

Case Report

Turner syndrome with LADA and hashimoto thyroiditis: a case report and review of literature

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Abstract: Objective: We report a case of a patient with Turner syndrome (TS) accompanied with Latent Autoimmune Diabetes In Adults (LADA) and Hashimoto thyroiditis (HT). Case: A 47-year-old patient initially presented to the Department of Otolaryngology with a chief complaint of recurrent left ear discharge with hearing loss for more than 20 years. She was subsequently referred to the endocrinologists due to high blood glucose and short stature. Standard otolaryngologic examination indicated chronic left suppurative otitis media. Typical clinical features and karyotype of 45,XO confirmed the diagnosis of turner syndrome. Elevated fasting plasma glucose (FPG) and glycosylated hemoglobin A1c established the diagnosis of diabetes mellitus (DM), and low levels of C-peptide and positive GAD-antibody indicated that the type of diabetes was LADA. Based on an abnormal thyroid ultrasound and significantly raised thyroid autoantibodies, we made the diagnosis of HT. She was treated with insulin injections, calcium supplementation and modified radical mastoidectomy. Conclusion: Hearing loss is one of the major clinical manifestations of TS. And endocrine-metabolic anomaly such as thyroid abnormality, glucose and lipid metabolism abnormality are also the typical clinical features of TS. There is an increased risk of autoimmune diseases among women with Turner syndrome, such as hashimoto thyroiditis, type 1 diabetes mellitus, dupuytren's contracture and ulcerative colitis. The presence of autoimmune diseases should be noticed in the case of TS to prevent misdiagnosed and mistreatment.

Keywords: Turner syndrome, hashimoto thyroiditis, LADA

Introduction

Turner syndrome is the only known sex-chromosomal monomer disease, affects 20-50 per 100000 live born girls, usually detected at puberty due to short stature and secondary dysplasia. Otitis media and hearing loss are also two of the reasons for the diagnosis. The typical clinical presentation in TS patients includes short stature, high arched palate, narrow maxilla, short webbed neck, shield-shaped thorax, shortened metacarpal IV, cubitus valgus, cardiac malformations, kidney malformations, poor breast development, rudimentary ovaries, no menstruation and infertility. Recently, a relationship between Turner syndrome and autoimmune diseases has been reported. There is an increased risk of autoimmune diseases among women with Turner syndrome, such as hashimoto thyroiditis, type 1 diabetes mellitus, dupuytren's contracture and ulcer-

ative colitis. Here, we report a combination of Turner syndrome with these other clinical entities, and review the relevant literatures.

Case report

A 47-year-old woman was admitted to the department of otolaryngology with a chief complaint of recurrent left ear discharge with hearing loss for more than 20 years. She was subsequently referred to the endocrinologists due to high blood glucose and short stature. Her parents are non-consanguineous and she has 3 elder brothers. Her mother's height is about 130 cm but her father's and brothers' heights are within the normal range from 160 cm to 165 cm. She was born through natural childbirth but her birth weight was unknown. According to the patient, she was weak and she had short stature since childhood. Her academic performance ranked in the middle of her

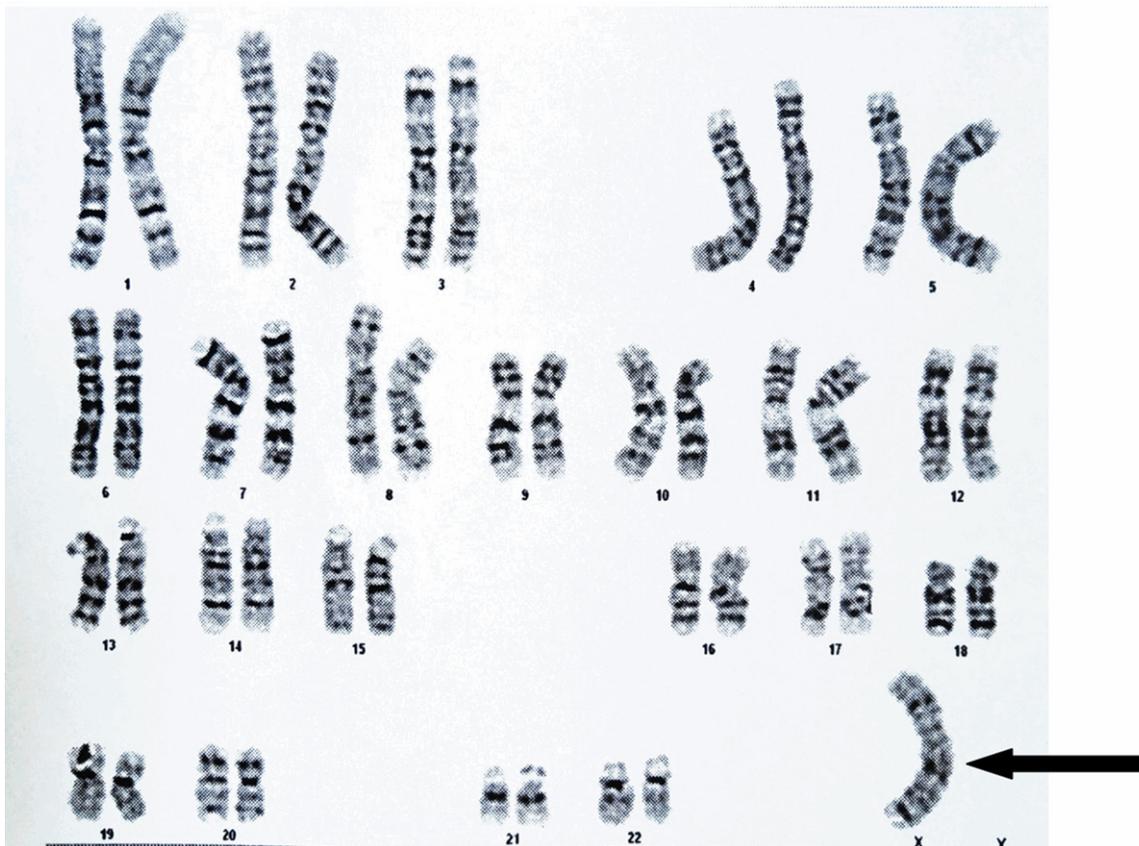


Figure 1. Karyotype from the patient (1-22 are the normal euchromosomes, there is only one normal X chromosome, the other missing X chromosome is indicated by the arrow).

class. Pubic hair and armpit hair are absent. She has no menstruation and has never been pregnant. She has no history of diabetes mellitus and has no symptom of polydipsia, polyuria, polyphagia or weight loss.

On physical examination, her weight, height and body mass index were 32 kg, 130 cm, and 18.9 kg/m², respectively. A high arched palate, narrow maxilla, short webbed neck, shield-shaped thorax and left cubitus valgus were noted. The low posterior hairline was not remarkable. No finger deformity was found. No armpit hair, pubic hair growth, or breast development were noted. The reproductive organs were infantile. The external auditory canal of the left ear was moist and binaural hearing was lost. The remainder of the examination was unremarkable.

Laboratory evaluations showed an elevated follicle-stimulating hormone (FSH) level (19.63 mIU/mL) as well as low estradiol (<10.00 pg/

mL) and progesterone (0.10 ng/ml) levels. The luteinizing hormone (LH) level of 3.16 mIU/mL and the testosterone level of 0.43 nmol/L were within normal limits. Thyroid function was normal, but both the thyroglobulin antibody (573.61 IU/L) and thyroid peroxidase antibody (414.93 IU/ml) were elevated. The FPG was 15.29 mmol/L and the HbA1c was 10.17%. The low levels of fasting plasma C-peptide (215.50 pmol/L) and 2-hour C-peptide (455.50 pmol/L) revealed poor islet function. Furthermore, the GAD-antibody was positive and the other two (ICA and INS-Ab) were negative. ECG revealed sinus tachycardia, and a short PR interval. The renal ultrasound was normal. The thyroid ultrasound showed diffuse lesions and a right lobe thyroid nodule. The echocardiogram showed mild mitral and tricuspid valve regurgitation. The uterus and ovaries could not be visualized by abdominal ultrasound. Furthermore, vaginal ultrasound showed an infantile uterus; bilateral ovaries could not be detected. Bone density scans indicated osteopenia. The hand X-ray

was normal, and no shortened metacarpal IV was observed. A karyotype confirmed a 45,XO genotype (**Figure 1**).

The clinical diagnosis was Turner syndrome, latent autoimmune diabetes in adults, hashimoto thyroiditis, thyroid nodule and chronic suppurative otitis media (left ear). She was treated with insulin injections, calcium supplementation and modified radical mastoidectomy. Because the thyroid function was normal and she had no signs of malignancy in the thyroid nodule (size of about 0.43*0.27 cm, regular shape, distinct boundary, cystic, rough echo, with no calcification and no obvious blood flow signal), as follow up we plan to do thyroid function tests and ultrasound.

Discussion

Turner syndrome is a condition of congenital ovaries agenesis, caused by a partial or total deletion of an X chromosome with structural abnormalities, occurring in 1:5,000 to 1:2,000 females [1-5]. The common chromosome karyotype of TS is 45,XO, accounts for about 48 percent of the cases of TS. The typical clinical features of TS include short stature, absent or incomplete development of gonadal and secondary sex characteristics, body dysmorphic and osteoporosis, congenital gut malformation, an endocrine-metabolic anomaly and lymphedema. Patients of TS can have average or below-average intelligence. This case was in line with all of the clinical features except congenital gut malformation and lymphedema. Because the typical karyotype of Turner syndrome (45,XO) was found, the patient was diagnosed with Turner syndrome. The diagnosis of DM was confirmed by the elevated FPG and HbA1c. Furthermore, the type of DM was LADA based on low levels of C peptide and positive GAD antibody. Due to an abnormal thyroid ultrasound and significantly raised thyroid autoantibodies, the diagnosis of HT has been made.

A high prevalence of autoimmune disease has been reported in patients with Turner syndrome. Women with Turner syndrome are at significantly increased risk of specific autoimmune diseases, such as hashimoto thyroiditis, type 1 diabetes mellitus, dupuytren's contracture, and ulcerative colitis [6]. Among these autoimmune diseases, hashimoto thyroiditis is by far the

most common [7]. According to published research studies, the prevalence of TS with HT ranges from 13.3% to 55% [8], and in those with Turner Syndrome, their risk of having hypothyroidism is increased 5.8 fold [7]. In a cross-sectional study in 107 Danish TS patients, the prevalence of anti-TPO was 45% among patients with TS, which was significantly higher than that among the general population (13%) [9]. Another investigation involving 66 Italian TS patients showed that the prevalence of thyroid autoimmune disorders was 39.4%, of which 21.2% had hashimoto thyroiditis with clinical or subclinical hypothyroidism [10]. Other studies found that hashimoto thyroiditis affected about 50% of TS patients [11, 12]. The frequency among different studies varied greatly, this variation may be due to selection bias, different the inclusion criteria (some included pediatric patients and some included adult patients) and various karyotypes [10].

An 11.6-fold increased risk of getting type 1 diabetes has been reported in patients with TS [7]. An investigation showed that Danish women with TS had a 4-fold increased risk of developing male-predominant autoimmune diseases such as insulin dependent diabetes mellitus (type 1 diabetes) compared with Danish women in general [6]. Also they found that the prevalence of anti-GAD-65 was 4%, which was significantly higher than the prevalence among general population that was only 1.1% [9].

Although large studies have demonstrated an increased incidence of autoimmune diseases among patients with TS, the reason why patients with TS are predisposed to autoimmune diseases remains unclear. Factors associated with ovarian failure or a complex interaction between genetic and environmental factors may increase the rate of autoimmune disease [14-16]. Haploinsufficiency of genes on the X chromosome could be responsible for the lack of self-protein exposure in the thymus and escape of autoreactive T cells, thus resulting in autoimmunity [15].

Autoimmunity has been recognized as one of the most prominent characteristics of TS [17]. Therefore, early diagnosis and timely treatment are particularly important. Early detection of thyroid dysfunction would have a positive effect on thyroid disease itself and the prevention of cardiovascular events. Thyroid function

in women with Turner syndrome should be monitored often, and adequate replacement therapy with levothyroxine should be started promptly once hypothyroidism is diagnosed.

We have described a patient with Turner syndrome associated with LADA and Hashimoto thyroiditis. Review of the literature, both the combination of TS with LADA and TS with HT are well-documented. However, there is few literature reported regarding the combination of the three. As the prevalence of TS is 1:5,000 to 1:2,000 in live born females, this is a rare case report and their co-existence should be considered and further investigated.

Disclosure of conflict of interest

None.

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References

- [1] Cordts EB, Christofolini DM, Dos Santos AA, Bianco B, Barbosa CP. Genetic aspects of premature ovarian failure: a literature review. *Arch Gynecol Obstet* 2011; 283: 635-643.
- [2] Freriks K, Timmermans J, Beerendonk CC, Verhaak CM, Netea-Maier RT, Otten BJ, Braat DD, Smeets DF, Kunst DH, Hermus AR, Timmers HJ. Standardized multidisciplinary evaluation yields significant previously undiagnosed morbidity in adult women with Turner syndrome. *J Clin Endocrinol Metab* 2011; 96: E1517-1526.
- [3] McCarthy K, Bondy CA. Turner syndrome in childhood and adolescence. *Expert Rev Endocrinol Metab* 2008; 3: 771-775.
- [4] Sybert VP, McCauley E. Turner's syndrome. *N Engl J Med* 2004; 351: 1227-1238.
- [5] Verver EJ, Freriks K, Thomeer HG, Huygen PL, Pennings RJ, Alfen-van der Velden AA, Timmers HJ, Otten BJ, Cremers CW, Kunst HP. Ear and hearing problems in relation to karyotype in children with Turner syndrome. *Hear Res* 2011; 275: 81-88.
- [6] Jørgensen KT, Rostgaard K, Bache I, Biggar RJ, Nielsen NM, Tommerup N, Frisch M. Autoimmune diseases in women with Turner's syndrome. *Arthritis Rheum* 2010; 62: 658-666.
- [7] Gravholt CH, Juul S, Naeraa RW, Hansen J. Morbidity in Turner syndrome. *J Clin Epidemiol* 1998; 51: 147-158.
- [8] Medeiros CC, Marini SH, Baptista MT, Guerra G Jr, Maciel-Guerra AT. Turner's syndrome and thyroid disease: a transverse study of pediatric patients in Brazil. *J Pediatr Endocrinol Metab* 2000; 13: 357-362.
- [9] Mortensen KH, Cleemann L, Hjerrild BE, Nexø E, Locht H, Jeppesen EM, Gravholt CH. Increased prevalence of autoimmunity in Turner syndrome—influence of age. *Clin Exp Immunol* 2009; 156: 205-210.
- [10] Grossi A, Crinò A, Luciano R, Lombardo A, Cappa M, Fierabracci A. Endocrine autoimmunity in Turner syndrome. *Ital J Pediatr* 2013; 39: 79.
- [11] Larizza D, Calcaterra V, Martinetti M. Autoimmune stigmata in Turner syndrome: when lacks an X chromosome. *J Autoimmun* 2009; 33: 25-30.
- [12] Germain EL, Plotnick LP. Age-related anti-thyroid antibodies and thyroid abnormalities in Turner syndrome. *Acta Paediatr Scand* 1986; 75: 750-755.
- [13] Bolar K, Hoffman AR, Maneatis T, Lippe B. Long-term safety of recombinant human growth hormone in Turner syndrome. *J Clin Endocrinol Metab* 2008; 93: 344-351.
- [14] Bakalov VK, Gutin L, Cheng CM, Zhou J, Sheth P, Shah K, Arepalli S, Vanderhoof V, Nelson LM, Bondy CA. Autoimmune disorders in women with Turner syndrome and women with karyotypically normal primary ovarian insufficiency. *J Autoimmun* 2012; 38: 315-321.
- [15] Bianchi I, Lleo A, Gershwin ME, Invernizzi P. The X chromosome and immune associated genes. *J Autoimmun* 2012; 38: J187-J192.
- [16] Fierabracci A. Unravelling the role of infectious agents in the pathogenesis of human autoimmunity: the hypothesis of the retroviral involvement revisited. *Curr Mol Med* 2009; 9: 1024-1033.
- [17] Bondy CA; Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner syndrome study group. *J Clin Endocrinol Metab* 2007; 92: 10-25.