CASE REPORT

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Turner's Syndrome and Hashimoto's Thyroiditis: An Association between Genetics and Autoimmunity

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Abstract

Worldwide approximately 1.5 million women suffer from Turner Syndrome . X chramasome aberrations can be of different types, which comprise of the X monosomies like (45, X) and mosaicism (50 - 70%), which includes 45X/46 XX, 45 X/46 XY, 45 X/46 XX/47 XXX, 45 X/46 X, i (Xq), 45 X/46, and X del (Xp), as well as structural aberrations, such as the total or partial deletion of the short arm of an X chromosome (46, X del (Xp)), the isochromosome of the long arm of an X (46, X, i (Xq), ring chromosome (46, X, r (X), and marker chromosome (46, X + m). It has been seen that, the presence of two X chromosomes and skewed inactivation of one of them are thought to play a protective role in females, who generally mount a stronger immune response to different types of pathogens. However, the hyperresponsiveness of the immune system in females results in a predisposition towards auto-immune diseases. Autoimmune diseases are 2 - 3 times more frequent in women with Turner syndrome.

Key words: Turner syndrome, Hashimoto's Thyroiditis, X chromosomes

Introduction

Turner syndrome (TS) is a genetic disease characterised by quantitative or structural aberrations in one of two X chromosomes with frequent mosaicism. Incidence of Turner syndrome (TS) is estimated between 1 in 2000 to 1 in 2500 live female births[2,3].

There is no correlation between the onset of TS and age of the parents, environmental factors, or use of specific drugs/ toxins. Turner syndrome is observed in all races all over the world, and it is not hereditary; therefore, it can occur even in families with healthy individuals.

Women with Turner syndrome show typical phenotypic features, including short stature; a short and webbed neck; cubitus valgus; a broad chest with widely spaced nipples; and lymphoedema of the hands and feet, which is particularly common at birth. The characteristics of Turner Syndrome comprise low positional and dysplastic ears, antimongoloid slant, epicanthus, poor facial expression, low descending hairline on the neck, gothic palate, and micrognathia. The frequency of signs and symptoms varies in different patients with Turner syndrome and may depend on the type of X chromosome aberrations.

Individuals with Turner syndrome (TS) are prone to develop autoimmune disorders, particularly thyroiditis, the most frequent of which is Hashimoto's disease. Thyroid autoimmune diseases are characterised by abnormal lymphocytic activation, directed against self-antigens. The cause of autoimmune diseases in TS remains unclear, although there are several mechanisms that suggest a potential correlation between the X-isochromosome and increased prevalence of anti-thyroid peroxidase (TPO-Ab) antibodies. Other researchers, in turn, suggested that a genetic factor located on the X-gene could play a role in the development of thyroid autoimmune diseases. This claim can be confirmed by screening each TS women for thyroid diseases. Nonetheless, the risk of hypothyroidism or hyperthyroidism in Turner syndrome remains independent of the karyotype, and the treatment of thyroid abnormalities do not differ from those established for healthy populations. We present the case of young lady who was diagnosed as Turner syndrome and Hashimotos thyroiditis.

Case report

A 23-year-old lady presented with complaints of generalised weakness, constipation facial puffiness and primary amenorrhoea along with not gaining height and weight according to her age. Her mother also complained about her poor scholastic performance as compared to other children of same age.

Obstetric history: She was borne of a non-consanguineous marriage, normal vaginal delivery with normal milestones according to her age and sex up to 8 years.

On examination her height was120 cm, the weight was 28 kg, and body mass index was 19.4 kg/m^2. Her heart rate was 84 beats/minutes, blood pressure was 98/68 mm Hg.

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She had mild pallor, webbed neck, broad shield chest, cubitus valgus and her external genitalia were juvenile, with a pubertal state of A1M1P1 (Tanner staging). All other systemic examination was normal. As phenotypic examination was in favour of Turner syndrome (Fig. 1), we sent hormonal assays, chromosomal karyotyping, abdominal and pelvic ultrasound, thyroid profile, X-ray chest PA view and X-ray of forearm for confirmation of her age, ECG, echocardiography and other routine examination were done. X-ray chest showed cardiomegaly. Her bone age was 12 - 13 years, which lagged behind her chronological age.

The results of karyotyping demonstrated a gene karyotype of 46, X, psu idic (X) (q28).

Thyroid function analysis showed that the thyroid-stimulating hormone (TSH) level was >100 μIU/mL (normal range, 0.35 - 4.94 μIU/mL), free FT4 level <0.4 ng/dL (normal range 0.7 - 1.48 ng/dL), freeT3 level <1.5 pg/mL (normal range 1.58 - 4.91 pg/mL), and anti TPO 829.67 IU/mL (normal range 0 - 5.61 IU/mL).

Fig. 1: *Phenotype of Turner Syndrome.*

Other hormonal tests showed the prolactin level was 6.62 ng/mL (reference range 5.18 - 26.53 ng/mL), luteinizing hormone level was 7.7 mIU/mL, and the of follicle-stimulating hormone was 73.08 mIU/mL.

Ultrasound whole abdomen was suggestive of a hypoplastic uterus with bilateral streak and atrophic ovaries. Ultrasound of thyroid gland was suggestive of multiple small cystic nodules in bilateral lobes of with normal size. ECG was suggestive of low voltage complexes, and 2D Echo showed moderate circumferential pericardial effusion. After complete evaluation, patient was diagnosed as a case of Turner syndrome with autoimmune thyroiditis. She was given symptomatic treatment in the form of thyroxine 62.5 microgram per day, and diuretic. Patient and her mother were counselled about treatment and prognosis. She was discharged in satisfactory condition.

Discussion

Autoimmune thyroid disorders are the most common autoimmune condition seen in patients with Turner syndrome, with a prevalence significantly higher than in the general population. The absence of one X chromosome is thought to contribute to immune dysregulation, and increasing susceptibility to autoimmune diseases.

The largest number of immune-related genes is housed on the X chromosome, where genes FOXP3 and PTPN22 are presumed to contribute most commonly to the pathogenesis of Turner syndrome. Women suffering from TS present at higher-than-average risk of developing autoimmune thyroid diseases, where hypothyroidism appears most commonly, mainly in the subclinical form, occurring in about 58% of TS women. It may develop not only in adolescence and adult age, but also in childhood, and is characterised by elevated TSH levels, while maintaining normal T4 concentrations. Scientific literature also provides a case of Hashimoto's encephalopathy co-existing with Turner syndrome, which is a rare disease with an autoimmune pathogenesis. Nevertheless, up to now, the autoimmune mechanism underlying this syndrome has not been completely understood and, requires further research.

Due to a higher incidence of autoimmune diseases in patients with TS, current guidelines recommend screening for hypothyroidism at the time of diagnosis using TSH and a fT4 (free-thyroxine), which should commence in early childhood

and be subsequently performed annually. However, there are no recommendations for routine testing of thyroid antibodies.

Patients with TS suffer from an increased risk of celiac disease, vitiligo, psoriasis, type 1 diabetes, adrenocortical insufficiency, juvenile idiopathic arthritis, and inflammatory bowel disease.

Another noteworthy issue is the screening for cardiovascular abnormalities of TS itself. Both congenital heart malformation and acquired disorder such as ischaemic heart disease contributes greatly to morbidity and mortality in patients with TS. Bicuspid aortic valve is the most common congenital malformation with a prevalence of 14 - 34%. Other common phenotypic characteristics of heart include coarctation of the aorta (7 - 14%) and aortic dilation/ aneurysm (3 - 42%)[4]. These cardiovascular malformations can occur in isolation or in combination in patients with TS[13]. Hypertension occurs in 50% of patients with TS[4]. Persistent elevation of systolic blood pressure is a risk factor for aortic root dilation and the consequent aortic dissection.

Hypothyroidism in Turner syndrome can worsen growth failure, delay puberty, and affect cognitive performance. Therefore, early detection and prompt treatment is essential. Gravholt *et al* in their study demonstrated that the genes IL3RA and CSF2RA located on the X chromosome are differentially methylated in women with Turner syndrome in comparison to healthy women with a karyotype of 46, XX. Furthermore, they hypothesized that IL3RA could be associated with an increased risk of autoimmune diseases in Turner syndrome, such as thyroiditis[4].

The causes of pericardial effusion are numerous, among which hypothyroidism is an uncommon one. The prevalence of pericardial effusion is 3 - 6% in patients with mild disease and 80% in myxoedema. It is revealed during cardiovascular evaluation in most cases, but can also be the initial presentation. Increased capillary permeability and reduced lymphatic drainage result in gradual accumulation of fluid in the pericardial space, though the mechanism has not been fully elucidated[6]. The process usually takes from months to years, as the severity and chronicity of hypothyroidism varies[7]. Mortensen *et al* and Chen *et al* reported an increased frequency of AITDs with age[8,9]. In our patient also X-ray chest, ECG and echocardiography suggested pericardial effusion. Her chronological age did not correspond with her bone age which may be due to both Turner syndrome as well as thyroid disorder. Though euthyroidism is a common clinical phenotype, transition to subclinical or overt hypothyroidism can occur, emphasizing the importance of screening for thyroid diseases through the life-span[10,11]. A higher prevalence of autoimmune thyroiditis was reported in iso-chromosome Xq population[2,12]. Further studies are required to elucidate the underlying mechanism. Despite the well documented role of oestrogen in AITDs, no association between oestrogen administration and the occurrence of AIDs was revealed in TS patients.

The exact genetic and epigenetic mechanism of cardiopathies in TS remains unclear. Acquired heart abnormalities are associated with obesity, dyslipidaemia, hypertension, diabetes mellitus and low oestrogen levels. Cardiovascular diseases, both congenital and acquired ones, should be screened in patients with TS.

In conclusion, this case highlights that hypothyroidism should be screened in patients with pericardial effusion, and also emphasized the link between autoimmune thyroid diseases and Turner Syndrome.

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