine replacement, but 2 patients still have impaired growth hormone secretion and a low growth rate. Since thyroxine is a stimulating factor for GH synthesis, GH production may be reduced in hypothyroic children(3). This is a very important phase of their height increase in pre-puberty; so after the complete disappearance of enlargement in the pituitary, rhGH was given to these 2 patients. The combination levothyroxine with GH can be highly effective in increasing final height. No recurrence of pituitary enlargement was found in the 8 follow-up cases.

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TABLE I DATA OF PATIENTS WITH PITUITARY ENLARGEMENT DUE TO PRIMARY HYPOTHYROIDISM, BEFORE AND AFTER 22 MONTHS OF THYROXINE THERAPY

Pateint	Values before starting therapy						Values after 22 months therapy					
no/sex	CA (y)	BA (y)	Height (cm)(SDS)	Thyroid scan	GV(cm/ year)	Pituitary size (mm)	CA (years)	BA (years)	Height (SDS)	Thyroid scan	GV (cm/ year)	Pituitary size (mm)
1/ F	5.3	3.0	91.5(-3.3)	irregular#	2.8	13.0	7.1	6.0	111.5(-0.8)	Normal	12.6	6.1
2/F	6.8	3.5	103.5(-3.1)	hypoplasia	2.3	15.0	8.6	7.5	119.0(-0.8)	Normal	11.3	5.8
3/F	6.6	3.5	103.5(-3.1)	irregular#	3.8	16.0	9.3	7.5	123.5(-0.4)	Normal	12.6	5.9
4/M	9.2	5.5	112.0(-3.0)	irregular#	3.4	22.0	11.0	10.5	132.5(-1.7)	Normal	12.1	5.8
5/M	7.5	4.0	108.5(-3.0)	irregular#	3.1	14.0	8.4	8.0	125.0(-0.4)	Normal	11.7	5.5
6/M	5.1	2.0	91.0(-3.2)	hypoplasia	2.6	31.0	6.9	5.5	111.5(-1.3)	Normal	12.9	5.3
7/M	6.8	4.5	102.5(-3.1)	hypoplasia	3.5	15.0	8.6	7.5	121.5(-0.9)	Normal	11.6	5.4
8/M	7.8	4.5	106.5(-3.0)	irregular#	3.4	17.0	9.6	8.0	125.5(-0.5)	Normal	11.7	5.3
Mean	6.9±1.3	3.8±1.1	102.4±7.5 (-3.1±0.1)		3.11±0.5	17.9±2.1	8.7±1.3	7.6±1.5*	121.5±7.2* (-0.9±0.5*)		12.1±0.6*	5.6±0.3*

*# irregular distribution; CA: Chronological age; BA: bone age; GV: growth velocity; *compared to before therapy, P<0.01.*

TABLE II RESULTS OF HORMONAL EVALUATION BEFORE AND AFTER TREATMENT

Pateint	Thyroid profile at star					Thyroid profile at followup				
no/sex	FT3 (pmol/L)	FT4 (pmol/L)	TSH (mU/L)	PRL levelsat start (ug/L)	GH levels at start (ng/mL)	FT3 (pmol/L)	FT4 (pmol/L)	TSH (mU/L)	PRL at followup (ug/L)	GH at followup (ng/mL)
1/ F	2.2	5.6	82.2	45.2	>10	4.3	20.5	0.42	10.9	>10
2/F	1.8	7.8	75.4	56.7	<5	4.7	13.4	0.34	11.3	<5
3/F	1.9	4.5	68.9	34.6	>10	3.9	15.6	0.37	9.3	>10
4/M	2.9	10.1	89.2	38.9	>10	5.6	17.8	0.41	3.8	>10
5/M	3.1	6.7	68.3	36.9	5-10	4.5	15.9	0.25	8.9	7.5
6/M	3.0	4.4	54.2	43.2	>10	3.9	20.4	0.29	2.5	>10
7/M	1.6	6.3	80.3	30.9	>10	6.2	16.7	0.36	4.5	>10
8/M	2.4	7.2	68.7	28.5	>10	4.5	18.4	0.38	5.7	>10
Median (ref range)	2.4±0.6 (3.6-6.8)	6.5±1.9 (12-22)	73.3±10.9 (0.27-0.42)	38.4±9.0 (1.6-13.8)		4.7±0.8*	17.3±2.4*	0.4±0.1*	7.1±3.4*	>10

**compared to before therapy, p<0.01; FT3: free triodothyronine; FT4: free thyroxine; TSH: thyrotropin; PRL: prolactin.*

WHAT THIS STUDY ADDS?

- After adequate thyroxine replacement treatment, regression of the pituitary hyperplasia due to primary hypothyroidism occurs in the majority and in its absence, growth hormone deficiency should be considered.

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