

## Utility of MRI in assessment of pituitary iron overload

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### Abstract

Beta thalassemia is highly prevalent in Pakistan with a carrier rate of 5-8%. The main complication of beta thalassemia major is iron overload, especially in reticuloendothelial system, heart, joints and endocrine glands. Pituitary siderosis leads to hypogonadotropic hypogonadism and growth hormone deficiency. Measures of plasma ferritin levels and hepatic iron level are used for assessing body iron overload but these are limited for various reasons particularly in case of pituitary siderosis. Magnetic Resonance Imaging (MRI) is a reliable, non invasive and easily available utility for assessing tissue siderosis. We assessed a 20 year old female beta thalassaemic diagnosed with hypogonadotropic hypogonadism and pituitary siderosis using routine spin echo (SE) T1 and T2 weighted sequences of MRI and special Gradient Recalled Echo (GRE) sequence of MRI. We found MRI signal intensity to be decreased on all three sequences but most so on GRE suggesting its greatest sensitivity to pituitary iron deposition. MRI signal hypo-intensity due to paramagnetic effects of iron has been validated for liver siderosis but is still under investigation for pituitary siderosis. Our findings suggest that MRI especially GRE sequence can be used in conjunction with laboratory data to evaluate pituitary siderosis and to prevent further pituitary dysfunction.

### Introduction

Beta thalassemia is highly prevalent in Pakistan, afflicting 5000 children each year in the country. This combined with frequent consanguineous marriages results in a carrier rate of 5-8%.<sup>1,2</sup> The main complication of  $\beta$  thalassemia major is iron overload. Excess iron is initially deposited in the reticuloendothelial system and then in all parenchymas especially the heart, liver and endocrine glands. Deposition of iron in the pituitary gland and the hypothalamus leads to hypogonadotropic hypogonadism and growth hormone deficiency.<sup>3</sup>

Accurate assessment of the body iron is essential for managing iron chelating therapy. Plasma ferritin provides indirect estimates, and its levels are also influenced by inflammation, infection, liver disease, haemolysis, ineffective erythropoiesis and ascorbate deficiency. Liver biopsy with chemical analysis of tissue iron content is the most direct and accurate means of assessing iron overload.

However the risk and the discomfort of the procedure, limit its acceptability. An international workshop conducted in April 2001 by the National Institute of Diabetes and Digestive and Kidney Diseases identified the pressing clinical need to develop a noninvasive means of measuring body iron overload. MRI was recognized as a widely available tool for this purpose. Recommendations were made for further research in improving the technique in this regard.<sup>4</sup>

The presenting case highlights the utility of MRI for evaluating pituitary iron overload.

### Case

A 20 year old Pakistani female, known case of beta thalassemia major presented for evaluation of primary amenorrhoea and delayed puberty. She had been receiving blood transfusions every 3 weeks alongwith 1.5 g desferoxamine sub-cutaneously 5 times a week, since the age of 9 months. There was no report of hepatic involvement, and she was an average student in school.

On examination her height was 147 cm (below 5th centile), weight was 34 kg (below 5th centile), blood pressure was 100/64 mmHg and pulse 112/minute. She had no breast development, and Tanner stage 1 axillary and

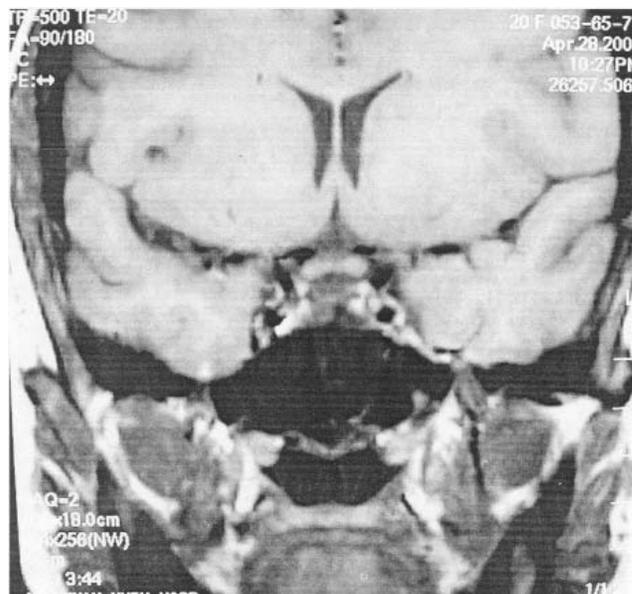


Figure 1. Coronal MRI sections through pituitary gland demonstrating hypointense signal from adenohypophysis (a) T1-weighted image (b) T2-weighted image (c) GRE T2\*-weighted image.



Figure 1b.

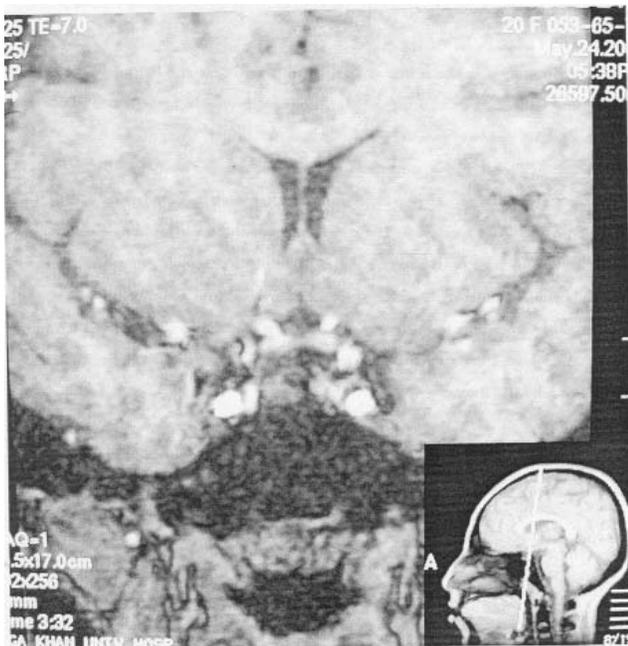


Figure 1c.

pubic hair. External genitalia were infantile. Rest of the examination was unremarkable.

Laboratory data was remarkable for elevated serum ferritin levels of 8948ng/ml and a decreased serum haemoglobin level of 8.9 g/dL (Hct 27.3%). An x-ray for bone age done according to Greulich-Pyle method showed significant delay, with a bone age of 13 years according to wrist and less than 16 years according to pelvis. Her FSH was 0.95 mIU/ml, LH was < 0.2 mIU/ml, and serum

estradiol was < 20 pg/ml. Her TSH, FT4, prolactin, serum calcium and phosphate were within normal ranges. Provocative testing for Growth Hormone with insulin induced hypoglycemia was normal. Other biochemical parameters included ALT of 64 IU/L, PT of 14.4 seconds (control 12.0 seconds) and aPTT of 47 seconds (control 30.0 seconds). A diagnosis of hypogonadotropic hypogonadism was made and a pituitary MRI requested for further evaluation.

MRI brain was performed using standard departmental protocol which included coronal and sagittal thin sections through pituitary gland. Dynamic contrast enhanced images of the pituitary gland were also obtained. Coronal T1-weighted images of the pituitary gland (Figure 1a) showed signal of the gland to be slightly hypointense than normal.<sup>5</sup> Coronal T2-weighted images also showed lower signal intensity within the gland (Figure 1b). The gland was normal in size and no focal mass was seen. Posterior pituitary also showed normal signal on MRI. No abnormal signal was detected on post contrast images.

In view of history, iron overload in the pituitary gland was suspected. Further images using coronal gradient recalled echo (GRE) were obtained. These images showed a further decrease in the signal intensity of the anterior pituitary gland confirming our previous findings (Figure 1c).

## Discussion

Use of non invasive means of assessing tissue iron overload has received considerable attention in literature. Two such techniques are magnetic resonance imaging (MRI) and biomagnetic susceptometry. Without going into details, the latter technique has been validated and calibrated to provide accurate non invasive means of measuring tissue iron stores. But its complexity, cost and unavailability has restricted its clinical application.<sup>4</sup>

MRI on the other hand is easily accessible and available. A decrease in signal intensity, due to magnetic field inhomogeneities created by iron<sup>6</sup>, is seen in tissues with iron overload. Clinical application of various MRI sequences such as spin echo (SE) and gradient recall echo (GRE), and parameters (T1, T2, signal intensity ratios) for assessing tissue siderosis are gradually being established. These properties of the MRI have found usefulness and predictability in assessing iron stores in the liver.<sup>7</sup> Its role for the same is under investigation for the pituitary and other tissues. As with other tissues, the adenohypophysis with iron overload shows low signal intensity. The normal signal of the adenohypophysis is isointense to brain both on SE T1 and T2 weighted images while that of the neurohypophysis is hyperintense on T1 weighted images.<sup>5</sup>

In the present case, the signal intensity of the gland was slightly reduced on both T1 and T2 weighted SE sequences. For confirmation, GRE T2\* weighted sequence was performed, which showed marked decrease in the signal intensity of the pituitary gland.

In fact, among the various imaging techniques that have been investigated, the best predictor of adenohypophyseal iron overload has been the signal intensity reduction in the anterior lobe of the pituitary gland on GRE T2\*-weighted images.<sup>8</sup> The work by Argyropoulou's group and another group reported GRE T2\* weighted images to be the most sensitive sequence for establishing iron overload in the pituitary gland.<sup>8,9</sup>

Pituitary involvement results in hypogonadotropic hypogonadism, as it did in this patient with B thalassemia.<sup>3</sup> Thyroid, adrenals and gonads are also affected in these patients; however this patient was spared. Cytotoxic effect of iron overload is considered to be dose dependent and in the case of hypothalamic-pituitary axis an initial reversible and a later irreversible phase of pituitary dysfunction has been suggested.<sup>10</sup> Early detection of pituitary iron overload may be useful in preventing irreversible loss of pituitary function or in planning of future treatment.

### Conclusion

Pituitary siderosis in patients with thalassemia is not uncommon. However its development, onset and progression do not correlate with hepatic iron overload.

MRI of the pituitary with GRE T2\* sequence provides useful information regarding pituitary siderosis and can be used in conjunction with laboratory data to prevent development of further pituitary dysfunction.

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