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Short Communication

Health problems in Turner syndrome

Mehdi Salek, Ahmad Reza Okhovvat**, Masoumeh Sadeghi***, Hamid Reza Roohafza***, Roya Kelishadi***, Pooneh Memar Ardestani****, Masoumeh Raoufei****, Mohammad Hossein Moaddab*****, Hossein Nejadnik******

Abstract

BACKGROUND: Although cardiovascular malformations are well-recognized congenital anomalies in Turner syndrome (TS), other clinical features and a great variety of dysmorphic signs can also be observed. There are few studies about different medical problems in pre-selected groups of patients with Turner syndrome. Therefore, in this study we aimed to assess the prevalence of some medical problems in Turner syndrome.

METHODS: This was a case series from April to October 2005. We studied 40 patients with TS who attended the Endocrine and Metabolic Research Center. Audiometry, echocardiography, ultrasonography of kidneys and urinary tracts, thyroid function tests, fasting blood sugar, lipid profile as well as anthropometric and blood pressure measurements were assessed in all patients and collected data were analyzed by SPSS version 10.

RESULTS: Of the 40 subjects 62.5% (n = 25) had cardiac anomalies, 20% (n = 8) had high blood pressure, about 60% (n = 24) suffered from hearing loss and 15% (n = 6) suffered from duplication or dilatation of urinary collecting system. The relative frequency of hypothyroidism, hypercholesterolemia and hypertriglyceridemia was 25% (n = 10), 30% (n = 12) and 32.5% (n = 13), respectively.

CONCLUSIONS: Medical problems are common in TS patients and the routine screening of their health conditions should be performed at the time of diagnosis and at regular intervals.

KEY WORDS: Turner syndrome, health problems, hypertension, heart disease.

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The designation "Turner syndrome" (TS) is a clinical characterization caused by a complete or partial absence of the second sex chromosome which affects 1 in 2000 to 5000 live-born females and it is characterized by reduced adult height, female phenotype, gonadal dysgenesis, sexual infantilism and somatic abnormalities that leads to primary amenorrhea, delayed pubertal development and infertility [1]. Congenital and acquired anomalies and a great variety of dysmorphic signs may also be observed. But, the etiology of the abnormalities that leads to this rather substantial increase is not clear [2].

Although short stature is the most prominent characteristic of this disorder, a wide range of associated medical problems have been reported, which may lead to a three-fold increase in overall mortality and morbidity as well as reduced life expectancy by up to 13

*Assistant professor, Department of Pediatrics, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
** Assistant Professor, Department of ENT, Isfahan University of Medical Sciences, Isfahan, Iran.
***Assistant Professor, Cardiovascular Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
****Researcher and Medical Doctor, Isfahan University of Medical Sciences, Isfahan , Iran.
*****Researcher and Medical Doctor, Endocrine and Metabolic Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
Correspondence to:Dr Mehdi Salek, Assistant professor, Department of Pediatrics, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: salek@med.mui.ac.ir

years [3]. Cardiovascular and renal anomalies, hearing difficulties and an increased incidence of autoimmune disorders are frequent comorbidities which increase life time risks. Disorders of glucose intolerance, type 2 diabetes, dyslipidemia, obesity and liver dysfunction often are delayed until adulthood and primary hypothyroidism occur both in childhood and adulthood [4]. The prevalence of these problems varies in different studies which may be due to factors such as karyotype and age [3]. Strategies for long term surveillance of TS patients may be made if the risks can be stratified regionally .We did not have any data on the frequency of different health problems of TS patients in Isfahan. Therefore, the aim of our study was to assess some medical problems in TS patient in Isfahan city, Iran.

Methods

Forty children and adolescents aged 10 to 20 with diagnosed TS were included in this case series at the Endocrine and Metabolic Research Center, in Isfahan University of Medical Sciences from April to October 2005. Ultrasonography of kidneys and urinary tract, audiometry, cardiac echocardiography, thyroid function tests, fasting blood sugar, lipid profile, as well as anthropometric and blood pressure measurements were assessed in all patients. Weight and height were measured in each subject and BMI was calculated as weight/height^2 (kg/m^2). Being overweight was defined as a BMI-for-age at or above the 95th percentile and "at risk of overweight" was defined as a BMI-for-age between the 85th and the 95th percentile (on the gender specified charts)[5]. All subjects underwent auscultatory mercury manometer blood pressure measurement and hypertension (HTN) was defined as systolic or diastolic blood pressure above the 95th percentile for age [5]. Standard pure tone threshold audiometry was carried out in a soundproof room using a Madsen OB822 clinical audiometer (Denmark). Echocardiography of subjects was done by a Wingmed (Norway) echocardiograph, and ultrasonography (US) of kidneys and urinary tract were performed by a G50 Siemens (Germany) sonograph. Each of these assessments were done by one person in all the subjects.

Serum level of triglycerides (TG), total cholesterol and LDL-C were analyzed enzymatically using the Pars Azmoon kits (Iran), FBS was measured by Man kits, TSH and T4 were measured by immunoradiometric assay (IRMA) and radioimmunoassay using Iran Kavoshyar kits. The normal range of T4 was 4.5-12 μg/dl and for TSH was 0.3-4 mu/l. Hypothyroidism was defined by low T4 level (<4.5 μg/dl) and high TSH level (>4 mu/L). Dyslipidemia was defined as total cholesterol, LDL-C and /or TG above the 95th percentile as well as HDL-C lower than the 5th percentile [6]. Cytogenetic analysis was performed in all patients on peripheral blood lymphocytes. Data were analyzed using the statistical software SPSS version 10 (SPSS Inc, IL, USA) and were presented as mean ± SD and relative frequency (percentage). $P<0.05$ was considered statistically significant.

Results

We studied 40 subjects aged 11 to 20 (mean 15.84 years) with TS that was proven by the cytogenetic study performed on peripheral blood lymphocytes. Their karyotype distribution was as the following: 45X 37.5% (n = 15), mosaicism 62.5% (n = 25). Characteristics of subjects are summarized in table 1. According to CDC cutoffs, 19.5% (n = 8) of our subjects were at risk of being overweight but none of them were overweight. The height of 77.5% (n = 31) was under the 5th percentile. Overall, 67.5% (n = 27) of our patients were under growth hormone treatment but most of them did not follow their treatment due to the high prices of the drugs.

Of the subjects studied, 85% (n = 34) had normal US, 10 % (n = 4) had dilatation of the urinary collecting system and 5% (n = 2) had a duplication of the urinary collecting system. In addition, 25% (n = 10) of patients were hypothyroid. According to the audiometry, 27.5% (n = 11) had hearing loss (CHL) and 32.5% (n = 13) had sensorineural hearing loss (SNHL),

Table 1. Characteristics of the subjects.

Variable	Mean ± SD	Range
Age (years)	15.84 ± 2.3	11-20
Weight (kg)	41.5 ± 8.2	17-63
Height (cm)	140.3 ± 11	104-164
Total cholesterol (mg/dl)	178.6 ± 15.3	139-221
LDL (mg/dl)	125.3 ± 18.4	83-184
HDL (mg/dl)	49 ± 4.4	41-60
TG (mg/dl)	110.51 ± 22.3	48-198
FBS (mg/dl)	84.73 ± 6.6	74-90
TSH (mu/l)	2.5 ± 1.6	0.2-9.3
T4 (µg/dl)	8.4 ± 3.1	1.9-14

Table 2. Findings of echocardiogram of the subjects with Turner syndrome

	number	percentage
Normal	15	37.5
Mitral valve prolapse	7	17.5
Aortic coarctation	4	10
Mitral valve prolapse or regurgitation	4	10
Bicuspid aortic valve	3	7.5
Mitral valve regurgitation	1	2.5
Aortic valve incompetence	1	2.5
Irregular abdominal aorta	1	2.5
Aortic valve stenosis and Mitral valve prolapse	1	2.5
Irregular abdominal aorta and Mitral valve prolapse	1	2.5
Ventricular septal defect and Mitral valve prolapse	1	2.5
Bicuspid aortic valve and Mitral valve regurgitation	1	2.5

37.5% (n = 15) had normal hearing and one of the patients didn't cooperate to perform the test. Among 16 patients with a history of recurrent otitis media (OM), 50% (n = 8) had CHL and 25% (n = 4) had SNHL. We found significant association between history of recurrent OM and presence of hearing loss in audiometry (P = 0.03). The results of echocardiography indicated that 62.5% (n = 25) of patients had cardiac abnormalities of which 32% were multiple anomalies. As presented in table 2, the most common anomaly was mitral valve prolapse (MVP). Also, 20% (n = 8) of our patients had HTN. HTN without the presence of coarctation of aorta was observed in 7 patients. Overall, 30% of subjects had hypercholesterolemia and 32.5% hypertriglyceridemia. LDL-C of 15% (n = 6) of patients was above the 95th percentile and HDL-C of 7.5% (n = 3) was under the 5th percentile curve. No case of abnormal blood glucose was found.

Discussion

Our findings indicated that medical problems are highly common in TS patients and 97% of our cases had at least one abnormality. Much of the increased morbidities and mortalities noted in TS are attributable to different heart conditions [3]. The cause of congenital heart defects in TS remains unknown. An increase in aortic root diameter, a risk factor for developing aortic dilatation and later rupture, is often seen and probably depends on blood pressure [7]. In the present study, we studied TS patients who were not cardiologically preselected and attended to the endocrine clinics just because

of short stature and/or delayed puberty. Mitral valve prolapse or regurgitation was the most common cardiac problem. Lower frequency has been reported in other studies (ranging from 0.6 to 8.9 %) [8-12]. The second most common cardiovascular problems were bicuspid aortic valve and aortic coarctation.

Nearly similar percentages ranging from 12.5 to 17.5% have been reported for bicuspid aortic valve in previous series and it has been the most common congenital abnormality in most of the previous studies [3,8-13](3, 8-13). Aortic coarctation was previously documented as the most frequent cardiac anomaly in TS patients with a prevalence varying from 15-67 % [14]. Among patients younger than 21, aortic dilation without a risk factor was observed in only 3 of 15 surveyed patients and 1 of 67 patients reported in the literature [15]. However since 1992, lower prevalences ranging from 6.9 to 14 % have been reported [8]. Prospective studies are needed in order to study how the risk of aortic dissection can be reduced.

It is recognized that HTN may develop due to coarctation of the aorta and/or intrarenal vascular changes in TS patients. However, renal malformations that lead to scars are also risk factors for hypertension. The etiology of hypertension could not be clearly explained. [15]. The risk of hypertension is increased 3-fold in these patients estimating to occur in 7–17% of children and 24–40% of adults [16] and this is similar to our study. 50% of cases with HTN had aortic coarctation, urinary duplication or dilatation. The reported incidence of renal malformations in TS patients varies between 33 to 66% [17]. Also, according to previous studies horse shoe kidney occurs in 15% and collecting system abnormalities in about 10 % of them [3]. Although prevalence of renal anomalies in our study was lower than in previous studies and no case of horse shoe kidney was found, the frequency of urinary collecting system abnormalities in our study was in accordance with the previous reports [3]. A study in Italy revealed that by the age of 15.5, 27% of TS girls are hypothyroid and this prevalence increases with age [18]. In other studies, the reported prevalence of hypothyroidism varies from 25 to 30% [3]. Our data shows a prevalence of hypothyroidism which is consistent with previous studies.

It is well documented that SNHL becomes increasingly common with age in TS [3]. It is reported in 58% of TS girls as young as 6, and in up to 61% of TS patients aged more than 35. As this disorder increases with age, over a quarter of them require a hearing aid [19]. Although we found a high frequency of hearing loss in TS, it was lower in other studies. In addition, in one study the prevalence of SNHL and CHL was the same as in our study [20]. In addition, we found a correlation between a history of recurrent OM and presence of CHL similar to other studies.

Type 2 DM is 2-4 times more frequent in TS women compared with the general population and tends to develop at a younger age [21]. In adolescents and adults a large proportion of TS patients exhibit impaired glucose intolerance or overt type 2 diabetes during an oral glucose tolerance test [21,22]. But in a recent cross-sectional study similar to our study elevated fasting glucose was not a concern in TS [16]. However, all our subjects had normal levels of FBS but we believe that hyperglycemia and type 2 diabetes would increase with age. Hypercholesterolemia has been seen in TS patients as young as 11 and in one study higher levels of total cholesterol, LDL -C and TG were found in TS than in controls [23]. Our youngest patient with abnormal lipid profile was aged 12 and had total cholesterol, LDL-C and TG levels above the 95th percentile curve. Hypertriglyceridemia occurs with increased frequency in TS and may be a direct consequence of obesity and hyperinsulinemia [4]. Obesity can be a problem in girls with TS [24]. However of all the 40 subjects, BMI of 19.5% (n = 8) was above the 85th percentile which is comparable with general population.

Short stature is an almost invariable finding in girls with TS, present in all with monosomy X and in more than 96% of mosaic females or those with a structurally abnormal X chromosome [25]. Most of our patients had a height un-

der the 5th percentile that is similar to other studies [25]. At the time that TS is diagnosed, all patients of any age should have a baseline cardiologic evaluation including echocardiography. In most cases, echocardiography should not be ordered as an isolated test, but only in the broader context of a careful clinical examination, considering the age of patient and availability of medical care. This is optimally performed under the direction of a pediatric or adult cardiologist who is usually best qualified to correlate clinical and diagnostic findings.

Given the different common health problems in TS patients, we conclude that a routine screening should be performed in all of them at the time of diagnosis and they should be followed throughout adulthood. By doing these, it is hoped that the life expectancy and the quality of life of the TS patients would improve.

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