

Case Report

Sexual precocity in a girl with early-onset Graves' disease

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Abstract. We describe the case of a girl diagnosed with Graves' disease (GD) at 2 yr of age, who developed early puberty. Preoperative examination for craniosynostosis revealed thyrotoxicosis. While she was tall and her bone age was advanced at GD onset, her linear growth attenuated after commencement of anti-thyroid treatment. However, at approximately 6 yr of age, breast budding was recognized. Hormonal analysis revealed pubertal levels of LH response to a GnRH stimulation test and serum E2. Gonadal suppression therapy with GnRH agonist was initiated, and her adult stature slightly exceeded the genetic potential. Although accelerated growth and skeletal maturation are often reported to occur at GD onset in prepubertal patients, early puberty is unusual, and this is the first reported case of sexual precocity in a girl with GD.

Key words: Graves' disease, early puberty, craniosynostosis

Introduction

While delayed pubertal onset is generally observed in children with hypothyroidism, the effect of thyrotoxicosis on pubertal development has not been well defined. Accelerated growth and bone maturation are often described features of childhood-onset Graves' disease (GD) (1–6), and therefore, thyroid hormone excess may accelerate the tempo of somatic growth leading to early pubertal onset. However, growth rate usually attenuates after euthyroidism is

achieved with anti-thyroid treatment (1–3). Consequently, the timing of pubertal onset and menarche are not influenced, and adult stature is not impaired (2–4). Thus, the growth acceleration and skeletal maturation at disease onset do not seem to influence the timing of puberty, and early pubertal development in girls with GD appears to be rare. Here, we report the case of a girl with GD onset at 2 yr of age, who developed early puberty at 6 yr. After gonadal suppression therapy, her adult height was slightly taller than her target height.

Case Presentation

The patient has been reported upon in a case previously reported elsewhere (7). A 29-mo-old Japanese girl was referred to our clinic for thyrotoxicosis, which was revealed on preoperative examination for craniosynostosis. She had no family history of thyroid disorder.

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She exhibited exophthalmos at 16 mo of age. She was born at 38 wk after an uneventful pregnancy and delivery, and her birth weight was 2,714 g. Her developmental milestones were not delayed, and her developmental quotient was 98. Her height and weight were 98.6 cm (+ 3.41 SD) and 14.5 kg (+ 2 SD), respectively, while her head circumference was 47 cm (25th percentile). She also presented with diffuse goiter, hypertension (140/50 mmHg), and tachycardia (128 bpm at rest). Thyroid function results (free T3, 18.5 pg/ml; free T4, 3.7 ng/dl; and TSH, 0.008 mIU/l), positive anti-TSH receptor antibody (TRAb, 53.7%), and an ultrasound revealing low echogenic diffuse goiter without nodule lead to the diagnosis of GD. Bone age (BA) was advanced (6 yr 0 mo by the Greulich and Pyle atlas) for her chronological age (CA). Cranial CT showed the closure of all sutures compatible with premature craniosynostosis. Thiamazole was immediately initiated, and euthyroidism was achieved after 3 mo without any adverse events. At 34 mo of age, fronto-orbital advancement was performed using distraction osteogenesis, as previously reported (7).

Following anti-thyroid therapy, her linear growth slowed and her height SD score remained at approximately + 2.5 SD after 4 yr of age (Fig. 1). However, at approximately 6 yr of age, breast development was recognized. Her height was + 2.59 SD, and BA (8 yr 6 mo) was advanced for CA (6 yr 1 mo). As gradual breast development continued, hormonal examination, including a GnRH stimulation test, was performed. Serum E2 was 26.1 pg/ml, peak LH was 7.5 (reference range for pubertal children: 5.70–18.50) mIU/ml, and peak LH-to-FSH ratio was 0.71 (reference range for pubertal children: 0.74–1.40). These results were compatible with early puberty. No intracranial lesions were detected on MRI. Thyroid function test showed euthyroidism with a maintenance dose of thiamazole. Early puberty in this case conformed to the criteria of central precocious puberty as outlined by the diagnostic guidelines in Japan, which include

early breast budding below age 7 yr 6 mo, tall stature with advanced BA, and pubertal levels of LH in response to GnRH and serum E2. After discussion with her family, gonadal suppression therapy with a GnRH agonist was initiated at 6 yr 9 mo to reduce the risk of further BA advancement, shortened adult stature, and early menarche. Further breast development did not progress during treatment while pubic hair appeared at 7 yr 6 mo. Treatment with the GnRH agonist continued until 10 yr 6 mo, and menarche commenced 1 yr after the last dose (11 yr, 6 mo). TRAb result was negative since 9-yr-old and anti-thyroid medication was discontinued at 12 yr after menarche to avoid probable fluctuation of thyroid function during puberty (8), and euthyroidism was approximately maintained after cessation of therapy (Fig. 2). At her most recent visit, she was 14 yr of age, with the adult height of 158.8 cm (target height: 156.0 cm).

Discussion

Several studies have demonstrated that prepubertal children with GD often show accelerated growth with skeletal maturation (1–6). In a study published in 1977, 66% of patients with GD diagnosed before 14 yr of age were above the 75th percentile in height for CA, of which 32% were above the 97th percentile (5). In more recent studies among younger patients, mean SD score for height was + 2.6 ± 0.7 in 7 patients aged 6.4 ± 2.4 yr (1) and + 1.25 in 14 children aged 3.4–7.5 yr (6). In these studies, bone maturation was also accelerated; for example, the patients' mean BA-to-CA ratio was 1.39 ± 0.35 (1), and the mean SD score for BA was + 1.03 ± 1.45 (2). The increased height gain with bone maturation appears to be more characteristic in younger patients (1).

Few studies have analyzed growth outcome in children with GD. Height SD scores showed a slight reduction with anti-thyroid therapy, but remained positive, and adult height SD scores

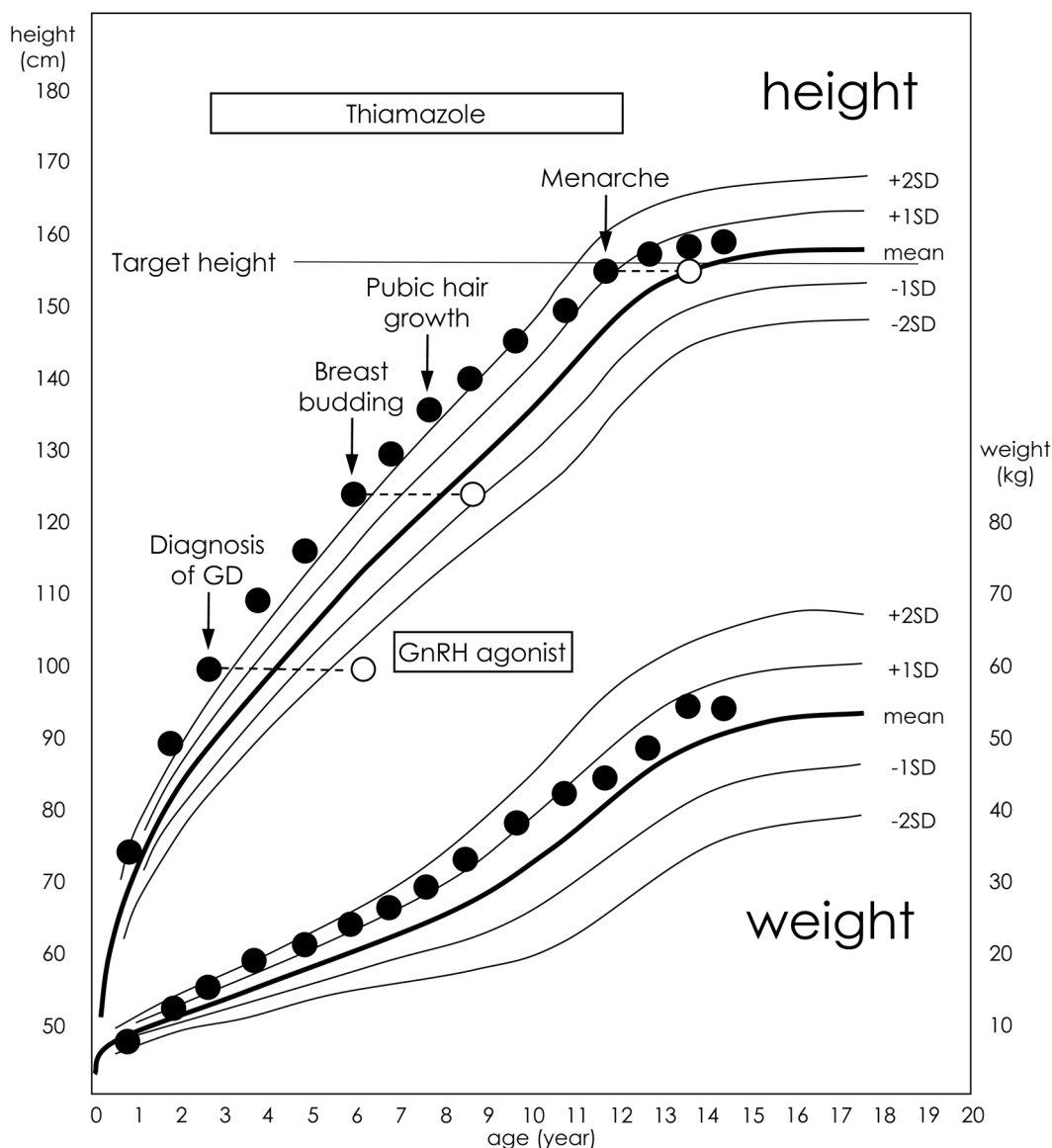


Fig. 1. Growth chart and clinical events of the patient. Diagnosis of Graves' disease was made at 2 yr 5 mo. Breast budding was recognized at approximately 6 yr. GnRH agonist was started at 6 yr 9 mo, and was ceased at 10 yr 6 mo. Pubic hair growth was noticed at 7 yr 6 mo, and menarche occurred at 11 yr 6 mo. Adult height is 158.8 cm which exceeded the target height (156.0 cm). Open circles indicate bone age.

were greater than their genetic potential (2–4). In one study, mean height SD score at GD onset was $+0.67 \pm 1.11$ (age: 7.6 ± 2.9 yr; $n = 33$) and in adulthood was $+0.28 \pm 1.10$ SD, (164.2 cm, target height 160.8 cm; $n = 22$) (2). In another study, the mean SD scores for height at GD onset and at adult were $+0.9$ (age, 2.6–12.1 yr; $n = 18$) and

$+0.5$ ($n = 12$) (3). In these two studies, the mean age at the beginning of puberty was 10.6 yr and 11.3 yr, and the mean age at menarche was 12.6 yr and 12.9 yr, respectively, all of which were within the normal range (2, 3). Thus, growth acceleration with skeletal maturation at GD onset does not seem to influence the timing of

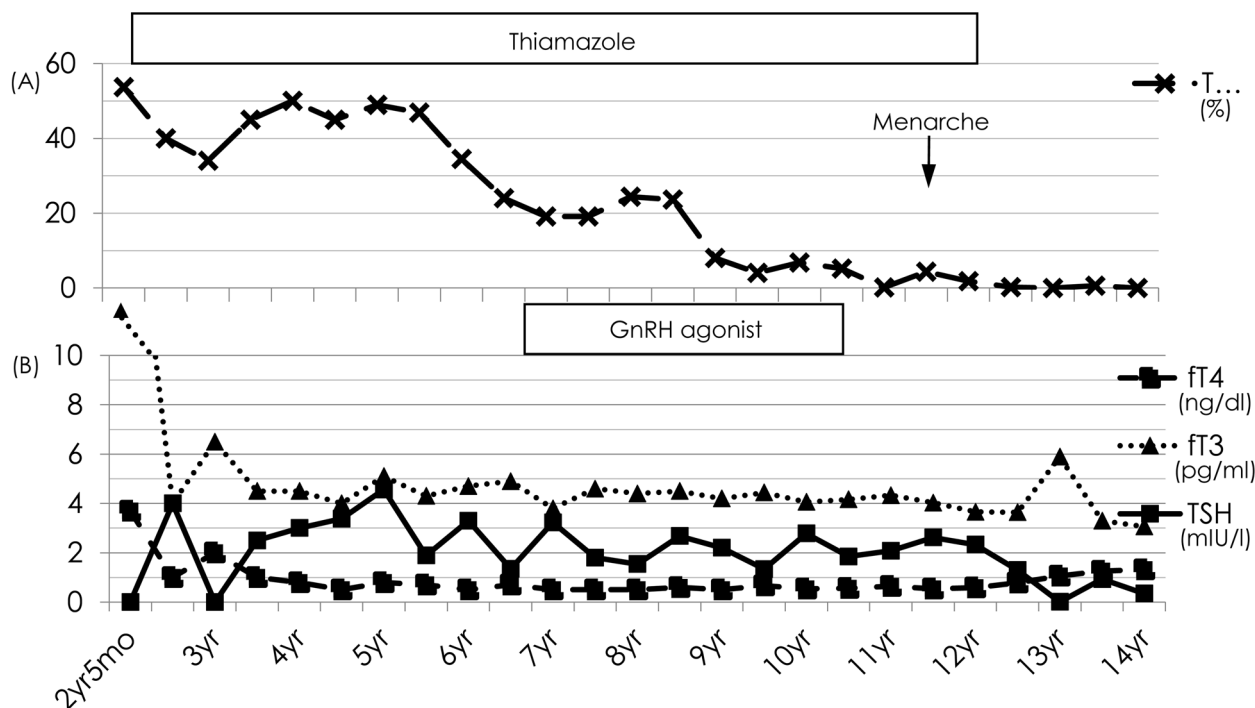


Fig. 2. Thyroid function of the patient. (A) TRAb (%) and (B) thyroid function (fT3, pg/ml; fT4, ng/dl; TSH, mIU/l) are shown. She was treated with thiamazole since 2 yr 5 mo until 12 yr. TRAb has been negative (below 10%) since 9-yr-old. Thyroid function approximately remained stable after age 3-yr.

puberty, and early pubertal onset in the girl with GD presented here appears to be a rare observation. However, as there is limited data concerning age at the beginning of puberty in younger children diagnosed with GD when they were toddlers, as in our case, mainly due to the rarity of GD in this age group, accumulation of such data is anticipated.

The reasons for early puberty in this case are unclear, as euthyroidism was maintained during treatment and the intracranial lesion was excluded. In general, taller girls tend to show earlier sexual maturation; however, this may not explain the current case, as early puberty has not been reported in tall girls with GD. Any influence by craniosynostosis is possible, as elevated intracranial pressure due to hydrocephalus, encephalitis, among others could potentially cause central precocious puberty. However, association between craniosynostosis and early puberty has not been documented to date. On the

other hand, thyrotoxicosis may not influence the timing of pubertal onset, in contrast to pubertal delay in hypothyroidism, as shown in a recent animal study (9). Consequently, although age at the start of puberty in girls with early-onset GD is yet to be elucidated, early puberty in this patient likely occurred by coincidence.

The present case showed early breast budding with LH activation, which is consistent with precocious puberty. However, tall stature and advanced BA might not be due to the result of pubertal development, but instead due to the preceding thyrotoxicosis, because height SD score and BA-to-CA ratio at pubertal onset were less than those at GD onset. Therefore, suspending the GnRH agonist therapy until growth acceleration became apparent could have been an option. However, considering the possible impairment of adult height by further BA advancement and unwillingness of sexual maturation at a young age, the treatment was

commenced with agreement by her family.

Premature craniosynostosis may be a common feature of GD: roentgenography studies have revealed early closure of skull sutures in many children with thyrotoxicosis (10). However, increased intracranial pressure or skull deformity, which would require surgical procedure, appears to be rare in older children (10) because such adverse phenomenon could only occur during early childhood when rapid head growth is required for intracranial development. Although the incidence of clinically apparent craniosynostosis in children with GD is unknown, two out of fifteen and one out of twelve patients (including one patient replicate) under 4 yr of age were listed in previous publications (11, 12).

In conclusion, we describe the first reported case of a girl with GD who developed early puberty. With gonadal suppression therapy by GnRH agonist, her adult height was not impaired, although the effect of the treatment remains inconclusive. Early puberty in this patient likely occurred by coincidence, since thyrotoxicosis-induced growth acceleration at GD onset does not appear to influence the timing of puberty. However, the average age at which puberty begins in girls with GD who are diagnosed during their toddler years is yet to be investigated.

References

1. Lazar L, Kalter-Leibovici O, Pertzalan A, Weintrob N, Josefsberg Z, Phillip M. Thyrotoxicosis in prepubertal children compared with pubertal and postpubertal patients. *J Clin Endocrinol Metab* 2000;85: 3678–82. [\[Medline\]](#) [\[CrossRef\]](#)
2. Cassio A, Corrias A, Gualandi S, Tato L, Cesaretti G, Volta C, *et al.* Influence of gender and pubertal stage at diagnosis on growth outcome in childhood thyrotoxicosis: results of a collaborative study. *Clin Endocrinol (Oxf)* 2006;64: 53–7. [\[Medline\]](#) [\[CrossRef\]](#)
3. Buckler JMH, Willgerodt H, Keller E. Growth in thyrotoxicosis. *Arch Dis Child* 1986;61: 464–71. [\[Medline\]](#) [\[CrossRef\]](#)
4. Wong GWK, Lai J, Cheng PS. Growth in childhood thyrotoxicosis. *Eur J Pediatr* 1999;158: 776–9. [\[Medline\]](#) [\[CrossRef\]](#)
5. Barnes HV, Blizzard RM. Antithyroid drug therapy for toxic diffuse goiter (Graves disease): thirty years experience in children and adolescents. *J Pediatr* 1977;91: 313–20. [\[Medline\]](#) [\[CrossRef\]](#)
6. Bossowski AT, Reddy V, Perry LA, Johnston LB, Banerjee K, Blair JC, *et al.* Clinical and endocrine features and long-term outcome of Graves disease in early childhood. *J Endocrinol Invest* 2007;30: 388–92. [\[Medline\]](#) [\[CrossRef\]](#)
7. Higashino T, Hirabayashi S. A secondary craniosynostosis associated with juvenile hyperthyroidism. *J Plast Reconstr Aesthet Surg* 2013;66: e284–6. [\[Medline\]](#) [\[CrossRef\]](#)
8. Marwaha RK, Tandon N, Desai AK, Kanwar R, Sastry A, Narang A, *et al.* The evolution of thyroid function with puberty. *Clin Endocrinol (Oxf)* 2012;76: 899–904. [\[Medline\]](#) [\[CrossRef\]](#)
9. Kiyohara M, Son YL, Tsutsui K. Involvement of gonadotropin-inhibitory hormone in pubertal disorders induced by thyroid status. *Sci Rep* 2017;7: 1042. [\[Medline\]](#) [\[CrossRef\]](#)
10. Johnsonbaugh RE, Bryan RN, Hierlwimmer R, Georges LP. Premature craniosynostosis: A common complication of juvenile thyrotoxicosis. *J Pediatr* 1978;93: 188–91. [\[Medline\]](#) [\[CrossRef\]](#)
11. Segni M, Leonardi E, Mazzoncini B, Pucarelli I, Pasquino AM. Special features of Graves disease in early childhood. *Thyroid* 1999;9: 871–7. [\[Medline\]](#) [\[CrossRef\]](#)
12. Ho YH, Chung EC, Park SAA. A 3-year-old girl with Graves disease with literature review. *Ann Pediatr Endocrinol Metab* 2014;19: 154–8. [\[Medline\]](#) [\[CrossRef\]](#)