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Early Detection and Treatment of Metabolic Syndrome in a 14-Year-Old Teenage Girl with Turner Syndrome: A Longitudinal Case Study

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ABSTRACT

Young women with TS are susceptible to various medical complications, such as autoimmune disorders, overweight and obesity, and an increased risk of metabolic disorders, such as glucose intolerance or dyslipidemia and hypertension. This article presented the case of a 17-year-old girl with Turner syndrome, hypertension, insulin resistance, and obesity. This patient has been treated with Estradiol 1.5 mg every 24 hours for two months, continued with Microgynon 1 tablet daily for four months, Lisinopril 4 mg every 24 hours, and Metformin 250 mg every 8 hours and are advised to visit the Paediatric Endocrinology Polyclinic at Dr Soetomo Hospital once per month. After six months of treatment, the patient has a regular menstrual cycle and improved metabolic measurements. This paper highlighted the importance of early detection and prompt treatment of metabolic complications in Turner syndrome patients.

Keywords: Turner syndrome; insulin resistance; overweight; children

INTRODUCTION

Turner syndrome (TS) is a condition caused by the loss of all (monosomy) or part (partial monosomy) of the second sex chromosome. This disorder is usually associated with growth retardation, reduced adult height, and gonadal dysgenesis [1]. Young women with TS are prone to various medical problems, including autoimmune disorders, overweight and obesity, and increased risk of metabolic disorders such as glucose intolerance or dyslipidemia, and hypertension. In addition, TS patients are also at risk for congenital lymphedema, renal malformations, sensorineural hearing loss, and osteopenia/osteoporosis [2].

Patients usually have normal intelligence but may have deficiencies in nonverbal, social, and psychomotor skills. Nearly all women with Turner syndrome are infertile, although some can become pregnant with the help of reproductive technology. Patients with TS are also known to be prone to emotional and mental problems [3].

TS occurs in one in every 2500 to 3000 live female births [3]. In a large epidemiological study of 781 women with TS in Denmark, the standard mortality ratio of women with TS compared to the general population was 3.5 for coronary heart disease and 2.2 for cerebrovascular disease. The relative risk of type 2 diabetes mellitus is three to five times higher in women with TS, accounting for 22% of all deaths in the Danish cohort. These data support the need to carefully examine the risk factors for metabolic syndrome in children with TS [4]. Meanwhile, regarding emotional mentality, a high prevalence of mental health disorders is found in adult TS patients, with most disorders being depressive [5].

Given the complexity of Turner syndrome, and its metabolic and psychosocial effects, pediatricians play an essential role in coordinating multidisciplinary management and directly managing the risk factors and complications of Turner syndrome [2]. This paper will comprehensively review the clinical implications and management of adolescents with Turner Syndrome and metabolic syndrome.

CASE PRESENTATION

A 17-year-old girl diagnosed with Turner syndrome confirmed by Karyotyping examination with a result of 45,X came with complain of have not experienced menstruation, accompanied by small breasts and undergrown pubic and axillary hair. The patient's mother and father had no history of growth, development, or hormonal disturbances. Several people in the patient's extended family suffer from obesity, hypertension, and type 2 diabetes mellitus.

From head and neck examination, we found facial dysmorphic features, a low hairline, ptosis, low-set ears, a webbed neck, and acanthosis nigricans. A shield-shaped chest was found to be asymmetrical on thoracic examination. On extremity examination, we found that the fourth fingers and toes are shorter. On examination of the breasts and genitalia, the breasts were found to be Tanner stage 3 and the pubic hair was Tanner stage 2. An anthropometric examination revealed a 17-year-old girl with a weight of 42 kg (0 SD) and height of 129 cm (<-1SD). Ideal body weight is 26.5 kg (~162%). The patient's body mass index is 25.8 kg/m2 (>+1 SD), which is interpreted as overweight.

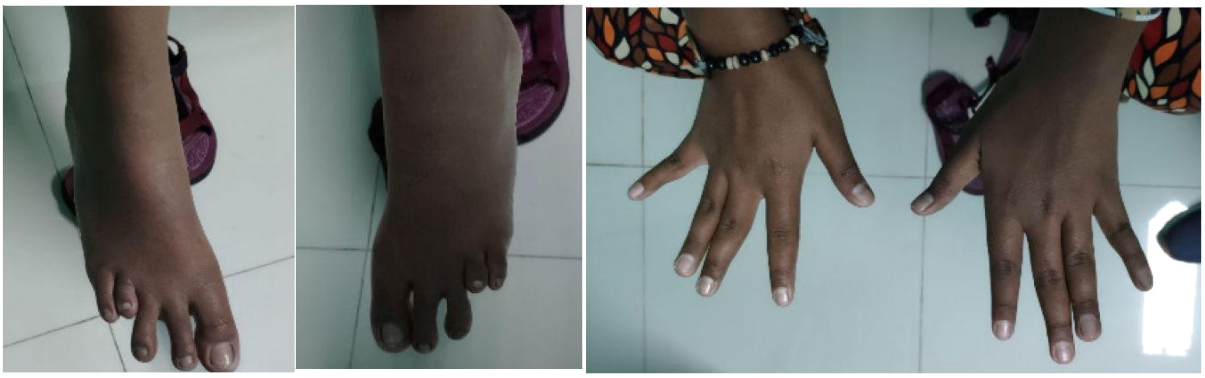

FIGURE 1: Extremity examination, the 4th finger and toes are shorter.

Previous examination already done in 2018:

- Karyotyping examination with 45,X results.
- Ultrasound of the genitalia showed a uterus measuring 1.77 x 0.63 cm, with an adnexa that was difficult to evaluate.
- Upper-lower abdominal ultrasound results showed a normal picture.

A blood test was performed on the patient with the results of BUN 8, Serum Creatinine 0.5, Glomerular Filtration Rate 142, Random Blood Sugar 88, HbA1c 5.4%, Insulin 11.05, HOMA IR 2.4%, Total Cholesterol 171, Triglycerides 63, HDL 49, and LDL 107. The bone age results revealed complete bone ossification.

Based on the following examinations, the patient was diagnosed with Turner syndrome, hypertension, insulin resistance, and overweight. The patient is then advised to adjust the diet with a calorie count of 1,590 – 1,696 kcal daily and start physical activity in 2-3 sessions per day for 60 minutes each. Patients are advised to continue therapy with Estradiol 1.5 mg every 24 hours, Lisinopril 4 mg every 24 hours, and Metformin 250 mg every 8 hours. Patients are advised to control every month to the Paediatric Endocrinology Polyclinic at Dr. Soetomo Hospital. After six months of observation, the patient is 18 years old and was advised to move to the Internal Medicine Polyclinic to continue treatment.

Parameters	Observation					
	1st month	2nd month	3rd month	4th month	5th month	6th month
Blood pressure	170/110 mmHg	130/90 mmHg	120/80 mmHg	120/80 mmHg	135/85 mmHg	120/80 mmHg
Metabolic examination HbA1C HOMA-IR Fasting blood glucose LDL HDL Triglycerides Total cholesterol	5,4% 2,4% 88 107 49 63 171					- - 93 79 44 58 135
Growth Weight (Weight-for-age z-score) Height (Height-for-age z-score) Body mass index (BMI-for-age z-score)	42 (-1–0 SD) 129 (<-1 SD) 25,2 (+1SD)		40 (-1–0 SD) 129 (<-2SD) 24 (0-1SD)			39 (-1–0 SD) 129 (<-2SD) 23,4 (0-1SD)
Secondary sex characteristics development Tanner stage Menstruation	A1M3P2 -	A1M3P3 -	 +	 +	 +	A1M3P3 +
Medication advices	- Estradiol 1x1.5 mg - Nifedipine 3x10 mg - Lisinopril 1x4 mg - Metformin 3x250 mg	- Estradiol 1x1.5 mg - Nifedipine 3x10 mg - Lisinopril 1x4 mg - Metformin 3x250 mg	- Microgynon 1 tablet daily - Nifedipine 3x10 mg - Lisinopril 1x4 mg - Metformin 3x250 mg	- Microgynon 1 tablet daily - Nifedipine 3x10 mg - Lisinopril 1x4 mg - Metformin 3x250 mg	- Microgynon 1 tablet daily - Nifedipine 3x10 mg - Lisinopril 1x4 mg - Metformin 3x250 mg	The patient was advised to continue treatment in Internal Medicine Polyclinic in collaboration with Obgyn.

DISCUSSION

This longitudinal case study concerns a child with Turner syndrome and delayed puberty, she has not experienced menstruation until the age of 17 years. Ovarian failure in Turner syndrome begins at 18 weeks of gestation, after which there is rapid fibrous degeneration of the ovarian follicles. Normal FSH and LH levels will increase in infancy and early childhood, decrease gradually until the age of 6 years, and then increase again at puberty [6]. In Turner syndrome, most sufferers will show signs of ovarian failure. Only one-third of girls with Turner syndrome will experience spontaneous pubertal development, that is, those with a mosaic karyotype, and only a minority will experience spontaneous menarche [7]. Hormone replacement therapy Estrogen should be given according to physiological conditions, where puberty begins between the ages of 11 and 12 years and after that, hormone levels will increase in 2-3 years. Progestin should be added after menstruation or after two years of Estrogen treatment. Estrogen and Progestin combination pills are a therapeutic option that can be used [8]. The patient received estradiol therapy for 2 consecutive months to induce menstruation, then after menstruation the therapy was replaced with microgynon.

Turner syndrome is linked to a number of diseases, most of which are thought to be caused by a lack of normal expression of genes on the second X chromosome [9]. In this patient, we screened for metabolic disease (hypertension, lipid profile, liver function, and HbA1c). From the vital signs examination in the first month of observation, the patient showed high blood pressure. Sixty percent of adults and 40% of adolescents with Turner syndrome have elevated blood pressure [4,10]. Patients with Turner syndrome have higher morbidity and mortality in middle age than the average population [11]. Hypertension is a significant morbidity because it can predispose to a nearly seven-fold increased risk of aortic dissection in the Turner syndrome population [4]. One of the major risk factors contributing to cardiovascular events is hypertension, which occurs in 25% of adolescents and 40–60% of adults with Turner syndrome [9].

Based on laboratory tests, it is known that the patient has a fasting insulin level of 11.05, a fasting blood glucose level of 88 mg/dL, and the HOMA IR of 2.4. The HOMA-IR cut-off value for insulin resistance was 2.67 in boys and 2.22 in girls in the prepubertal period; 5.22 in boys and 3.82 in girls during puberty [12]. Because this patient was not menstruating, the cut-off for HOMA IR in this patient was 2.2; therefore, the patient could be diagnosed with insulin resistance. The pathogenesis of type 2 diabetes in children is thought to be related to two main factors: insulin resistance and impaired insulin secretion. Longitudinal studies in adults have shown that insulin resistance strongly predicts the development of type 2 diabetes. Furthermore, studies in obese children have shown that insulin resistance is associated with glucose metabolism abnormalities, such as impaired glucose tolerance or type 2 diabetes mellitus [12].

T2DM is a complication in endocrinology with a prevalence of 2-4 times more often in women with Turner syndrome, which can occur at any stage of life with an onset of age 30–40 years [13]. The phenotype of diabetes in Turner syndrome patients is similar to maturity-onset diabetes of the young, caused by haploinsufficiency of genes involved in B-cell glucose sensing (glucokinase) or function (hepatic nuclear factor) [14]. This patient's insulin resistance therapy is lifestyle modification (reducing calorie intake and increasing physical activity) and metformin 500 mg three times daily.

Lifestyle modification, reducing caloric intake, and increasing physical activity are still the most important treatments for insulin resistance. However, several systematic reviews have shown that using 1,000–2,000 mg of metformin daily in divided doses for 6–12 months can slightly reduce BMI and improve insulin sensitivity in obese and insulin-resistant children and adolescents [15]. Low-dose metformin (850 mg/day) in children with obesity and insulin resistance has a good effect and is well tolerated. Metformin also has potential long-term benefits for improving body composition and inflammatory markers [16]. At the end of observation, the patient's fasting blood sugar and insulin levels were normal.

From the examination of the lipid profile panel (total cholesterol, triglycerides, HDL, and LDL), the patient's HDL and LDL showed abnormal results. However, statin therapy was not given to patients. Visceral fat depots in patients with Turner syndrome are associated with abnormal lipid profiles. However, pathological parameters correlate with genetic and therapeutic factors [1].

CONCLUSION

Turner syndrome patients are more susceptible to various metabolic problems, including overweight and obesity, as well as an increased risk of metabolic disorders such as glucose intolerance, dyslipidemia, and hypertension. Therefore, it is important to screen for metabolic diseases in children with Turner syndrome to prevent the development of metabolic disorders in the future. Medication should be considered in children with a risk of metabolic disorders. Given the complexity of Turner syndrome, pediatricians play an essential role in coordinating multidisciplinary management and directly addressing the risk factors and complications of Turner syndrome.

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AUTHOR CONTRIBUTIONS

All authors have contributed equally. All authors read and approved the final manuscript.

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DECLARATIONS

This study is in accordance with the Helsinki Declaration, and the patient and parents have consent for patient information and images to be published.

CONSENT FOR PUBLICATION

Informed consent was obtained from the patient for publication of this case report.

COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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