

CASE REPORT

Turner's syndrome with concomitant hypopituitarism

Zoe Efstathiadou and Agathocles Tsatsoulis¹

Endocrine Unit, Department of Internal Medicine, University Hospital of Ioannina, Ioannina, Greece

¹To whom correspondence should be addressed at: Department of Medicine, University of Ioannina, Ioannina 45110, Greece.
E-mail: atsatsou@cc.uoi.gr

The unique case of a young woman with concomitant pituitary insufficiency and gonadal dysgenesis due to Turner's syndrome is described. At the age of 17 years, when first examined elsewhere, this patient was prepubertal and short and a diagnosis of growth hormone deficiency was made. One year later, while on growth hormone (GH) substitution, thyrotrophin deficiency and hypogonadotrophic hypogonadism were confirmed and thyroxine and sex steroid substitution therapy was initiated. Upon evaluation in our clinic, at the age of 30 years, the low final height achieved with the GH substitution therapy, a number of clinical characteristics and the absence of ovarian tissue on ultrasound led to examination of the patient's karyotype, which revealed concurrent gonadal dysgenesis due to Turner's syndrome. This case illustrates that the co-existence of primary and secondary hypogonadism may obscure and delay the diagnosis of Turner's syndrome, a diagnosis which alters the counselling of the patient from the reproductive perspective.

Key words: growth hormone deficiency/hypogonadotrophic hypogonadism/pituitary insufficiency/short stature/Turner's syndrome

Introduction

Turner's syndrome is the most common sex chromosome abnormality in females. The two features that best characterize the condition are gonadal dysgenesis and short stature. Due to lack of negative feedback from the ovaries, the hypogonadism in Turner's syndrome is hypergonadotrophic with marked increases of luteinizing hormone (LH) and follicle stimulating hormone (FSH) during the first months after birth and then again from the age of 8–9 years onwards. Short stature is usually not attributed to pituitary insufficiency of growth hormone (GH) secretion, although GH therapy has proven effective (Saenger, 1996).

We describe a unique case of concurrent pituitary insufficiency and Turner's syndrome.

Case report

A 30 year old woman was referred to the outpatient's clinic for evaluation of pituitary insufficiency. The patient was first examined at the age of 17 years because of short stature and delayed puberty. At that time, her height was 126 cm (Z-score –6), her body mass index (BMI) 20.8 kg/m², and her bone age corresponded to that of a 12 year old girl. A glucagon stimulation test revealed growth hormone deficiency with a normal cortisol response. The patient's thyroid function was within normal limits. The rest of the laboratory investigations were unremarkable. Growth hormone substitution therapy was initiated and continued for a period of 4 years. At the age of 18 years, the diagnosis of hypogonadotrophic hypogonadism was made on the basis of delayed puberty and low concentrations of basal and gonadotrophin releasing hormone (GnRH)-stimulated gonadotrophins. Consequently, cyclic administration of conjugated oestrogens and medroxyprogesterone was initiated. At the same time, the patient was started on thyroxine replacement therapy for secondary hypothyroidism.

The present examination, in our institution when the patient was aged 30 years, revealed an overweight young woman (BMI = 28.3 kg/m²), with a central pattern of fat distribution. The patient's height was 148cm (Z-score –2.35). She had a round face with micrognathia and her neck was short without the presence of webs. A number of pigmented naevi were observed in her face and body. Secondary sex characteristics were present and she had cyclic vaginal bleeding while on oestrogen and progestin administration. The rest of the clinical examination was negative.

In order to achieve a global perspective of the patient's problem, in view of lack of complete records of the previous medical history, it was decided to re-evaluate the hypothalamic–pituitary axis after discontinuation of current treatment. Consequently, a combined insulin tolerance, GnRH and thyroid releasing hormone (TRH) test was performed and confirmed growth hormone, gonadotrophin and thyrotrophin deficiency, whereas a sufficient response of cortisol was noted suggesting intact function of adrenocorticotroph cells (Table I). Prolactin concentrations were normal. A magnetic resonance imaging (MRI) scan of the hypothalamic and pituitary region revealed hypoplastic pituitary and ectopic localization of the neurohypophysis to the tuber cinereum. Ultrasound sonography of the patient's pelvis showed an hypoplastic uterus whereas the ovaries were not possible to visualize.

In view of the patient's clinical features and the lack of ovarian ultrasonographic visualization, a karyotype analysis

Table I. Results of dynamic testing of hypothalamic–pituitary axis by combined insulin tolerance, thyroid releasing hormone (TRH) and gonadotrophin releasing hormone test

	Duration (min)				
	0	30	60	90	20
Glu (mmol/l)	5.27	2.22	3.77	4.1	4.77
Cortisol (nmol/l)	389	309	662	560	460
GH (pmol/l)	4.65	4.65	4.65	4.65	4.65
TSH (mIU/l)	0.03	0.11	0.1		
LH (IU/l)	1	0.7	1		
FSH (IU/l)	0.5	1.2	1.5		

GH = growth hormone; TSH = thyroid stimulating hormone; FSH = follicle stimulating hormone; Glu = glucose.

was done and this was 45,X with no evidence of mosaicism, establishing the diagnosis of Turner's syndrome.

The patient continued substitution therapy with levo-thyroxine and cyclic administration of conjugated oestrogens and progestagen. She was checked for cardiac and renal manifestations of Turner's syndrome and the results were negative. In addition, future fertility options were discussed and explained to the patient.

Discussion

Turner's syndrome, first described 60 years ago, affects about 1 in 1500–2500 live-born female infants (Saenger, 1996). A number of characteristic clinical features involving the eyes, ears, mouth, jaws, skin, neck and skeleton lead to a suspicion of this syndrome early in life. Once the diagnosis has been confirmed by chromosomal analysis, attention should be drawn to certain aspects of this syndrome. On the one hand, attention should be given to the revelation of clinical characteristics of the syndrome such as aortic coarctation and renal deformities. On the other hand, management of short stature and hypogonadism should be planned. If the diagnosis is missed in early childhood, hypergonadotrophic hypogonadism is the basis of diagnosis later in adolescence.

To our knowledge, there are only four cases of Turner's syndrome associated with hypogonadotrophic hypogonadism in the literature. The first was in a girl with thalassaemia major and pituitary insufficiency was attributed to haemochromatosis (Afonso Lopes *et al.*, 1995). In the second and third cases the hypogonadotrophic hypogonadism was attributed either to an auto-immune process, or to the presence of arachnoidocele (Valenta *et al.*, 1984), and in a fourth case it co-existed with combined immunodeficiency (Donti *et al.*, 1989). Thus, our case is unique, in that in our patient Turner's syndrome co-exists with primary pituitary insufficiency and low concentrations of gonadotrophins. Thyroid function is abnormal in 20–30% of patients with Turner's syndrome, and is usually associated with Hashimoto's thyroiditis (Pai *et al.*, 1977). Despite this observation, our patient had secondary hypothyroidism that was apparent during her follow-up for the GH deficiency.

There have been two case reports associating Turner's syndrome with idiopathic diabetes insipidus (Otsuka *et al.*,

1971; Balkin *et al.*, 1978). Our patient did not have any symptoms indicating the existence of diabetes insipidus and urine-concentrating capacity was normal. The MRI finding of ectopic neurohypophysis and hypoplastic adenohypophysis has been found in a number of patients with hypopituitarism (Badawy *et al.*, 1994; Hamilton *et al.*, 1998), indicating that pituitary deficiency could be part of a large spectrum of midline brain abnormalities. Turner's syndrome is known to be associated with congenital malformations but, to our knowledge, the association with this specific anatomical abnormality is the first to be described.

The revelation of the 45,X gonadal dysgenesis in this young woman was crucial. First, because of the existence of Turner's syndrome, a thorough evaluation of cardiac and renal deformities was imperative in order to rule out abnormalities necessitating special care. Second, because the approach in regard to fertility problems differs between these two situations: in hypogonadotrophic hypogonadism, pregnancy can be achieved by ovulation induction, whereas in Turner's syndrome it could only be achieved with donated eggs.

References

- Afonso Lopes, A., Benador, D., Wacker, P. *et al.* (1995) Turner's syndrome and hypogonadotrophic hypogonadism: thalassaemia major and hemochromatosis. *J. Pediatr. Endocrinol. Metab.*, **8**, 73–77.
- Badawy, S.Z., Pisarska, M.D., Wasenko, J.J. *et al.* (1994) Congenital hypopituitarism as part of suprasellar dysplasia. A case report. *J. Reprod. Med.*, **8**, 643–648.
- Balkin, M.S., Hoffman, R. and Willner, J. (1978) Idiopathic diabetes insipidus occurring in a patient with Turner's syndrome. *Mt Sinai J. Med.*, **45**, 742–747.
- Donti, E., Nicoletti, I., Venti, G. *et al.* (1989) X-ring Turner's syndrome with combined immunodeficiency and selective gonadotropin defect. *J. Endocrinol. Invest.*, **12**, 257–263.
- Hamilton, J., Chitayat, D., Blaser, S. *et al.* (1998) Familial growth hormone deficiency associated with MRI abnormalities. *Am. J. Med. Genet.*, **80**, 128–132.
- Otsuka, K., Kunitake, A., Fujimatsu, S. *et al.* (1971) Case of Turner's syndrome associated with idiopathic diabetes insipidus. *Saishin Igaku.*, **26**, 416–421.
- Pai, G.S., Leach, D.C., Weiss, L. *et al.* (1977) Thyroid abnormalities in 20 children with Turner's syndrome. *J. Pediatr.*, **91**, 267–269.
- Saenger, P. (1996) Turner's syndrome. *N. Engl. J. Med.*, **335**, 1749–1754.
- Valenta, L.J., Elias, A.N. and Bocian, N. (1984) Atypical biochemical findings in Turner's syndrome: identification of a possible subset. *Fertil. Steril.*, **42**, 798–802.

Received on April 6, 2000; accepted on July 14, 2000