Endocrinopathies in beta-thalassemia major

Prevalence, risk factors, and age at diagnosis in Northwest Saudi Arabia

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ABSTRACT

الأهداف: تحديد نسبة وعوامل إنتشار مضاعفات الغدد الصماء بمرضى البيتا الثلاسيميا وفي أي مرحلة عمرية تحدث هذه المضاعفات لمرضى الثلاسيميا المراجعين لمركز الثلاسيميا بنطقة المدينة المنورة شمال غرب المملكة العربية السعودية.

الطريقة: تم معاينة المرضى المراجعين لمركز الثلاسيميا في عيادة مشتركة بين الاستشاريين المختصين في الغدد الصماء عند الأطفال والمختصين في أمراض الدم عند الأطفال، وتم تقييم المرضى اكلينيكياً، وكذلك إجراء الفحوصات المخبرية عند الزيارة الأولى لتحديد نسبة المصابين بمضاعفات الغدد الصماء، وأيضاً تم تحديد عوامل الخطورة للإصابة بالمضاعفات من خلال المعلومات الديموقرافية والتحاليل المخبرية.

النتائج: تم دراسة 81 مريض وكان منهم 42 ذكر وأعمارهم تتراوح بين 2–28 عام. كان لدى 46.9% من المرضى مضاعفة واحدة أو أكثر من مضاعفات الغدد الصماء، ومن هؤلاء 11 من 28 (28.9%) كانوا أقل من 10 عام. تأخر البلوغ كان من أكثر المضاعفات ويمثل 23.4%، ويتبع ذلك قصر القامة 20.9%. و أظهرت النتائج أن المرضى الذين لديهم مضاعفات قد تم نقل دم لهم لفترة طويلة، كذلك كان هناك تأخر في البدأ في استخدام عقار طارد الحديد. وأظهرت النتائج أيضاً أنه ليس هناك علاقة بين معدل الحديد وحدوث المضاعفات

خاتمة: نسبة مضاعفات الغدد الصماء عند مرضى الثلاسيميا بمركز الثلاسيميا عالية جداً، لذا نوصي بأن يتم الكشف عن هذه المضاعفات قبل سن البلوغ، وأيضاً نحن نعتقد بأن تجربة العيادة المشتركة بين أطباء الغدد الصماء وأمراض الدم تجربة ممتازة ولها آثار إيجابية في تحسين الرعاية الصحية، وهذا النموذج نأمل أن يتم تطبيقه في المراكز الأخرى المماثلة.

Objectives: To define the prevalence, risk factors, and age at diagnosis of endocrinopathies in beta-thalassemia major (BTM) in Northwest Saudi Arabia.

Methods: This retrospective cross-sectional study included patients with BTM attending a combined endocrine-hematology clinic in Al-Madinah, Kingdom of Saudi Arabia from March 2009 to December 2010. Clinical and biochemical data from the initial clinic visits were used to define the prevalence and age of diagnosis of endocrinopathies. Demographic and laboratory variables were analyzed to identify significant risk factors.

Results: Eighty-one patients (42 males), aged 2-28 years were screened. Thirty-eight of them (46.9%) had at least one endocrinopathy. Of these, 28.9% (11/38) were aged less than 10 years. Hypogonadism was the most common complication detected in 52.7% (19/36) of patients of pubertal age group and 23.4% (19/81), of all cohort followed by short stature in 20.9% (17/81), subclinical hypothyroidism in 14.8% (12/81) and hypoparathyroidism in 11.1% (9/81). Patients with endocrinopathies were older (p=0.001), had longer duration of transfusion (p=0.001), and were started at a late age on chelation than those without endocrinopathies (p=0.07). Recent serum ferritin was poorly correlated to endocrinopathies (p=0.15).

Conclusion: Endocrinopathies are common in our BTM cohort, and patients with this condition benefit from regular endocrine screening within the first 10 years of life. Although endocrinopathies were more prevalent in older patients; further, longitudinal studies are needed to define the exact age of onset and independent risk factors for these complications.

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Beta-thalassemia major (BTM) is a severe autosomal recessive hemolytic anemia caused by the absence or marked deficiency of the hemoglobin ß globulin chain. The condition usually presents clinically within the first 2 years of life and it is mainly managed by regular blood transfusion and chelation. Intensive transfusion regimens and the use of modern chelating agents increased the survival of these individuals;[1] however, patients remain at risk of developing iron toxicity in various body tissues including the endocrine organs. Studies from different populations have reported evidence of various endocrine dysfunctions in BTM patients with delayed puberty/hypogonadism and short stature being the most frequent complications followed by hypoparathyroidism, hypothyroidism, and diabetes.[2-9] In addition to iron overload, other factors have been linked to slow growth and endocrinopathies in BTM such as poor nutrition, chronic anemia, chelating agents, liver disease, and genetic susceptibility.[2-4] As the prevention of BTM related endocrinepathies remains a challenge, it is recommended that patients with BTM should be screened regularly for early detection of growth delay and endocrine dysfunction.[10] However, it is not clear when this process should start or what is the best procedure for conducting it as the age of onset of these endocrinopathies is not well defined. In the Kingdom of Saudi Arabia (KSA), thalassemia is mainly prevalent in the Eastern, Southwest, and Northwestern parts of the country.[11] However, data on BTM related endocrinopathies are limited to a few studies from the central KSA.[12-14] We have recently established a combined endocrine-hematology clinic to facilitate the screening and management of patients with transfusion dependent hemoglobinopathies in Northwest KSA.

In the present study, we retrospectively define the prevalence, age at diagnosis and risk factors for BTM related endocrinopathies in our cohorts based on the initial data from patients attending this joint clinic.

Methods. This retrospective cross-sectional study was conducted in the Hereditary Blood Diseases Center at the Maternity and Children's Hospital, Al-Madinah, Northwest of Saudi Arabia where all patients with BTM and other hemoglobinopathies from the whole region are referred, the center was established in 1992 to provide a comprehensive service for children and young adults with transfusion dependent blood disorders. The diagnosis, clinical details, and management of our BTM patients were reported.[15] In March 2009, we established an age-banded monthly combined endocrine-hematology clinic to facilitate the screening and management of growth and endocrine dysfunction in all patients attending the center. Prior to the study, patients with suspected endocrine dysfunction were referred to the endocrine clinic and often waiting for a long period before obtaining an endocrinological opinion. Our joint clinic has a multi-disciplinary team consisting of hematologist, endocrinologist, nurse specialist, dietician, and psychologist with access to a gynecologist. Patients were seen in the clinic on the same day when they attended for their regular blood transfusions. Clinical assessment and investigations were performed according to a locally designed protocol and the frequency of follow-up visits was based on the patient's needs (**Figure 1**). Height was measured by the same nurse using the standard anthropometric techniques[16] and puberty was staged by a pediatric endocrinologist and in females by a female pediatrician based on Tanner's criteria.[16] Venous blood samples for biochemical tests were collected prior to transfusions. We included all children and adults with transfusion dependent BTM attending the clinic from March 2009 to December 2010 inclusive. Patients with other transfusion dependent hemoglobinopathies were excluded from the study. All steps of the study were conducted according to principles of Helsinki declaration and the protocol was approved by the Ethics Committee of Maternity and Children Hospital, Al-Madinah, Saudi Arabia.

Data collection. Clinical, auxological, hormonal and biochemical data from the initial screening visits of all patients (**Figure 1**) were collected from the clinic charts and were used to calculate the prevalence of endocrinopathies. When the initial hormonal results were inconclusive, the results from the follow-up visits were used to confirm the presence of endocrinopathies. Other information such as demographic data, details of disease management (duration and age at the start of transfusion and chelation) as well as mean serum ferritin, hemoglobin, and liver enzymes during the previous 12 months were used to identify risk factors for developing endocrinopathies. The frequency of growth/endocrine dysfunction in patients aged 10 years or less was compared to the rest of the group to analyze whether the screening in the first decade of life was justified.

Definition of endocrinopathies. Short stature was defined as height below the third percentile on the 2005 Saudi height chart.[17] Subjects were considered to have

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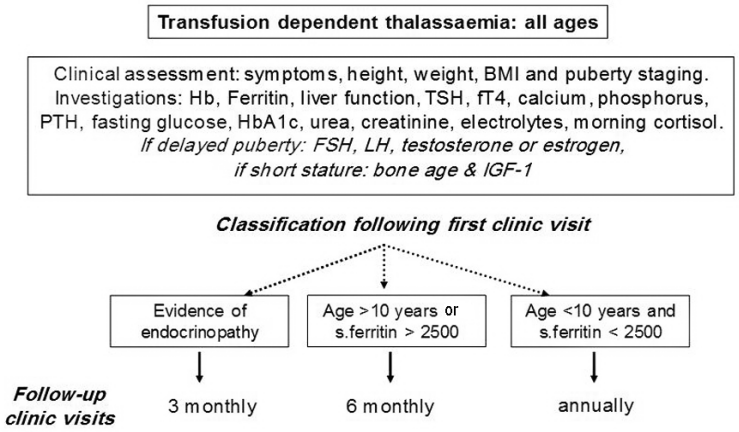

Figure 1 - Guidelines for the screening and follow-up of patients with beta thalassaemia major attending the combined endocrine - hematology clinic, Northwest, Saudi Arabia. BMI - body mass index, Hb - hemoglobin, TSH - thyroid stimulating hormone, FT4 - free thyroxin, PTH - parathyroid hormone, HbA1c - hemoglobin A1c , FSH - follicular stimulating hormone, LH - luteinizing hormone, IGF-1 - insulin like growth factor-1, s-ferritin - serum ferritin

hypogonadism if they had delayed puberty, incomplete (arrested) puberty, or secondary amenorrhea. Delayed puberty was defined as absence of breast development by the age of 13 years in girls or absence of genital development at 14 years in boys and incomplete puberty was defined as primary amenorrhea in females at 17 years or failure to reach Tanner genitalia stage 5 in males by the age of 18 years. Patients with hypogonadism and prepubertal basal follicular stimulating hormone (FSH) and luteinizing hormone (LH) levels were considered to have hypogonadotrophic (central) hypogonadism, and those with high basal FSH and LH levels were defined as having gonadal (primary) failure. Overt hypothyroidism was defined as subnormal free thyroxin (FT4) with raised thyroid stimulating hormone (TSH) and subclinical hypothyroidism as normal FT4 with high TSH on more than 2 consecutive occasions. Hypoparathyroidism was defined as subnormal serum calcium with high phosphate with subnormal or inappropriately low parathyroid hormone (PTH) level in the presence of hypocalcemia. Patients were considered to have diabetes if their fasting glucose was >7.8 mmol or if symptomatic with random blood glucose of more than 11.1 mmol/l. Adrenal insufficiency was defined as morning (09:00 hours) serum cortisol <170 nmol/L with or without abnormal serum sodium and potassium.

Statistical analysis. All numerical data are expressed as mean and standard error of mean (±SEM). In bi-variate analysis, continuous data were compared by the non-parametric Mann-Whitney test, and dichotomous data were compared using Chi square test. Statistical significance was described when p-value <0.05. Data were analyzed using Instat Statistical Software Package.

Results. Eighty-one patients (42 males) with BTM, age-range 2-28 years, with a mean age of 12.2 years ± 6.85 SD, were screened for growth and BTM related endocrinopathies within 8 months of opening the clinic. The monthly clinic list comprised 8-12 patients and all patients >10 years were assessed within the first 4 months (median waiting time 2 months) and younger children were seen during the following 4 clinics.

Prevalence of endocrinopathies. Clinical or biochemical evidence of at least one endocrinopathy was detected in 38/81 (46.9%) patients with an equal gender distribution. Of these, 28.9% (11/38) were aged less than 10 years and 16/38 (42.1%) had multiple endocrine dysfunctions. The most common endocrine dysfunction was hypogonadism, which was identified, in 19 of the total 81 patients (12 females >13 years and 7 males >14 years). This number accounts for 23.4% (19/81) of the whole group and 52.7% (19/36) of patients of pubertal age group. Out of the subjects with hypogonadism, 11/19 (57.8%) had incomplete puberty, 6/19 (31.5%) had delayed puberty, and 2/19 (16.6% of females) had secondary amenorrhea. All patients with hypogonadism have prepubertal basal FSH (mean: 2.268 mU/L ± 0.23 SEM) and LH (mean: 1.79 U/L± 0.19 SEM), and at least one other endocrine dysfunction. Short stature was detected in

Table 1 - Hormonal and biochemical results of subjects with beta-thalassemia major with (yes) versus without (no) subclinical hypothyroidism or hypoparathyroidism in Northwest Saudi Arabia.

Results	Yes	No	*P*-value	95% CI
Subclinical hypothyroidism: n (%)	12 (14.8)	69 (85.2)	0.0001	
Thyroid stimulating hormone (0.3-5.0 mU/L)	8.4±0.54	2.6±0.12	0.0001	5.0 - 6.5
Free thyroxine (12-22 pmol/L)	15.9±0.59	17.7±0.22	0.004	0.56 -2.91
Hypoparathyroidism: n (%)	9 (11.1)	72 (88.9)	0.0001	
Serum calcium (2.2-2.6 mmol/L)	1.73±0.13	2.4±0.1	0.0001	0.56 - 0.77
Serum phosphate (0.78-1.6 mmol/L)	2.0±0.6	1.2±0.3	0.0001	0.6 - 1.1
Serum parathyroid hormone (15-65 pg/ml)	19.1±16.5	40.1±15.	0.0002	10.2 - 31.8

All values are expressed in mean ± standard error of mean. Values in brackets represent the normal ranges.

Table 2 - Prevalence of endocrinopathies in beta-thalassemia major in children less than 10 years old compared to the rest of the group in Northwest Saudi Arabia.

Endocrinopathy	Age 2-9 years (n=36)	Age 10-28 years (n=45)*	OR	95% confidence intervals	*P*-value
Any endocrinopathy	11 (30.5)	27 (60.0)	0.29	(0.12 - 0.74)	0.007
Short stature	3 (8.3)	14 (31.1)	0.2	(0.05 - 0.77)	0.02
Subclinical hypothyroidism	6 (16.6)	6 (13.3)	1.3	(0.38 - 4.44)	0.4
Hypoparathyroidism	3 (8.3)	6 (13.3)	0.59	(0.14 - 2.55)	0.8
Diabetes	0	1 (2.2)	0.41	(0.02 - 10.29)	1.0

*36 patients of pubertal age group (girls >13 years and boys >14 years), OR - odds ratio

17/81 patients (9 males); 20.9% of the whole cohort. Of the short stature patients, 58.8% (10/17) also have delayed or incomplete puberty. None of our cohort had overt hypothyroidism; however, 12 (5 males) out of the 81 patients (14.8%) have subclinical hypothyroidism of whom 50% (6/12) were younger than 10 years and 83% (10/12) had no other endocrinopathies. The TSH and FT4 levels of these 12 patients compared with the rest of the group are shown in **Table 1**. Hypoparathyroidism was present in 9/81 (11.1%) of patients. Their serum phosphate, calcium, and PTH levels in comparison to those with normal parathyroid function are shown in **Table 1**. Seven of these had other endocrine dysfunction and 3 were younger than 10 years. Only one young adult, aged 18.3 years, has non-autoimmune secondary diabetes with no family history of hyperglycemia. At presentation, the blood glucose was 33.1 mmol/l and hemoglobin A1c (HbA1c) was 11.9%. He was not obese but has deranged liver enzymes and multiple endocrinopathies. The mean HbA1C and fasting blood glucose for the other 80 patients were 5.04% ± 0.06 SEM and 4.9 mmol/L ± 0.1 SEM. Serum urea, creatinine sodium, and potassium were normal in all patients (mean Sodium: 136.9 mmol/L ± 0.38SEM, mean Potassium: 4.67 mmol/l ±0.08SEM, mean urea: 2.51 mmol/l ±0.07SEM and creatinine: 47.5mmol/l ±SEM) and they have no evidence of significant adrenal dysfunction (mean morning serum cortisol: 386.75 nmol/l ±11.8 SEM) .

Age at diagnosis of endocrinopathies. **Table 2** compares the prevalence of endocrinopathies between children aged less than 10 years and other patients. Eleven patients aged less than 10 years have at least one endocrine dysfunction. This number accounts for 30.1% (11/36) of all thalassemia patients of this age group and 28.9% (11/38) of the number of thalassemic subjects with endocrinopathies. Endocrine dysfunction were more prevalent in older patients 27/45 (60%) versus 11/36 (30.5%), (p=0.007); however, there was no significant difference in the frequency of hypoparathyroidism or subclinical hypothyroidism between the 2 groups, (p=0.4, p=0.8). The number of patients with endocrinopathies aged 0-9 years were 11.

Risk factors for endocrinopathies. **Table 3** shows the results of analysis of demographic, clinical, and laboratory variables in relation to the development of endocrinopathies. Patients with endocrine complications were significantly older (p=0.001), had longer duration of blood transfusions (p=0.001), longer period of receiving chelation (p=0.004) and were started on chelation at older ages (p=0.07) than those without endocrinopathies. Mean recent annual serum ferritin was higher in the endocrinopathy group, but was not significantly different (p=0.15). There was no significant difference between endocrinopathy and non-endocrinopathy groups in the gender ratio, mean annual Hb level, percentage of splenectomy or levels of liver enzymes (**Table 2**).

Table 3 - Demographic, hematological, and biochemical variables related to the risk of developing endocrine dysfunction in beta-thalassemia major patients with or without endocrinopathies in Northwest Saudi Arabia.

Variable	Endocrinopathies n=38 (46.9)	No endocrinopathies n=43 (53.0)	95% Confidence Interval	*P*-value
Mean age in years (mean±SEM)	15.1 ± 1.1	9.4 ± 1.1	8.46 - 2.93	0.001
Age at diagnosis (mean±SEM)	1.76 ± 0.4	1.13 ± 0.16	-1.533 - 0.2672	0.14
Male gender n (%)	19 (50)	23 (53.0)	.45 - 2.57	0.92
Female gender n(%)	19 (50)	20 (47.0)	0.45 -2.56	0.92
Age at starting transfusion in years (mean±SEM)	1.72 ± 0.4	1.26 ± 0.7	1.30 - 0.36	0.24
Duration of transfusion in years (mean±SEM)	13.19 ± 0.4	8.67 ± 0.9	.24 - 1.799	0.001
Transfusion index (mean±SEM)	150.16 ± 5.9	158.8 ± 4.7	-6.87 - 23.27	0.27
Age at starting chelation in years (mean±SEM)	5.03 ± 0.6	3.55 ± 0.5	-2.92 - 0.18	0.07
Duration of chelation in years (mean±SEM)	10.01 ± 0.9	6.37 ± 0.8	6.08 - 1.19	0.004
Hemoglobin gm/dl (mean±SEM)	8.49 ± 0.3	8.56 ± 0.2	-0.49 - 0.63	0.81
Serum ferritin ng/ml (mean±SEM)	3697.7 ± 536.9	2816.3 ± 335.7	-2148.6 - 385.70	0.15
Serum ferritin < 2500 ng/ml (%)	44.7	58.1	0.24 - 1.41	0.27
Splenectomy (%)	60.5	67.4	0.29 - 1.84	0.67
Alanine transaminase IU/L	82.11 ± 8.5	92.41 ± 10.4	-16.58 - 37.17	0.45
Asparte transaminase IU/L	71.54 ± 7.8	78.36 ± 8.9	-16.79 - 30.44	0.57

Discussion. This is the largest study to date that defines the prevalence of endocrine complications of BTM in KSA and the first report of experience of combined endocrine-hematology clinic in the country and probably in the Middle East. The study was conducted in one of the key demographic focuses of thalassemia in KSA and included patients of all age groups thus providing data on the prevalence of BTM related endocrinopathies in children, adolescents, and young adults. We identified clinical and/or biochemical evidence of at least one endocrine abnormality in less than half of our patients which is higher than European countries,[4,5] but lower than Iran,[6] Oman,[7] and India.[8] This lower rate than neighboring countries could be explained by the younger age of our cohort, a difference in cut-off hormone levels and/or variation in management protocols and patients' compliance between different centers.

The majority of our patients with endocrine complications (60%) were older than 10 years. However, approximately one third of children aged 2-10 years had some endocrine dysfunction (short stature, hypoparathyoidism, and subclinical hypothyroidism) indicating that periodic screening for growth delay and endocrine complications in patients with BTM should be started within the first decade of life. We found no significant difference in the recent mean annual serum ferritin between patients with endocrinopthies and those with normal endocrine function. This poor correlation between endocrinopathies and recent serum ferritin had been reported by another study[3] and indicates that endocrine complications could be related to iron toxicity in early life rather than at the time of screening. It also suggests that recent serum ferritin levels are not a sensitive marker for tissue ferritin deposition. As reported by others,[3-6] our patients with endocrinopathies had a longer duration of transfusion and were started on chelation at an older age compared to those without endocrinopathies.

Hypogonadism was the most common endocrinopathy in our patients similar to other populations.[2-9] However, the prevalence of hypogonadism, even in patients with pubertal age (52.7%), was lower than previously reported from most populations including neighboring areas such as central KSA,[12] Egypt[18] and Iran.[19] An impact of the genotype on gonadal function of subjects with BTM has been documented,[20] Therefore, it is possible that some of our patients have certain mutations associated with a lower risk of hypogonadism. All our patients with hypogonadism had low basal FSH and LH indicating that their hypogonadism was due to pituitary rather than gonadal damage. This means that providing regular follow-ups and maintaining compliance with hematology and hormonal management can help these patients achieve fertility by exogenous gonadotropin therapy.[10,21] Short stature was the second most common form of endocrine dysfunction identified in 20.9% of our cohort, which is lower than most studies.[2-9] The most likely reason for the relatively lower prevalence of short stature in our cohort was the use of the local population growth chart rather than using the USA center for disease control (CDC) charts. The growth delay in our patients was observed in all age groups and

was more prevalent in those with delayed and arrested puberty confirming an etiological link to inadequate gender steroid production and pubertal growth spurt.[21]

None of our patients had overt hypothyroidism; however, subclinical hypothyroidism was detected in 14.8% of our cases. This figure is comparable to data from Italy[22] and Greece,[23] but lower than reported from Pakistan,[24] and Thailand.[25] None of our patients had clinical thyroid enlargement, and testing for thyroid autoantibodies was not part of our initial screening process; therefore, it is difficult to be certain whether the high TSH in our patients was entirely related to BTM. We noticed that in some patients, the TSH was corrected following improvement of their serum ferritin indicating that the observed subclinical hypothyroidism was at least partially related to iron overload. Hypoparathyroidism (HPT) is considered to be a late and uncommon complication in BTM.[10] However, 11.1% of our cohort has HPT, which was identified even in young children (**Table 1**). This high frequency of HPT was also reported from central KSA,[13] and could be related to the high rate of vitamin D deficiency in the country.[26,27] Low vitamin D levels were documented in BTM patients[28] and an assessment of vitamin D level in our patients would clarify this suspicion. Only one patient in our cohort had diabetes, which is probably the lowest reported rate of diabetes in thalassemia cohorts. The highest body mass index (BMI) in our cohort was 22.8. It is possible that the lower BMI in our cohort (mean 17.4) had some role in delaying the onset of diabetes. Further study of the relationship between glucose hemostasis and body composition is needed to test this hypothesis. Adrenal dysfunction had been reported in some BTM patients;[29] however, none of our patients had abnormal electrolytes or low morning cortisol level to justify further assessment of adrenal function.

Our experience with the combined endocrine hematology clinic indicated that this model of care has potential benefits. Patients were assessed by an endocrinologist, hematologist, and dietician on the same day in the environment where they receive their regular blood transfusions and therefore, they had less hospital visits and a shorter waiting time to have endocrinological opinion. The age-banded nature of our clinic ensured that older patients, who were at more risk to develop endocrine complications, were seen earlier (within 4 months; mean waiting time 2 months). In addition, we were able to identify patients with subtle or symptomatic endocrinopathies at an earlier stage and providing treatment and follow-up for those with various endocrine dysfunctions (results not shown). Finally, the clinic was an opportunity for the staff to learn from each other and to collect longitudinal data that can be used to understand the nature and prognosis of endocrinopathies in BTM.

Study limitations. The cross-sectional nature of the study does not allow us to define the exact age of onset of endocrinopathies; however, regular screening of patients via the combined clinic would allow us to collect longitudinal data to answer this question in the near future. We relied on recent mean annual Hb, and serum ferritin to define risk factors for endocrine dysfunction, which may not necessarily reflect their levels at onset of endocrinopathies.

In conclusion, thalassemia related endocrinopathies in our cohort are high and our data indicated that some of these endocrinopathies could develop in the first 10 years of life demonstrating that patients with BTM would benefit from endocrine screening well before puberty. Although endocrine dysfunction were more prevalent in our older patients, further longitudinal studies are needed to define the exact age of onset of endocrinopathies and to explain the high frequency of hypoparathyroidism and the lower prevalence of diabetes in our cohort.

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