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(CASE REPORT)

Endocrine complications of beta-thalassemia major: Primary amenorrhea as a revealing feature of hypogonadotropic hypogonadism

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Abstract

Beta-thalassemia major is a hereditary hemoglobinopathy requiring lifelong blood transfusions, leading to chronic iron overload responsible for multiorgan endocrine complications, of which hypogonadism is the most frequent. We report the case of a 22-year-10-month-old female patient, followed for β-thalassemia major since the age of 3, presenting with primary amenorrhea. Clinical examination revealed late-onset breast development at Tanner stage II and pubic hair at Tanner stageIV. Hormonal workup confirmed isolated hypogonadotropic hypogonadism, with the following results: estradiol<24pg/mL, follicle-stimulating hormone 1.14 uIU/mL (ref: 3.03–8.08), luteinizing hormone 0.2uIU/mL (ref:2.39–6.6), prolactin 9.8ng/ml and serum ferritin at 7288µg/L sixty times above upper limit on deferiprone 500mg, three tablets three times daily. Pituitary MRI demonstrated an age-appropriate gland with T2*-weighted-hypo-intensity consistent with pituitary siderosis, providing objective imaging evidence of iron deposition at the gonadotroph level as the underlying mechanism of central hypogonadism. Bone assessment by bone densitometry revealed osteoporosis at multiple sites. Workup for other iron overload-related endocrinopathies returned within normal limits. The patient was initiated on transdermal-17beta-estradiol at progressively increasing doses starting at0.25mg/day.

The pedagogical originality of this case report lies in the association between primary amenorrhea — reflecting gonadotroph damage early enough to prevent pubertal completion — and pituitary siderosis directly visualized on MRI, offering a didactically valuable illustration of the causal link between chronic iron overload and central hypogonadotropic hypogonadism. This case underscores the importance of systematic and early endocrine screening in transfusion-dependent thalassemia patients, and highlights the need for prompt hormone replacement therapy initiation and optimized iron chelation to prevent irreversible endocrine complications.

Keywords: Beta-thalassemia major; Primary amenorrhea; Hypogonadotropic hypogonadism; Pituitary iron overload

1. Introduction

Beta-thalassemia major is a hereditary hemoglobinopathy requiring lifelong repeated blood transfusions, leading to iron overload responsible for multiorgan complications, particularly endocrine complications. Hypogonadism is the most frequently reported endocrine complication. Hypogonadotropic hypogonadism is the most common form, secondary to iron infiltration of the hypothalamo-pituitary axis, and classically presents as delayed puberty or primary amenorrhea in women. Pituitary T2*-weighted MRI has emerged as a valuable tool for the non-invasive demonstration of iron deposition at the gonadotroph level, providing a direct imaging correlate of the underlying mechanism. The prevalence and severity of hypogonadism in thalassemia major vary across studies, depending on the age group studied,

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the thalassemia genotype, the extent of transfusions, the age at treatment initiation, and the type of iron chelation therapy [1]. Differences are also observed between individuals born before and after the introduction of iron chelation therapy [2].

We report an illustrative case of primary amenorrhea revealing hypogonadotropic hypogonadism in a young woman with beta-thalassemia major, in whom pituitary siderosis was objectified on T2*-weighted MRI.

2. Case Report

We report the case of a 22-year-10-month-old female patient, the eldest of two siblings, born of a first-degree consanguineous marriage. She has been followed since the age of 3 years for beta-thalassemia major requiring regular monthly blood transfusions (1 to 3 packed red blood cell units), combined with folic acid supplementation and iron chelation therapy with deferiprone since the age of 12. Currently on deferiprone 500 mg, three tablets three times daily with good treatment adherence, with periods of combination chelation therapy using deferiprone and deferasirox during follow-up. The clinical course was marked by the development of severe bilateral coxarthrosis, requiring bilateral total hip replacement.

The patient was referred to our department for the investigation of primary amenorrhea. On admission, she was in good condition with stable hemodynamic parameters. Physical examination revealed a height of -2 SD from reference growth curves, within the corridor of her target height, a weight of -1 SD, and a body mass index within normal limits. Somatic examination revealed no dysmorphic features.

Regarding pubertal development, breast development at Tanner stage II was noted, with a late onset at the age of 19 years, along with pubic hair at Tanner stage IV, with no anomaly of sexual differentiation (Prader stage 0). The rest of the physical examination revealed no further abnormalities.

Hormonal workup confirmed isolated hypogonadotropic hypogonadism, with the following results: estradiol < 24 pg/mL, follicle-stimulating hormone 1.14 uIU/mL (ref: 3.03–8.08), luteinizing hormone 0.2 uIU/mL (ref: 2.39–6.6), prolactin 9.8 ng/ml and serum ferritin at 7288 µg/L sixty times above upper limit (Table 1).

Pituitary MRI showed a pituitary gland of age-appropriate size (5 mm), associated with a T2*-weighted hypointense signal consistent with pituitary iron overload (Figure 1-2). Pelvic MRI showed an anteverted anteflexed uterus of normal size, with a thin and regular endometrium, and no anomaly of the cervix or vagina. The ovaries were slightly reduced in size, measuring 11.5 × 32 mm in axial diameters on the right and 26 × 13 mm on the left, with a pauci-follicular appearance.

Hyperprolactinemia was excluded based on a normal prolactin level. Müllerian anomalies were ruled out by pelvic MRI.

The assessment of hypogonadism-related complications revealed osteoporosis affecting the lumbar spine, proximal femur, and distal radius, as evaluated by bone densitometry, with T-scores of −3,1 at the lumbar spine, −4,8 at the total hip, and −4,5 at the distal radius, currently managed in collaboration with the rheumatology team. Vitamin D deficiency was identified and supplementation was initiated.

In this context, iron overload-related target organ involvement was investigated, including secondary diabetes, hypothyroidism, and hypoparathyroidism; all corresponding workups returned within normal limits. Transthoracic echocardiography showed no abnormalities and abdominal ultrasound revealed cholelithiasis.

Pre-treatment laboratory investigations were within normal limits, except for mildly to moderately elevated liver enzymes, with AST at 64 UI/L (1.8× ULN) and ALT at 98 UI/L (2.8× ULN). A repeat liver function test confirmed stable values, with no significant progression. This hepatic injury likely reflects iron overload-related hepatic damage secondary to chronic transfusions. Immunological workup found no evidence of autoimmune hepatopathy, with all specific hepatic antibodies returning negative. A hepatic MRI with intrahepatic iron quantification has been requested but not yet performed.

The patient was initiated on substitutive estrogen therapy with transdermal 17β-estradiol at progressively increasing doses, starting at 0.25 mg/day and subsequently increased to the current dose of 0.5 mg/day, with sequential addition of progesterone planned. The transdermal route was deliberately chosen over oral formulations, as it bypasses hepatic first-pass metabolism, thereby avoiding hepatobiliary adverse effects, a particularly relevant consideration in the context of pre-existing liver enzyme elevation. This therapeutic decision was made in close collaboration with the

gastrohepatology team. A close multidisciplinary follow-up has been established, including regular clinical assessment, hormonal monitoring, liver function tests, and bone mineral density evaluation.

Table 1 Serial hormonal workup results

	10/11/2024	**21/12/2024**	**25/01/2025**
Estradiol (ref: 18–147 pg/mL)	< 24 pg/mL	< 24 pg/mL	< 24 pg/mL
FSH (ref: 2.9–12 uIU/mL)	1.40 uIU/mL	0.95 uIU/mL	1.46 uIU/mL
LH (ref: 2.39–6.60 uIU/mL)	0.26 uIU/mL	0.19 uIU/mL	0.20 uIU/mL
Prolactin	9.8 ng/mL	—	—
Cortisol	19 µg/dL	—	—
TSH (ref: 0.35–4.94 uIU/mL)	1.338 uIU/mL	—	—
Free T4 (ref: 0.7–1.48 ng/L)	0.83 ng/L	—	—
Serum ferritin (ref: 100-120) **Under ongoing iron chelation therapy with deferiprone 500 mg, 3 tablets three times daily*	7288 µg/L	5974 µg/L	5087 µg/L
Calcium	93 mg/l	—	—
Albumin	40 mg/l	—	—
Phosphorus	49 mg/l	—	—
Vitamin D	16 ng/ml	—	—

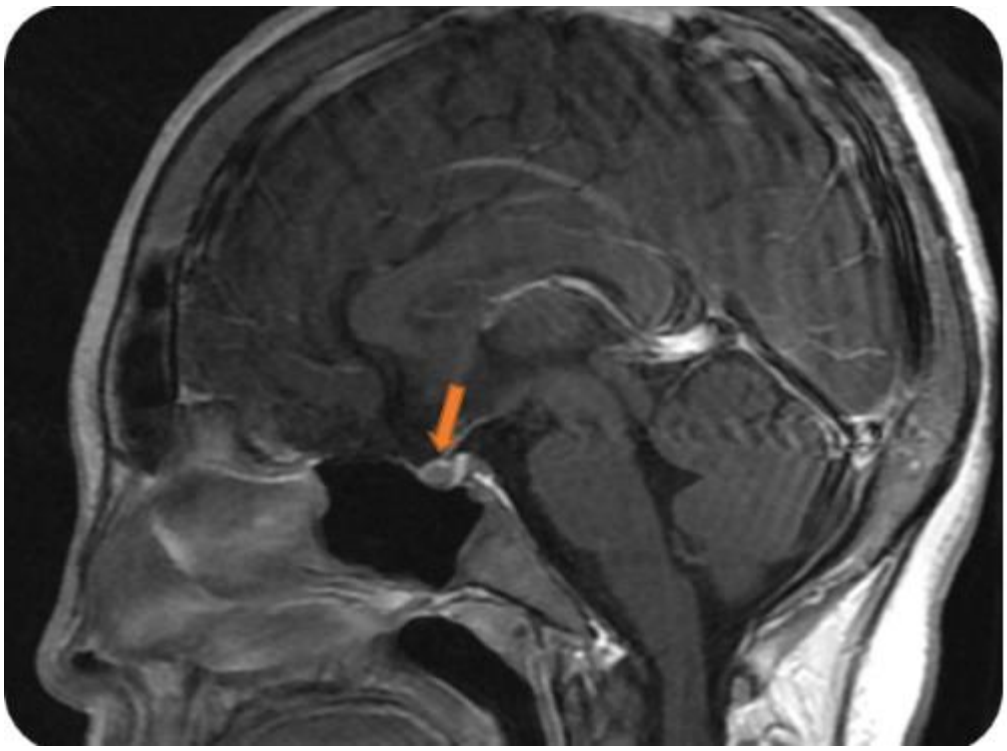

Figure 1 Gadolinium-enhanced T1-weighted sagittal section: Age-appropriate pituitary gland size, with no structural abnormality (Orange arrow)

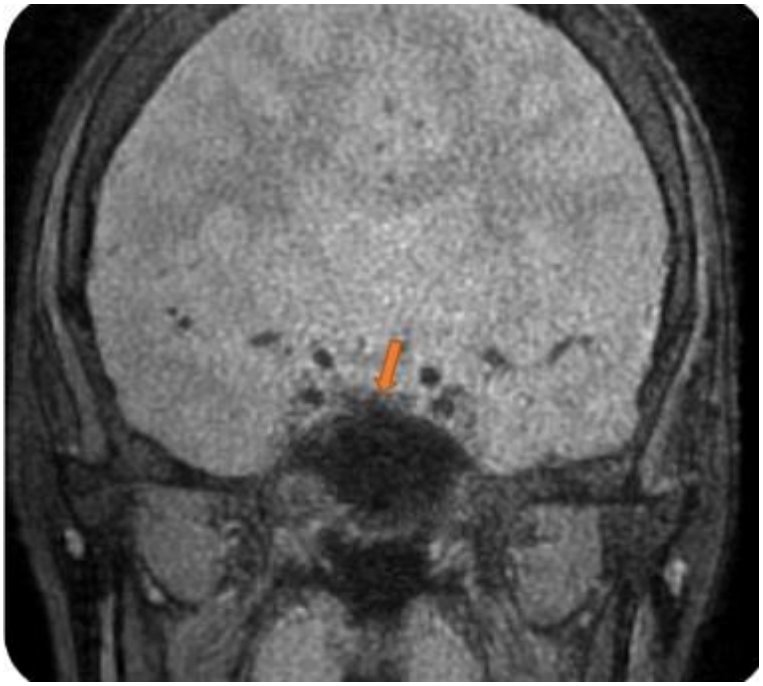

Figure 2 T2* weighted coronal section: Marked hypo-intensity of the pituitary gland (Orange arrow)

3. Discussion

Hypogonadism is the most common endocrine complication in patients with thalassemia major, with an estimated prevalence of 70 to 80% [3]. This condition is primarily related to chronic iron overload secondary to repeated transfusions, leading to iron deposits in various organs, particularly within the hypothalamo-pituitary-gonadal axis, as illustrated by the pituitary siderosis demonstrated on T2* weighted MRI in our patient.

From a pathophysiological standpoint, the absence of an iron excretion mechanism leads to progressive accumulation of circulating iron. When the transferrin binding capacity is exceeded, a highly toxic non-transferrin-bound iron fraction appears, generating oxidative stress and cellular damage [4]. Pituitary gonadotroph cells are particularly sensitive to this toxicity — due to their expression of transferrin receptors — explaining the predominance of hypogonadotropic hypogonadism in this population [5]. This mechanism is consistent with our patient's hormonal profile, which demonstrated markedly suppressed LH and FSH levels in the context of a serum ferritin sixty times above the upper limit of normal, confirming central gonadotroph failure.

Pituitary involvement begins early, sometimes within the first decade of life, but remains clinically silent for a long time before manifesting clinically at pubertal age [6]. The gonadotropin reserve decreases significantly, with markedly reduced spontaneous pulsatile gonadotropin activity, which may lead to irreversible damage to the hypothalamo-pituitary-gonadal axis [3]. In our patient, the absence of spontaneous pubertal progression until the age of 19 years, culminating in primary amenorrhea, reflects this silent and progressive pituitary damage.

Furthermore, additional mechanisms involving adipose tissue and leptin have been described. Iron overload impairs adipocyte function and decreases circulating leptin levels, a hormone essential for the activation of the hypothalamo-pituitary-gonadal axis via kisspeptin neurons [7]. This hypoleptinemia may contribute to the pubertal delay observed in these patients [8].

Direct peripheral gonadal involvement appears to be less frequent. In women, the ovarian reserve is relatively preserved [9]. In men, testicular histological abnormalities have been described, including interstitial fibrosis and rarefaction of Leydig cells [10].

Clinically, hypogonadism manifests as delayed puberty, arrested puberty, or established hypogonadism. Nevertheless, fertility remains possible, particularly in well-transfused and adequately chelated patients. Several studies have reported spontaneous pregnancies or pregnancies following ovulation induction, confirming the often-functional nature of gonadal involvement [11,12].

Dysfunction of the hypothalamo-pituitary-gonadal axis may present with low estradiol or testosterone levels, associated with serum LH and FSH levels that may be normal, decreased, or elevated, depending on the level of involvement.

MRI, particularly T2*-weighted sequences, plays a key role in the early detection of pituitary siderosis. Signal hypointensity is related to the paramagnetic effect of iron and constitutes an early marker of pituitary iron overload [13,14]. A reduction in pituitary volume, defined by a Z-score below −2 [15], is also a predictive factor for hypogonadism, although some patients maintain a normal volume despite significant iron overload. In our patient, pituitary MRI demonstrated a gland of age-appropriate size with a T2* weighted hypointense signal, confirming pituitary siderosis in the absence of volumetric reduction, illustrating that signal abnormality may precede structural atrophy.

The treatment of hypogonadism aims to achieve pubertal development, adequate linear growth, and, whenever possible, preservation of fertility, within a multidisciplinary management framework.

Management relies primarily on the prevention of iron overload. Modern chelation therapies have demonstrated their efficacy, with possible reversibility of hypogonadism in certain cases, particularly with the deferoxamine-deferiprone combination [14]. Our patient had been on deferiprone since the age of 12, with good reported adherence, yet developed severe iron overload with a ferritin peaking at 7288 µg/L. Despite ongoing deferiprone therapy, several factors may explain the severity of pituitary iron overload: a relatively late initiation of chelation at the age of 12, beyond the recommended window of 2 to 3 years of age; the potential insufficiency of deferiprone monotherapy in controlling a heavy transfusion-related iron burden; and possible individual variability in sensitivity to iron-induced oxidative stress. These observations reinforce the importance of early chelation initiation, regular ferritin monitoring and transferrin saturation (3-monthly), and timely escalation to combination chelation regimens when iron burden remains inadequately controlled, with the goal of maintaining serum ferritin between 500 and 1,000 µg/L to prevent irreversible organ damage, particularly at the pituitary level.

It should be noted that, following hematopoietic stem cell transplantation, hypergonadotropic hypogonadism may occur due to the gonadotoxicity of conditioning agents [17].

In cases of simple pubertal delay, induction with low doses of sex steroids followed by early reassessment is proposed [18]. In situations of persistent hypogonadotropic hypogonadism, gonadotropins may be indicated, whereas hypergonadotropic hypogonadism requires substitutive sex steroid therapy at progressively increasing doses.

Long-term management relies on sex-appropriate hormone replacement therapy, with regular monitoring and consideration of comorbidities, in order to induce and maintain secondary sexual characteristics and improve quality of life [19]. Fertility preservation should be discussed at an early stage.

In women, hormone replacement therapy, ideally consisting of natural hormones — transdermal 17beta-estradiol combined with oral micronized progesterone — is more physiological than oral estrogen administration, which exposes patients to a hepatic first-pass effect resulting in modification of coagulation factors [19]. Pubertal induction with low doses of sex steroids is effective in the majority of cases, and exogenous gonadotropins allow fertility induction in cases of persistent hypogonadotropic hypogonadism [18]. In line with these recommendations, our patient was initiated on transdermal 17beta-estradiol at progressively increasing doses starting at 0.25 mg/day, with sequential addition of oral micronized progesterone planned once the target estrogenic dose is reached, and fertility options have been discussed as part of her multidisciplinary follow-up.

A holistic approach is essential [20], integrating social and psychological support, lifestyle guidance, and flexible clinic scheduling adapted to patient's educational and professional commitments. Physical activity is encouraged following cardiovascular assessment. Nutritional supplementation is a key component of follow-up and includes vitamin D (2,000 IU/day) with 6-monthly monitoring, a calcium-rich diet, folic acid (up to 1 mg/day), vitamin C (2–3 mg/kg/day with deferoxamine), and vitamin E-rich foods. Zinc is reserved for cases of proven deficiency or poor growth. L-carnitine (50 mg/kg/day) may be beneficial with caution in thyroid dysfunction. Dietary iron restriction is advised in low-transfusion regimens. Annual bone mineral density assessment (DXA) is recommended from adolescence, complemented by yearly bone turnover markers (NTX, CTX, bALP). Regular physical activity and smoking cessation should be systematically encouraged. Optimal iron chelation and adequate transfusion regimens are essential to prevent iron-mediated bone toxicity and uncontrolled bone marrow expansion. Hormone replacement therapy should be initiated promptly upon diagnosis of hypogonadism, given the well-established deleterious impact of estrogen deficiency on bone metabolism. When indicated, bisphosphonates should be combined with calcium and vitamin D for no longer than two years.

Regarding pituitary assessment, an annual hypophysiogram is recommended as part of routine endocrine surveillance (20). Pituitary MRI with T2* sequences should be performed at baseline in all patients with hypogonadism or pubertal failure. However, no standardized frequency for its repetition has been established in the current literature, should therefore be guided by clinical evolution.

Thus, hypogonadism in thalassemia major illustrates the complexity of interactions between iron overload and endocrine dysfunction. Early and multidisciplinary management is essential to improve the functional and reproductive prognosis of these patients. *Our case further emphasizes the diagnostic value of pituitary T2*-weighted MRI as a non-invasive tool for objectifying the underlying mechanism, and underscores the importance of systematic endocrine screening from an early age in transfusion-dependent thalassemia patients.*

4. Conclusion

This case highlights the insidious nature of hypogonadotropic hypogonadism in beta-thalassemia major, where primary amenorrhea may represent the first clinical manifestation of pituitary iron overload. It underscores the importance of systematic and early endocrine screening in transfusion-dependent patients, particularly regarding pubertal development and gonadotropic function, combined with pituitary T2*-weighted MRI as a non-invasive early marker of pituitary siderosis, in order to prevent irreversible damage**.** Timely initiation of hormone replacement therapy with transdermal 17beta-estradiol is essential to ensure adequate pubertal induction, preserve bone mineral density, and optimize quality of life. This case further emphasizes that optimization of iron chelation therapy remains the cornerstone of prevention, and that a proactive multidisciplinary approach is indispensable to address the full spectrum of iron overload-related endocrine complications.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest, financial or non-financial.

Statement of ethical approval

This case report did not require formal ethical committee approval in accordance with applicable local regulations.

Statement of informed consent

Written informed consent was obtained from the patient for the anonymous publication of this case report and any associated data.

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