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CORRELATION BETWEEN PITUITARY MRI AND HYPOGONADOTROPIC HYPOGONADISM IN THALASSEMIA

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- **ABSTRACT**

Background: The thalassemias are among the most prevalent genetic diseases worldwide. There is a high incidence of thalassemia in Iran; one of the countries located on the so-called "thalassemia belt". Repeated blood transfusion in thalassemia may cause iron deposition in many tissues including endocrine organs.
Objective: To study the pituitary changes in thalassemia detected by MRI in correlation with hormonal changes.
Methods: Thirty-six patients with thalassemia major with mean age of 17.8?3 years (17 male and 19 female) were enrolled in this study. The control group comprised of 20 (10 male and 10 female) age- and sex-matched individuals. All of the patients and controls underwent clinical examination, hormonal study and MRI of the pituitary gland.
Results: Forty-seven percent of the girls and 53% of the boys with thalassemia major had small size pituitary gland. Fifty-three percent of the boys and 58% of the girls patients had low pituitary signal in T2 weighted image.Seventy -eight per cent of the patients had hypogonadotropic hypogonadism (H.H). There was a statistically significant correlation between low hormonal level (H.H) and both low pituitary signal ($P<0.012$) and small pituitary size ($P<0.04$).

Conclusion: A significant percent of thalassemic patients show small size and hyposignal pituitary gland in sagittal and coronal T_2 weighted MRI images which have a statically significant correlation with hormonal deficiency and pituitary dysfunction.

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Keywords: Thalassemia ? MRI ? pituitary gland ? hypogonadism, hypogonadotropic

Introduction

Thalassemia is one of the major health care problems in Iran.[1] This genetically inherited disease can involve many organs. Generally, the signs and symptoms are secondary to hemolysis and iron deposition. Endocrine complications of thalassemia, especially hypogonadism are the end results of iron deposition either in the pituitary gland or in the sex organs.[1]

In one study from Italy, the incidence of hypogonadism between ages of 12 and 18 years was given at 56% in males and 27% in females.[2] Another study by Danesi et al. on 12 thalassemic patients revealed high incidence of hypogonadism (8/12). In those cases low gonadotropin levels and their unresponsiveness to gonadotropin releasing hormone (GnRH) were felt to be due to a hypothalamic or pituitary damage.[3,4] Tolis et al. have shown that primary and secondary amenorrhea in thalassemia major is due primarily to pituitary hemosiderosis since ovulation can be achieved with the use of exogenous gonadotropin, provided that the ovaries are free from siderosis.[5] Jensen et al reported poor spermatogram in eight patients secondary to pituitary siderosis, which was felt to be due to zinc deficiency on account of desferrioxamine use.[6,7] In this study, we examined MRI of the brain and pituitary gland of the patients with thalassemia major in order to evaluate the pituitary gland and to determine signality and size of the gland.

Patients and Methods

Thirty six patients between the ages of 15 and 25 years (mean: 17.8?3 years) with thalassemia major were randomly selected. A control group of 20 age- and sex- matched individuals (10 male and 10

female) with no abnormal sign and symptom related to secondary sex characteristics served as control. These cases were also selected randomly with no regards to their secondary sex characteristics, hormonal study, frequency of blood transfusion or hemoglobin level. After obtaining informed consent, all of the patients and controls underwent MRI of the pituitary gland. MR images were obtained by a 0.3 Tesla MR unit (Hitachi 7000AD) using sagittal and coronal T1 (TR: 500, TE: 20), and T2 (TR: 4000, TE: 117) parameters. Blood was taken from the patients and frozen after serum separation to be examined under single IRMA method for gonadotropin measurement. Male patients with low gonadotropin titer had hypogonadotropic hypogonadism when they had low testosterone level.

Females with low or normal gonadotropin when combined with absence of menstruation were also considered to have hypogonadotropic hypogonadism.

Results

Table 1 shows the range of diameters and volumes of the pituitary gland in the control group. The volume of the pituitary gland was calculated using the following formula: AP diameter ? transverse diameter ? height (cm) ? 0.5. Accordingly, a range of volumes (0.175 to 0.505 cm^3) was obtained and volumes below 0.175 cm^3 were considered to be small.

We measured pituitary signal intensity by a computerized measurement of the region of interest (ROI). In this method, air has a zero signal in T2 and clear water has signal of 1200.

In the control group, the range of pituitary signal was 408.2 to 585. Hence, we found two ranges of pituitary signal in our patients Normosignal group with a range of 398 to 551 and hyposignal group had a range of 196 to 302. There was a distinct gap between the two groups.

We found no thalassemic patient with large pituitary gland and also none with empty sella. According to these measurements (Table 2) 50% and 55.5% of the patients had either small size pituitary or low pituitary signal intensity in T2 weighted images, respectively (Fig 1). Seventy-eight per cent of the patients had H.H.

The pituitary signal intensity was the same as that of the white matter in T1 weighted images, as anticipated. The mean ? SD pituitary volume of the patients with H.H (0.26 cm^3 ? 0.07) was significantly ($P< 0.04$) smaller than those of non-H.H patients (0.35 cm^3 ? 0.09). The pituitary signal intensity of the patients with H.H was also significantly lower ($P<0.012$) than those of non-H.H patients. However, there was no significant difference between female and male patients regarding size and signal of the pituitary gland.

Discussion

Patients with thalassemia major often have delayed puberty and growth retardation the etiology of which is not fully understood. Kwan et al. have reported a rate of respective 75% and 62% of growth retardation in thalassemic girls and boys in Hong Kong.[8] Wang et al. believe that the most possible site of damage might be a pituitary gland which does not respond to gonadotropin released hormone (GnRH).[9] Valenti et al suggested that the delayed puberty in thalassemia major might be characterized by a neuroendocrine dysfunction secondary to an impaired hypothalamic GnRH secretion, inadequate for proper pituitary stimulation. They felt that pulsatile GnRH treatment would partially reestablish the correct pituitary-gonadal function.[10] There are also reports indicating hemosiderin deposition in the

ovaries and endometrium.[11] Therefore, delayed puberty in thalassemia-major patients is apparently a multifactorial phenomenon. Direct evaluation of the pituitary gland, by imaging techniques, therefore, was deemed appropriate to shed light on this controversial issue. We used MRI with T2WI to assess thalassemia-induced changes of the pituitary gland and found that pituitary size and low T2 signal of the gland correlated well with low gonadotropin titer in most of the patients.

Atrophy of the gland can exaggerate hyposignality in T2 weighted images probably because of the increased ratio of iron deposition in relation to the volume of the gland. Thus, presence of normal signal intensity in 2 patients with normal size pituitary could be explained on the basis of normal bulk and cellularity of the pituitary gland versus the extent of iron deposition.

The normal pituitary gland yields a homogeneous brain-isointense signal in most of the pulse sequences which is best seen in sagittal and coronal images.[12] Decreased signal in T2-weighted image(T2 WI) is similar to basal ganglia which normally accumulate iron in aging. This signal loss probably arises from proton diffusion through local areas of magnetic inhomogeneity due to iron containing moiety.[13]

In a study from Hong Kong, Ky L et al.[14] evaluated pituitary gland and hypothalamus of a group of thalassemic children by MRI and found that there was no apparent characteristic MRI appearances of iron deposition in hypothalamus or pituitary gland.

There are, however, 3 differences between that study and ours:

1- MRI was performed with gradient echo sequence (TR: 400 msec and TE20 msec with flip angle of 15 degrees) which is less sensitive than T_2 weighted images for detection of iron deposition.

2- All of the patients had good medical care and in some the treatment has been started very early in childhood.[14]

3- The mean age of those patients was lower than ours.

In the present study, 36% of the girls and 12% of the boys had simultaneous normal secondary sex characteristics and low gonadotropin titers. This might be due to the fact that some patients develop secondary failure of the pituitary gland after puberty. Moreover, since the age of puberty is lower in girls than boys, secondary failure can have occurred during the time interval between the onset of puberty in the two sexes. Consequently, there are more girls who have normal secondary sex characteristics and low gonadotropin titer simultaneously.

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