Time Bound Regression of Pituitary Hyperplasia in Primary Pituitary Hypothyroidism Following Treatment

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ABSTRACT

Aim: The aim was to prospectively study radiological regression of pituitary hyperplasia following the treatment for primary hypothyroidism by serial magnetic resonance imaging (MRI). **Subjects and Methods:** Seven patients (1 male and 6 females) with profound hypothyroidism were included, age ranging from 13 to 42 years. MRI for pituitary was done at first visit and on follow-up. Pituitary size on imaging was matched with baseline T3, T4, thyroid-stimulating hormone (TSH), and thyroid peroxidase antibody antibodies and TSH on follow-up. **Results:** By 6 weeks all patients showed clinical improvement with near normalization of thyroid function tests in most patients. The TSH normalization was well correlated with regression of the pituitary enlargement on imaging at 6 weeks. The height of pituitary gland at baseline was 13.24 ± 3.61 mm, at first follow-up 9.68 ± 1.32 mm, and at second follow-up 7.80 ± 3.95 mm. The diameter of the pituitary gland at baseline was 14.47 ± 4.14 mm, at first follow-up 11.83 ± 3.99 mm, and at second follow-up 7.25 ± 4.59 mm. The height of the pituitary gland significantly reduced in first and second follow-up ($P < 0.05$) and reduction in diameter on second follow-up ($P < 0.05$). **Conclusion:** Pituitary hyperplasia secondary to primary hypothyroidism regresses with treatment within 6 weeks of initiation of treatment in its height however, it takes months for reduction in the diameter of the gland. We recommend repeat imaging in enlarged and homogenously enhancing pituitary gland in patients of primary hypothyroidism at 6 weeks of initiation of treatment to prove or disprove hyperplasia.

Key words: Hypothyroidism; magnetic resonance imaging; pituitary hyperplasia

Introduction

The occurrence of pituitary hyperplasia in primary or secondary hypothyroidism is well-documented.[1-4] However, this enlargement of the pituitary gland in hypothyroidism can also mimic pituitary adenoma.[5] Thus, it is important to understand this entity for proper diagnosis.

Current imaging tools like magnetic resonance imaging (MRI) can detect time bound radiological response during treatment of primary hypothyroidism.

Establishing gland size regression will differentiate hyperplasia from adenoma, as well as help guide treatment follow-up.

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Subjects and Methods

Seven consecutive patients (1 male and 6 females), age ranging from 13 to 42 years (mean 21) were included in the study presenting to our hospital over 18 months with profound hypothyroidism for 1st time with thyroid-stimulating hormone (TSH) >75. Exclusion criteria were known cases of hypothyroidism already on treatment and previous history of hypothyroidism but now not on treatment. All patients underwent routine blood investigations along with T3, T4, TSH, and thyroid peroxidase antibody (TPO) at baseline and at follow-up, TSH was done. MRI was done in 1.5 T (Wipro GE, Milwaukee, WI, USA) machine at first visit and at follow-up shown in Table 1. Contrast MRI was done at baseline with subsequent plain MRI on follow-up. Ethical approval was not obtained for the study as every patient had to undergo follow-up imaging at regular intervals for confirmation; this study was formulated and combined with it. Following magnetic resonance parameters were used for calculating the height and width of the pituitary gland (T1-weighted FSE coronal and sagittal TR740 TE18, ETL-4, bandwidth 20.83, FOV 18 × 16.2, slice thickness 3 mm with

0.3 mm interslice gap, NEX 4, frequency 384, phase 224, matrix 320 × 224) (T2-weighted coronal and sagittal TR 2940 TE112, ETL-22, bandwidth 20.83, FOV 18 × 16.2, slice thickness 3 mm with 0.3 mm interslice gap, NE × 4, frequency 384, phase 256, matrix 320 × 224). Meglumine gadopentetate - Magnevist (Bayer Zydus Pharma) contrast was used with 0.1 mmol/kg dose. Height was calculated in sagittal (T1-weighted) and coronal (T2-weighted) sequence, width in coronal sequence and anteroposterior diameter in sagittal sequence. Pituitary height and width were matched with baseline T3, T4, TSH and TPO antibodies, and TSH on follow-up.

Statistics

Paired Student's *t*-test was done for comparing the height and width of the gland at baseline and on follow-up and $P < 0.05$ was taken as significant.

Results

By 6 weeks, all patients showed clinical improvement with near normalization of thyroid function tests (TFTs) in most patients. The TSH normalization was well correlated with regression of the pituitary enlargement on imaging at <6 weeks as shown in Figure 1. The height of pituitary gland at baseline and at follow-up is given in Table 2. Table 3 shows baseline TFT. The height of the pituitary gland significantly reduced in first and second follow-up ($P < 0.05$) and reduction in diameter on second follow-up shown in Table 2. On follow-up, TSH returned to normal (not shown).

Discussion

Reactive enlargement of the pituitary gland due to hypothyroidism is a well-established entity and its regression following the treatment of thyroxine is also well-documented.[1,3,4] It is important to differentiate this entity from pituitary adenoma as both appear similar, but management differs.[5,6] This enlargement of the gland is due to decreased negative feedback causing increased release of thyrotrophin releasing and stimulating hormone leading to hyperplasia of thyrotroph cells in the pituitary gland, which regresses after replacement therapy.[3] There is also the correlation of volume of pituitary fossa and TSH.[7]

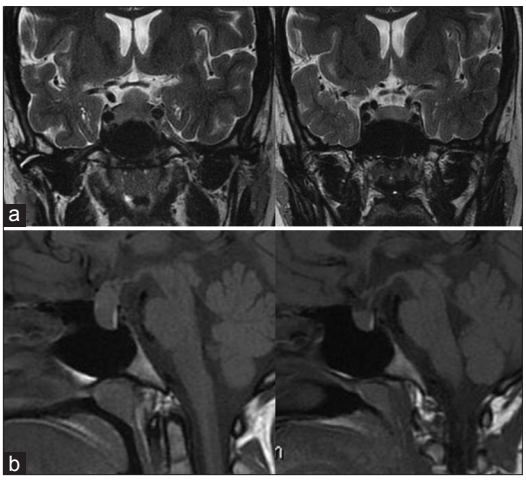

Figure 1: (a) Coronal T2-weighted and (b) sagittal T1-weighted images both pretreatment (left side images) and posttreatment (right side images) showing regression of the pituitary gland

In our current study, we intended to find time bound decrease in size of the pituitary gland after initiation of the treatment. We followed up the patients who had high TSH values at presentation with primary hypothyroidism and did baseline MRI and TFTs. All the patients had features suggestive of pituitary hyperplasia at presentation. Patients were followed up with MRI after initiation of treatment. Of all the 7 patients, 4 patients were imaged <6 weeks (2 patients at 1-week, 1 patient at 2 week, 2 patients at 4 weeks, and 1 patient at 6 weeks including follow-up) and 3 patients had imaging done after 6 weeks (16, 22, and 44 weeks) of initiation of treatment as shown in Table 1. The height of the pituitary gland was seen reduced in all the patients. The regression of the pituitary height was seen as early as 1-week and all the patients who were imaged before 6 weeks.

Sarlis *et al*. have shown regression of the pituitary hyperplasia at 1-week following treatment and other case report demonstrate regression at 12 weeks.[8,9] Thus, there is evidence of regression of pituitary hyperplasia as early as 1-week (including our 2 cases) but there are no studies, which demonstrate the exact time frame of regression. In our study, we have seen that the regression starts within 1-week of initiation of treatment and the gland normalizes by 6 weeks.

Table 1: Details of follow-up MRI

Age/sex	Follow up	Follow up in weeks
13/f	Baseline	
	1st	1
	2nd	6
21/f	Baseline	
	1st	4
	2nd	17
13/f	Baseline	
	1st	22
42/m	Baseline	
	1st	1
21/f	Baseline	
	1st	16
15/f	Baseline	
	1st	44
26/f	Baseline	
	1st	2
	2nd	4

Table 2: Pituitary gland measurements at baseline and follow up

	Baseline	1st follow up	2nd follow up	*P* value at 1st follow up	*P* value at 2nd follow up
Height of pituitary gland on Sagittal image (mm)	13.24±3.61	9.68±1.32	7.80±3.95	<0.05*	<0.05*
Anteroposterior diameter of pituitary gland on Sagittal image (mm)	10.14±1.41	9.24±1.52	9.05±1.48	NS	NS
Height of pituitary gland on coronal image (mm)	15.73±3.31	13.04±3.46	15.00±1.41	NS	NS
Diameter of pituitary gland on coronal image (mm)	14.47±4.14	11.83±3.99	7.25±4.59	NS	<0.05*

*Significant , NS – Not significant

Table 3: Baseline thyroid functions tests

Age	Sex	Weight (kgs)	TSH (0.4-4.0 µ IU/ml)	T3 (60-200 ng/dl)	T4 (4.5-12.0 µg/dl)	TPO antibodies (<34 IU/ml)
13	F	41	>75	51	1.1	356
21	F	52	>75	45	1.2	257
13	F	43	>75	34	1.29	153
42	M	68	>75	<40	<1.0	>600
21	F	56	>75	36	1.17	68
15	F	45	>75	48	1.34	27
26	F	54	>75	51	1.1	550

TSH – Thyroid stimulating hormone, TPO – Thyroid peroxidase antobody

In the study done by Shimono *et al*., the volume of pituitary gland shows a significant increase by 5 weeks after the patient becomes hypothyroid. This probably suggests that hyperplasia of thyrotroph cells in pituitary gland starts immediately after hypothyroid state and reaches its maximum by 5 weeks.[3]

Thus interestingly, pituitary gland increases in size by 5 weeks (after development of hypothyroid state) and decreases in size within 6 weeks after initiation of treatment in patients of primary hypothyroidism as shown in our study supported by previous case reports.[8,9]

Our study has important clinical implication. It shows that any patient with primary hypothyroidism can have enlarged pituitary gland, which suggests hyperplasia and this enlarged gland will decrease in size following treatment. However, if it does not decrease in size, then the possibility of adenoma should be considered requiring surgical treatment. Thus, in conclusion repeat imaging for enlarged pituitary gland should be done at 6 weeks after initiation of treatment in patients of primary hypothyroidism to prove or disprove hyperplasia and rule out adenoma.

The irregular follow-up is the only limiting factor for our study.

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