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CASE REPORT

Late Presentation of Turner Syndrome and Its Complications

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ABSTRACT

Turner syndrome is one of the most common sex chromosome abnormalities with an estimated true prevalence of 1 in 2,000 in newborns. This case report is of a girl who presented to the adult endocrinologist at 16 years of age and subsequently diagnosed with Turner syndrome. Despite frequenting clinics for unrelated ailments, her short stature was overlooked hence not investigated for a causative pathology. The aim of this report is to explore the diagnostics of Turner syndrome, hormone treatments available and the importance of starting treatment early.

KEYWORDS: Turner syndrome, short stature, primary amenorrhoea, osteoporosis

INTRODUCTION

Turner syndrome is a chromosomal condition where a missing X chromosome gives a karyotype of 45, X. It is a condition affecting females causing developmental disability and multi-systemic medical complications. It can be suspected antenatally by ultrasonography and diagnosed by genetic testing from amniocentesis or chorionic villous sampling. At birth, newborns may present with lymphoedema of the hands and feet as a result of poor lymphatic development. It is however most evident at the age of 6 years owing to short stature [3].

Early diagnosis is important as it entails thorough follow-ups in detecting multi-systemic complications. For example, as a result of hypogonadism, affected females are complicated by primary amenorrhea, infertility and young-onset osteoporosis. Other systemic involvements include coarctation of aorta, aortic valve disease, horseshoe kidney and other metabolic diseases. We report a case of Turner Syndrome diagnosed at a late age of 16 years.

CASE PRESENTATION

A 22-year-old lady who is currently under Putrajaya Hospital's endocrinology clinic follow-up was first referred for short stature at the age of 16 years. She was noticeably shorter than her peers since primary school but this was not picked up by both her parents and the general practitioners whom she visited on numerous occasions for minor ailments. She only sought medical attention for short stature and primary amenorrhoea at 16 years of age when the parents became increasingly worried. She was not known to have any medical or chronic childhood illnesses nor was she taking prescribed medications. Her paternal height was 176cm and maternal height was 150cm, giving a mid-parental height of 156.5cm ± 10cm. She had 3 younger siblings aged 20, 18 and 17 years who were all taller than her.

On her first clinic review, she measured 136cm in height and 37.1kg in weight which were markedly below the 5th centile. Her body mass index was 20 kg/m^2 with a blood pressure of 102/61 mmHg and pulse rate of 88 beats per minute.

(a)

(b)

Figure 1 (a) & (b) Short stature with broad shoulders, cubitus valgus and abnormal upper-to-lower body segment ratio are features of Turner syndrome. Short 5th metacarpals are also seen.

Clinically, breasts were at Tanner stage 3 and pubic hair Tanner stage 2. She was also found to have bilateral cubitus valgus (Figure 1). No other syndromic features, webbed neck, spinal deformity, lymphedema of the limbs or goitre were evident and systemic examination was unremarkable.

She had delayed bone age of an 11-year-old and blood investigations revealed low estradiol (<20 pg/ml), low progesterone (0.2ng/ml) with elevated Follicle Stimulating Hormone (110.53 mIU/ml) and Luteinizing Hormone (28.52 mIU/ml), suggesting primary hypogonadism. Thyroid function test, serum calcium, serum phosphate and blood counts were within normal levels. Her serum calcidiol was at an adequate level of 32 ng/dL. Chromosomal analysis from 7 analysable metaphase identified an isochromosome on the long arm of the X chromosome (q10;q10), confirming the diagnosis of Turner syndrome. Echocardiogram was normal with no coarctation of the aorta (CoA) or bicuspid aortic valve (BAV). Ultrasound of the kidney-ureter-bladder system showed a normal right kidney and multiple cysts occupying the left kidney. The largest cyst was at the renal pelvis which measured 4.4 x 4.7cm.

As she measured a mere 136cm at 16 years of age, a trial of 0.054 mg/kg/day growth hormone therapy (13.5mg a week) was initiated in October 2010. The growth hormone doses were divided to 1.9mg on weekdays and 2.0mg on weekends. Three months later, her height increased by 0.5cm and subsequently to 138.4cm at 12 months, giving a growth of 2.4cm in a year. Growth hormone was stopped after a year of therapy due to poor response. She attained spontaneous menarche at age 17 years which was of regular 28-day cycle with 3 bleeding days. However, as her menses stopped 4 cycles later, oral Premarin (conjugated oestrogen) 0.3125mg OD was started. This was increased to 0.625mg OD when she was 18 years following failure to menstruate on the initial dose. Menses eventually became regular at 19 years upon adding medroxyprogesterone acetate with 6 bleeding days per monthly cycle. She also attained Tanner breast stage 4 and grew axillary hair requiring weekly shaving.

Regular monitoring of blood sugar and cholesterol diagnosed her with type 2 diabetes mellitus in June 2011 (modified glucose tolerance test 5.6/11.7 mmol/L, HbA1c 6.1%) and she was commenced on oral Metformin 500mg BD. She was otherwise asymptomatic of diabetes mellitus. Fasting lipid profile revealed a total cholesterol of 5.5 mmol/L, high-density lipoprotein (HDL) of 1.1mmol/L, low-density

lipoprotein (LDL) of 2.72 mmol/L and hypertriglyceridemia (triglycerides 3.7mmol/L).

A bone mineral density (BMD) scan in March 2014 showed osteoporotic hips (femoral neck Z-score -3.6) and an osteoporotic spine (lumbar Z-score -3.1) for which calcium supplements were added to her hormonal treatment. A repeat BMD scan after 1 year 5 months yielded a lumbar Z-score of -3.1 and hip Z-score of -3.1.

When she was seen at the age of 22 years, she was still of short stature with cubitus valgus (Figure 1). She was consequently switched to combined hormonal therapy consisting of estradiol valerate 2mg and Norgestrel 500mcg OD. A repeat BMD scan is planned in 2 years.

DISCUSSION

Turner Syndrome is caused by a partial or complete absence of the X chromosome in a female, with manifestations including short stature, ovarian failure and cardiovascular disease. Several karyotypes exist, the most common being 45 X, followed by isochromosome Xq as seen in this reported case and mosaicisms [1]. Studies show that most patients are diagnosed at a median age of 6.6 years or 5 years after falling below the 5th height centile, with the isochromosomes and mosaic groups being diagnosed even later, as they present with a less typical phenotype as compared to the 45 X group [1-3]. However, due to diagnostic vigilance both prenatally and during childhood, the age at diagnosis is decreasing where more 45 X types are diagnosed before 1 year of age [3].

Many conditions are associated with the syndrome including hypertension, diabetes mellitus, hyperlipidemia, infertility, renal malformations e.g. horseshoe kidneys, autoimmune thyroiditis, coeliac disease, lymphedema, osteoporosis and cardiac anomalies especially bicuspid aortic valves and aortic coarctation [4, 5]. These cardiac anomalies, coupled with syndrome-associated risk factors like hypertension, diabetes, hyperlipidemia and oestrogen deficiency, put patients at an even higher risk of developing and dying from coronary heart disease than the general population, with a standardized mortality ratio (SMR) of 3.47 from Coronary artery disease (CAD) alone [1, 5]. Other common causes of death include congenital abnormalities (SMR 24.09), endocrinal/metabolic diseases (SMR 5.68), infections (SMR 4.68) and diseases of the nervous system, ears and eyes (SMR 4.38) [1].

Realizing the many associated conditions and complications of the syndrome, it is imperative that early recognition, diagnosis and treatment initiation by medical personnel are undertaken.

Diagnosis can be done as early as the prenatal period where non-specific ultrasonography findings such as nuchal translucency, cystic hygromas, cardiac defects, renal anomalies and growth retardation followed by a karyotyping study can predict Turner Syndrome [2, 4]. However, the ability to detect foetal abnormalities on ultrasonography is operator-dependent and karyotyping studies may yield false positivity as high as 30% [4]. Therefore, a repeat confirmatory karyotyping study is needed after birth.

Postnatal indications for karyotyping include lymphoedema which commonly presents during infancy up to 2 years of age, growth retardation, pubertal delay, left-sided cardiac anomalies, phenotypical features and chronic otitis media [2, 4]. A 30-cell karyotype is the recommended test by the American College of Medical Genetics for its ability to detect at least 10% of mosaicism [6]. Adequate number of cells is important to detect mosaicism which can be missed especially in women with little features to suggest Turner Syndrome. Should the patient also present with virilism, screening for Y-chromosome material is strongly advocated as there is a 5-30% risk of developing gonadoblastoma requiring gonadectomy [2, 4].

Management is multidisciplinary where primarily paediatricians, paediatric endocrinologists, adult endocrinologists and cardiologists are involved. In this case report however, only hormonal therapy in improving growth and pubertal induction is discussed.

Short stature is defined as a height of 2 standard deviations below the mean or a height below the lower limit of mid-parental height. As short stature is the predominant presentation, frontline clinicians should be cognizant of Turner syndrome when faced with a slow- growing child. Early referral to experts

for further work-up and treatment have been useful in preventing disease complications.

Management includes increasing height with growth hormone at an FDA-approved dose of 0.375mg/kg/week daily whilst monitoring height increment and IGF-1 levels [4]. A Canadian study has proven that with 0.3mg/kg/week of growth hormone, patients are able to grow 7.2cm taller than the control group after 5.7 years of therapy [7]. Treatment is commenced the moment growth failure is identified and discontinued when targeted height is achieved [4]. Note that final height is influenced by height at therapy initiation, parental height, duration of therapy and growth hormone dose [2].

Unfortunately, this patient had only achieved suboptimal height due to late diagnosis hence late initiation of therapy. According to the International Turner Syndrome Consensus Group 2017 guidelines, growth hormone therapy should be commenced around 4-6 years of age when there is evidence of growth failure [10].

Benefits of growth hormone therapy, apart from increased final height, include improved body proportions, lower diastolic blood pressure, improved lipid profiles and improved insulin resistance. The therapy, however, does not have an effect on bone mineral density [2]. Despite the known hyperglycemic effects of growth hormone, a 7-year study has shown that therapy with the hormone does not worsen glucose tolerance hence monitoring glucose tests or HbA1c on an annual basis is sufficient [8].

For girls above 9 years old with severe short stature, the anabolic steroid, oxandrolone may be added at a dose of 0.05mg/kg where an increase by 4cm in height is seen in comparison to patients on growth hormone therapy alone. However, side effects like altered liver enzymes, virilization, hypertension and underdeveloped breasts are cautioned [2]. Increasing final height by delaying pubertal induction is no longer recommended in view of its negative outcome on bone mineral density [2, 4].

Pubertal induction is done to achieve feminization (breast & uterine development) and to prevent osteoporosis by administering oestrogen to non-pubescent Turner syndrome patients. However, as up to 30% of patients may achieve spontaneous puberty, delayed puberty should be ruled out by measuring serum LH & FSH prior to initiating therapy [4].

The recommended age for oestrogen replacement initiation is 11-12 years [10]. While there is no fixed protocol on oestrogen regimes, the general consensus is to tailor the dose and forms to suit the normal pubertal development of the patient's age. The American CPG has set an adult oestrogen dose of 2mg/day for oral forms, 0.1mg/day for transdermal forms and 2.5mg/month for injectable forms. The recommendation is to start at 10% of the adult dose and to titrate up over 2-4 years [4]. Progestin is only added 2 years following oestrogen therapy initiation or upon breakthrough bleeding considering its ability to interfere with optimal breast & uterine development [2, 4]. Oral contraceptive pills are therefore not recommended for replacement due to its higher doses of oestrogen and presence of progesterone [4].

Theoretically, with pubertal induction, bone matures sooner hence the final height may be reduced. However, a recent Japanese study has shown that by starting at 1% of adult dose (ultra-low dose) of oestrogen and gradually titrating it up over the years does not interfere with growth but at the expense of an ideal bone mineral density [9]. This is supported by another study where initiating low-dose oestrogen therapy as early as 5 years of age as opposed to the recommended 12 years, may further increase final height by 2.1cm on top of improving cognitive and hepatic functions [2, 4]. Apart from using oestrogen at low doses, transdermal or depot forms are also alternatives should growth hormone therapy interferences, suboptimal final height and thrombophilia be of concern [2, 9].

The pitfall in this case was failing to identify a treatable cause of short stature in a timely fashion where family members, peers, educators and physicians overlooked the need to refer her for evaluation. This calls for increased public awareness that short stature should not be passed as a norm, perhaps through advertisement via the mass media. Attending doctors should be observant and not limit their clinical evaluations to the patient's unrelated presenting complaint at clinic visits. One way to

achieve this is through regular continuous medical education lectures on the relevant subjects.

CONCLUSION

This case report exemplifies the negative repercussions of diagnosing and treating Turner syndrome late. Due to delayed initiation, growth therapy failed to yield optimal final height. Hormone therapy also failed to prevent osteoporosis thus management was focused on slowing down osteoporotic progress and preventing fractures.

In terms of monitoring, annual assessment of lipids, thyroid function, glucose studies, cardiac function and bone mineral density is suggested. An ultrasound of the urorenal system should also be conducted at presentation to look for malformations.

Both healthcare providers and the public should be made aware of the importance of investigating short stature as some important causes are treatable. The need for mass newborn screening in Malaysia may not be practical at the current time unless a national epidemiological study on short stature and Turner syndrome recommends otherwise.

Conflict of Interest

Authors declare none

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