

DELAYED ADRENACHE IN THALASSAEMIA: A CASE SERIES

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ABSTRACT

Thalassemia major is a transfusion dependent genetically inherited haematological disorder that could lead to multiple endocrinopathies due to the chronic hypoxia and iron overload that is associated with this condition. Delayed adrenarche and thalassemia major is not commonly described. However, when it occurs, it is a condition of significant concern among affected individuals. We observed a significant delay in adrenarche compared to other secondary sexual characteristic changes that occurs during puberty among adolescents with thalassemia major. Coinciding with the clinical picture, dissociation in cortisol and adrenal androgen secretion was also noted. Chronic hypoxia, low body mass index and zinc deficiency associated with thalassemia major are thought to be the possible explanation for these observations. These observations raise the need for proper studies to identify the aetiology and the possible mechanisms of treating this clinical entity.

Running title: Delayed adrenarche in thalassaemia

Keywords: Thalassaemia, iron overload, delayed adrenarche, delayed pubarche

INTRODUCTION

Thalassemia major is a transfusion dependent blood disorder, where inadequate transfusion and oxygenation can affect all the systems of the body. Regular blood transfusions significantly increase life expectancy and quality of life of these patients. However, the iron overload associated with the regular transfusion has deleterious effects to most of the internal organs including endocrine glands. Studies have revealed higher prevalence of short stature, delayed puberty, hypothyroidism, retarded bone age, hypoparathyroidism and diabetes among thalassemia patients who are on regular transfusions (1,2). In addition to the well-known endocrinopathies, delayed adrenarche is also another clinical problem that occurs due to the effects of chronic iron overload and hypoxia among transfused patients with thalassemia major.

CASE SERIES

Here we describe five patients with thalassemia major who were referred to

our tertiary care endocrine center for annual endocrine assessment within a period of six months. Four of them were females. Their ages were ranging from 14 to 20 and their diagnosis of thalassemia major has been confirmed during the first year of life. All of them were transfusion dependent. Despite regular blood transfusions and iron chelation, their mean haemoglobin concentrations were ranging from 6 g/dl to 8 g/dl and the ferritin levels were ranging from 580ng/ml to 11,000 ng/ml. One girl who had reactions to several types of chelation methods had remarkably high serum ferritin (11,000ng/ml) levels and she also had primary hypothyroidism and diabetes mellitus secondary to pancreatic failure from the age of 13.

All of the patients were clinically eutypoid and none of them had symptoms suggestive of hypocortisolism. The body mass index (BMI) was below 18 in all the patients. None of them had goiters and their blood pressure was normal without a postural drop. All had normal thyroid function tests including the treated patient. Their serum calcium as well as the fasting blood glucose levels were

normal. Their 9 am serum cortisol levels ranged from 284 nmol/dl to 376 nmol/dl.

Puberty was delayed in all 5 patients. Interestingly, all the girls had low tanner staging for pubic hair when compared to breast tanner stages, indicating significant delay in pubarche than thelarche. None of the girls had attained menarche. The boy also had a low tanner staging for pubic hair when compared with the phallus size and the testicular volume (Table 1) Dehydroepiandrosterone sulphate (DHEAS) levels were low or were in the lower margin of the reference range for the pubertal stage in all patients (Table 2). All of them had delayed bone age when compared to chronological age.

DISCUSSION

Adrenarche refers to the onset of dehydroepiandrosterone (DHEA) and DHEA-sulphate (DHEAS) production from the adrenal zona reticularis and it is usually detected around 6 years of age. This elevation of adrenal androgen secretion leads



Table 1: Observed pubertal clinical parameters

Patient number	Gender	Chronological age (years)	Tanner stage (breast / phallus)	Tanner stage (pubic hair)	Testicular volume (ml)
1	Female	15	Stage 4	Stage 2	
2	Female	14	Stage 2	Stage 1	
3	Female	20	Stage 4	Stage 2	
4	Female	14	Stage 4	Stage 2	
5	Male	14	Stage 4	Stage 2	6ml

to pubarche (the development of axillary and pubic hair), which usually occurs at the age of about 8 in both girls and boys and it is unrelated to the pubertal maturation of the hypothalamic-pituitary-gonadal axis. Delay in pubarche can cause significant psychological distress and low self-esteem and it is a condition that has been well-documented in patients with transfusion dependent Thalassemia. However, the reason for delayed adrenarche in thalassemia is poorly understood.

The dissociation of adrenal cortisol and androgen (DHEAS and DHEA) production has been demonstrated in many patients with thalassemia. A series of thalassemic patients, who were treated with multiple transfusion and chelation therapy suggested a dissociation of adrenal cortisol and androgen secretion (Low basal DHEAS, DHEA levels compared to controls with normal cortisol response to ACTH infusion (3). Another small study done on forty-five beta-thalassemia major patients, ages ranged between 12 and 20 years, has shown a reduction in adrenal androgen production with the advancement of

the puberty (4). In our case series, none of our patients had symptoms and signs of hypocortisolism and their 9 am cortisol levels were not suggestive of adrenal insufficiency. However, ACTH stimulated cortisol levels could not be assessed due to limited availability of synacthen. Similar to the previous studies, all our patients had low DHEAS levels, which probably is one of the explanations for the delayed adrenarche hence pubarche in our patients.

Nutritional status of an individual may play an important role in the process of adrenarche. Lower body mass index around puberty, a common finding in transfusion dependent thalassemic patients, could be another important determinant of adrenarche in these patients. A small study done with thalassemic patients has described a relationship between BMI and adrenarche (5). In our case series, all the patients had BMI below 18 and it is possible that their poor nutritional status also could have had some effect on the initiation of adrenarche in these patients.

Apart from the hormonal imbalance, several none hormonal factors are also thought to be contributing to the devel-

-opment of this clinical problem. Chronic hypoxia is considered as one of the main such contributors. An Indian study suggests, chronic hypoxia as one of the main causes of delay in development of secondary sex characteristics in patients with thalassemia (6). Zinc is another important micro-nutrient that is essential for normal hair growth (7) and it is considered as one of the commonest causes of hair loss (8). Zinc deficiency is a common among thalassemic patients (9, 10). The chelation of Zinc together with iron due to the use of iron chelators and chronic haemolysis that causes Zinc release are thought to be responsible for zinc deficiency among these patients (9, 11). Although it's deficiency could lead to reduced hair growth and delayed pubarche in these individuals, a direct relationship between zinc deficiency and delayed pubarche has not been properly evaluated.

CONCLUSIONS

Delayed adrenarche is an uncommon problem documented among patients with transfusion dependent

Table 2: Observed biochemical parameters

Patient	FSH (miu/mL)	LH (miu/mL)	Estradiol (pg/dL)	Testosterone	9am cortisol (nmol/dL)	DHEAS (umol/L)
1	8.93	2.56	95		284	0.755 (0.9-13.1)
2	1.97	0.664	10		267	0.749 (0.9-13.1)
3	0.66	0.216	5		356	1.052 (0.9-13.1)
4	5.61	1.53	<6.36		292	1.1 (0.9-13.1)
5	0.78	1.79	-	8.98	289	1.84 (1.8-15.1)

Thalasaemia. It is a problem of significant concern to the affected patients and their parents. Although the exact pathophysiological process of this problem is not well understood, reduction in adrenal androgen production due to chronic hypoxia, under-nutrition and zinc deficiency are thought to be mainly responsible. There is very limited data available regarding this clinical problems and proper studies are needed in order to identify the pathophysiology and possible treatment strategies to overcome this clinical problem.

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