CASE REPORT

Low serum free thyroxine level in a girl with McCune-Albright syndrome

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SUMMARY

A 17-year-old girl with McCune-Albright syndrome (MAS) was suspected of having central hypothyroidism based on an inappropriately normal thyroid-stimulating hormone (TSH) and low free thyroxine (fT4). She was clinically euthyroid and her pituitary appeared normal on MRI. Treatment of hypothyroidism with levothyroxine resulted in suppression of TSH with a low fT4 and high free triiodothyronine (fT3) concentration and hence iatrogenic hyperthyroidism was diagnosed. After discontinuation of levothyroxine, the TSH and fT3 normalised while fT4 remained low. Increased conversion of thyroxine (T4) to triiodothyronine (T3) can be part of MAS. Therefore, fT3 and fT4 should both be measured when evaluating thyroid function in patients with MAS.

BACKGROUND

McCune-Albright syndrome (MAS) is a sporadic disease with an estimated prevalence of less than 1 in 100 000; it is classically defined by the triad of fibrous dysplasia, *café-au-lait* skin spots and gonadotropin-independent precocious puberty.^{1,2} It is frequently associated with other hyperfunctioning endocrinopathies including hyperthyroidism, growth hormone (GH) excess, renal phosphate wasting and Cushing's syndrome.^{1,2} The disease is caused by postzygotic activating mutations in the GNAS1 gene encoding the α subunit of the stimulatory G protein (Gs α), and mosaic distribution of the mutation-bearing cells explains variable involvement of skin, bone and endocrine tissues.²⁻⁴

Thyroid involvement is a common feature of MAS, often characterised by abnormal findings on ultrasound, usually in the absence of clinical symptoms of thyroid disease or less frequently by hyperthyroidism.^{1,2,5,6} In patients with MAS and thyroid involvement, increased T3 to T4 ratio can be found on laboratory testing, and is probably caused by increased conversion of T4 to T3 resulting from elevated activity of intrathyroidal type 2 and type 1 5'-deiodinases.^{5,6} Hypothyroidism has previously not been reported to be part of the syndrome.

CASE PRESENTATION

A 17-year-old girl, diagnosed with MAS at the age of 11, presented with a history of repeated bone fractures, tiredness and mild bone pains.

At the age of 2, she had been referred to an endocrinologist for precocious puberty. An ovarian cyst was detected and surgically removed. Nine years later the diagnosis of MAS was established based on *café-au-lait* skin spots, gonadotropin-independent precocious puberty, fibrous dysplasia

of bone and hypophosphatemia. The patient's history of multiple bone fractures of the lower extremities was due to relatively mild traumas. Her pubertal development was classified as Tanner stage 4 breast development (Ma4) and Tanner stage 4 pubic hair development (Pu4). Irregular menstruations had started at the age of 8. Her height was 142 cm (25th centile) and weight 44 kg (90th centile). After the diagnosis, therapy with phosphate and active vitamin D (dihydroxycholesterol) was initiated and lasted for about a year before discontinuation by the patient.

Owing to recurrent pathological fractures of long bones, combined treatment with alendronate, phosphate, calcium and vitamin D was restarted 1 year later. The patient's lumbar bone mineral density (BMD) Z-score was -1.7.

She was lost to follow-up for 3 years. At the latest presentation, *café-au-lait* spots were located on her left temple, behind the neck, on the right side of the thorax and on the back. Her height was 142 cm (<3th percentile) and weight 49 kg (10th centile). Blood pressure was 128/58 mm Hg and heart rate 68 bpm. She was at Ma4 and Pu4 by Tanner stages, her periods were still irregular. She was taking vitamin D, calcium and phosphate supplements.

INVESTIGATIONS

Hormone tests revealed alterations in the patient's serum thyroid hormone levels and a low level of insulin-like growth factor-1 (IGF-1)—67 μ g/L (194–680 μ g/L), suggesting possible central hypothyroidism and GH deficiency. Her serum thyroid-stimulating hormone (TSH) concentration was 2.18 mU/L (reference range 0.5–4.3 mU/L) and fT4 4.9 pmol/L (12.6–21.0 pmol/L). Thyroid ultrasound was normal. No antithyroid peroxidase antibodies were detected. She did not have clinical features typical of hypothyroidism except tiredness. Her cortisol, prolactin, follicle-stimulating hormone, luteinising hormone and estradiol levels were within the normal range. She had hypophosphatemia of 0.7 mmol/L (0.95–1.60 mmol/L).

Owing to her poor growth rate and low insulin-like growth factor 1, a GH stimulation test with arginine was performed, which was normal (peak of GH 56 mU/L). MRI of the pituitary was normal. Thus, isolated TSH deficiency was suspected.

The patient had extensive bone involvement on bone scintigraphy with ⁹⁹Tc-MDP, where significantly increased uptake of tracer in the skull, in both forearms, in the right femur, tibia and fibula was seen. Osteoporotic compression fractures were

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present on thoracic and lumbar spine radiographs. The lumbar BMD Z-score was -4.3 .

TREATMENT

The patient received a short course of levothyroxine (50 µg/die) due to the suspected hypothyroidism and many cycles of intravenous pamidronate for osteoporotic fractures.

OUTCOME AND FOLLOW-UP

After a month of treatment with levothyroxine, the TSH was 0.95 mU/L and fT4 9 pmol/L. Following treatment with levothyroxine for another month with increased dose of 75 µg, serum fT4 concentration still remained below the reference range (9.6 pmol/L), whereas the concentration of TSH was suppressed (0.03 mU/L). Additional measurement of fT3 revealed iatrogenic fT3-toxicosis (8.35 pmol/L; reference 3.93–7.70 pmol/L) and treatment with levothyroxine was discontinued.

Two months after levothyroxine was stopped, the serum TSH (2.2 mU/L) and fT3 (6.1 pmol/L) were normal while the patient's fT4 was still low (5.6 pmol/L). Clinically she remained euthyroid.

DISCUSSION

Thyroid involvement in MAS may occur as hyperthyroidism or by decreased T4/T3 ratio. The latter is caused by an elevated T3 level and is observed in many patients with abnormal thyroid ultrasound.^{5–6} Our case provides data that this can also occur without thyroid involvement on ultrasound and in the setting of low fT4 and normal fT3. T4 is a pro-hormone for T3 and is required for its action.⁷ This conversion is carried out by type 1 and type 2 deiodinase in thyroid as well as other tissues expressing these enzymes.⁸ Changes in the activity as well as mRNA levels of deiodinases have been reported to occur in different thyroid diseases such as thyroid carcinoma and Graves' disease, and may be the explanation for 'T3-toxicosis'.^{7–9} The normal range of fT4/fT3 ratio is between 3.1 and 3.3 (95% CI 2 to 5).^{10–11} It is slightly higher (4.3) in patients on thyroid replacement therapy.^{10–11} In our patient the fT4/fT3 ratio was in the range of 0.85–1.15 with and without treatment, suggesting the increased activity of deiodinases. Increased activity of type 1 and type 2 deiodinases have been reported in thyroid tissue taken from patients with MAS without hyperthyroidism as well as in cell culture carrying the GNAS1 mutation.⁵ The latter is supported in our case by the fact that no changes were observed in the thyroid by ultrasound.

Learning points

- ▶ Thyroid dysfunction should be considered in every patient with McCune-Albright syndrome (MAS).
- ▶ Abnormal thyroid function tests can occur in patients with MAS even with normal thyroid ultrasound.
- ▶ Serum concentrations of free T4 and free T3 should both be measured in patients with MAS when evaluating thyroid function.

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REFERENCES

- 1 Collins MT, Singer FR, Eugster E. McCune-Albright syndrome and the extraskeletal manifestations of fibrous dysplasia. *Orphanet J Rare Dis* 2012;7(Suppl 1):S4.
- 2 Dumitrescu CE, Collins MT. McCune-Albright syndrome. *Orphanet J Rare Dis* 2008;3:12.
- 3 Schwindinger WF, Francomano CA, Levine MA. Identification of a mutation in the gene encoding the alpha subunit of the stimulatory G protein of adenyl cyclase in McCune-Albright syndrome. *Proc Natl Acad Sci USA* 1992;89:5152–6.
- 4 Weinstein LS, Shenker A, Gejman PV, et al. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. *N Engl J Med* 1991;325:1688–95.
- 5 Celi FS, Coppotelli G, Chidakel A, et al. The role of type 1 and type 2 5'-deiodinase in the pathophysiology of the 3,5,3'-triiodothyronine toxicosis of McCune-Albright syndrome. *J Clin Endocrinol Metab* 2008;93:2383–9.
- 6 Feuillan PP, Shawker T, Rose SR, et al. Thyroid abnormalities in the McCune-Albright syndrome: ultrasonography and hormonal studies. *J Clin Endocrinol Metab* 1990;71:1596–601.
- 7 Bahn RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract* 2011;17:456–520.
- 8 Orozco A, Valverde-R C, Olvera A, et al. Iodothyronine deiodinases: a functional and evolutionary perspective. *J Endocrinol* 2012;215:207–19.
- 9 Ito M, Toyoda N, Nomura E, et al. Type 1 and type 2 iodothyronine deiodinases in the thyroid gland of patients with 3,5,3'-triiodothyronine-predominant Graves' disease. *Eur J Endocrinol Eur Fed Endocr Soc* 2011;164:95–100.
- 10 Wiersinga WM. Paradigm shifts in thyroid hormone replacement therapies for hypothyroidism. *Nat Rev Endocrinol* 2014;10:164–74.
- 11 Gullo D, Latina A, Frasca F, et al. Levothyroxine monotherapy cannot guarantee euthyroidism in all athyreotic patients. *PLoS ONE* 2011;6:e22552.

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