

# Adrenal Insufficiency in Patients with Beta-Thalassemia Major in the Southeast of Iran

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## Letter to Editor

Beta-thalassemia is a hereditary blood disorder in which the synthesis of the hemoglobin beta chain is halted or severely diminished, chiefly due to genetic mutations. Today, the province of Sistan and Baluchistan has the highest disease prevalence in southeast Iran, with about 3,000 thalassemia patients<sup>1</sup>. Adrenal dysfunction has been reported to arise in patients with beta-thalassemia major due to iron deposition in adrenal glands<sup>2</sup>. We aimed to determine the prevalence of adrenal insufficiency in children with  $\beta$ -thalassemia major who had been referred to Ali Asghar Hospital, Zahedan. The Local Ethics committee of Zahedan University of Medical Sciences approved the study's design (IR.ZAUMS.REC.1396.239).

Fifty patients (33 female and 17 male) with a mean of  $22.34 \pm 5.60$  with beta-thalassemia major were selected for the study. Before the scheduled blood transfusion at 8 a.m., 5 mL of blood was collected from each patient. Upon completing blood transfusion, the patients were intravenously injected with 250  $\mu$ g of cosyntropin to stimulate cortisol

release. Then, two consecutive series of blood samples were collected 30 and 60 minutes after the injection. The samples were sent to the hospital laboratory to evaluate total and post-stimulation serum cortisol levels.

As shown in Table 1, 30 minutes after the administration of cosyntropin, 100% of patients had experienced a significant rise in their basal cortisol level, and either had normal or higher than normal levels of cortisol in their blood ( $p < 0.001$ ). However, 60 minutes after the injection of cosyntropin, 100% of patients had cortisol levels above the normal range ( $p < 0.001$ ). Besides, of the 18 patients aged 18 and below, only 3 subjects (16.66%) had insufficient basal cortisol levels, whereas 15 (83.83%) had normal basal cortisol levels ( $p < 0.001$ ). We found that 60 minutes after the cosyntropin injection, all patients in both age groups had cortisol levels above the normal range ( $p < 0.001$ ). The resulting increase in the serum cortisol level of the 5 patients with subnormal baseline cortisol 30 minutes after

stimulation with cosyntropin indicated secondary adrenal insufficiency in these patients.

**Table 1:** Distribution of gender groups at cortisol levels at different times after injection in patients with thalassemia major

Time after injection	Cortisol level	Patients, n (%)			P
		Male	Female	Total	
8 a.m. (baseline)	Insufficient	2(4)	3(6)	5(10)	<0.001
	Normal	15(30)	30(60)	45(90)	
	Total	17(34)	33(66)	50(100)	
30 minutes	Insufficient	0(0)	0(0)	0(0)	<0.001
	Normal	17(34)	33(66)	50(100)	
	Total	17(34)	33(66)	50(100)	
60 minutes	Insufficient	0(0)	0(0)	0(0)	<0.001
	Normal	17(34)	33(66)	50(100)	
	Total	17(34)	33(66)	50(100)	

The results of this study favored the sensitivity of the low-dose ACTH stimulation test in the examination of the hypothalamic-pituitary-adrenal axis in patients with secondary adrenal insufficiency over the high-dose test. It concluded that in patients with a normal baseline cortisol level, the low-dose test could efficiently detect hidden secondary adrenal insufficiency<sup>3</sup>.

In 2017, 726 thalassemia patients aged between 2.5 and 80 were registered at 12 thalassaemic centers in 9 different countries, where 522 were registered from Qatar, Iran, Oman, Cyprus, and Jordan. In their population, the most common complications were osteopenia and osteoporosis, which accounted for 22.3 percent, hypogonadism, which accounted for 10.1 percent, and primary hypothyroidism, which accounted for 5.5 percent of the enrolled subjects. In the subpopulation multivariate analysis, older age was found to be a risk factor for osteoporosis (Odds ratio: 7.870, 95 percent confidence interval (CI): 4.729-13.099, P 0.001), hypogonadism (Odds ratio: 6.310, 95 percent confidence interval (CI): 2.944-13.521, P 0.001), and non-insulin-dependent diabetes mellitus (NIDDM). These findings suggest

the relatively high prevalence of endocrine complications in beta-thalassemia patients<sup>4</sup>.

Another study in 2015 sought to evaluate possible endocrine disorders in 150 patients with beta-thalassemia major aged 15 to 22. The results of this study revealed the prevalence of primary hypothyroidism (6%), hypoparathyroidism (3.7%), type 1 diabetes (3.7%), and adrenal insufficiency (only one patient) in this population<sup>5</sup>. Our study, however, only investigated the presence of adrenal insufficiency among a specifically selected population of beta-thalassemia major patients and revealed a 10 percent prevalence of this endocrine disorder.

Our study had limitations. First of all, a small population was included. Second, as the half-life of cortisol is twice as long as this duration, it would be helpful if this study also considered the individual differences in the clearance of cortisol from the bloodstream. Since stress, body mass index, corticosteroid-binding globulin, and hypothalamic-pituitary-adrenal axis can affect the adrenal response to cosyntropin; these factors should be taken into account in the future studies.

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