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Review Article

Presentation, Clinical Spectrum and Chromosomal Abnormalities of Children with Turner Syndrome: A Single-Centre Experience from Sri Lanka and Review of Literature

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Abstract

Background: Diagnosing Turner Syndrome at an early age (before 5 years) is important in achieving an optimal final adult. Significant delay in diagnosis has been reported worldwide. This study describes the presentation and clinical spectrum to create awareness for early referral.

Methods: Retrospective data on the initial presentation, clinical spectrum, and chromosomal abnormalities of 45 patients diagnosed with Turner Syndrome was extracted from the departmental database.

Results: The mean age of diagnosis is 8.0 years. The majority (46.5%) were diagnosed between 5 to 12 years of age and 29% in adolescence. 24.5% were diagnosed before the age of 5 years: 4.5% were diagnosed antenatally and 11% in the neonatal period. 80% of girls first presented to the endocrine service after 5 years.

Majority presented with short stature (67%), the rest with dysmorphic features (13%), neonatal lymphedema (4.5%), typical cardiac lesions (4.5%), and autoimmune hypothyroidism (4.5%). The majority were referred by pediatricians (51%) and cardiologists (17%).

The commonest karyotype (55.5%) was 45; XO. 48% had cardiac lesions including bicuspid aortic valves (18%) and Coarctation of the Aorta (9%). Renal anomalies were detected in 18% and ovarian abnormalities in 73%.

Other manifestations included recurrent otitis media in 18%, hearing impairment in 23%, ophthalmological defects in 27%, autoimmune hypothyroidism in 11%, and below-average school performances in 7%.

Conclusions: The majority were diagnosed and referred to endocrinology after 5 years of age. Delays in the evaluation of short stature and lack of awareness of TS clinical spectrum may have contributed.

Keywords: Turner syndrome; Short stature; Chromosomal abnormality

Introduction

Turner Syndrome (TS) is a common chromosomal disorder in females, described by Dr. Henry Turner in 1938 [1]. It affects 1 in 2500 live-born females and the incidence is even greater in aborted fetuses. It is estimated that 10% of spontaneous abortions are found to have karyotypes consistent with TS [2]. The diagnosis is made by the presence of characteristic physical features in phenotypic females with complete or partial absence of a second sex chromosome with or without cell line mosaicism [3].

The classical chromosomal abnormality seen in TS is 45, X monosomy, in about 45% of cases. The rest show a variety of structural abnormalities including mosaicism, deletions, translocations, isochromosomes, and ring chromosomes [4]. Those with ring X and Xq isochromosomes often present with features identical to those with monosomy X. Those with distal Xp deletions (including *SHOX* gene) present with short stature and associated skeletal abnormalities without other features of TS and low risk for ovarian insufficiency [2,3].

The commonest manifestation of TS is short stature, while other physical features can be greatly variable, including a webbed neck, shield-shaped chest, cubitus valgus, low posterior hairline, and lymphedema. It has a broad spectrum of multisystem involvement comprised of cardiac, renal, ophthalmological, ear, skeletal, reproductive, and autoimmune disorders. Phenotypic variability leads to delay in diagnosis which invariably affects the outcome of management.

It is recommended to initiate growth hormone treatment early (around (4 to 6) years of age) to achieve optimal adult height. Even

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though prenatal and neonatal diagnosis is possible in some patients, there is a significant delay in referring to paediatric endocrinology services worldwide.

This study describes the characteristics of diagnosed Turner patients in a tertiary care Paediatric Endocrinology center for the past 6 years. The study aims to emphasize presentation, and clinical spectrum to create awareness and prevent potential delays in referral to endocrinology services.

Materials and Methods

This retrospective study includes 45 patients diagnosed with Turner syndrome and followed up in Paediatric Endocrinology Service at Lady Ridgeway Hospital for Children in Colombo, Sri Lanka since 2014. The diagnosis was confirmed based on standard karyotype. One patient has been excluded as the karyotype showed 46, XX despite a typical Turner phenotype.

Data were extracted from the database maintained in the department and ethical approval was obtained from the hospital ethics committee.

Age of diagnosis, age of referral, the clinician who referred mode of presentation, variability of the clinical spectrum, chromosomal abnormalities, and management extracted from the database. Chromosomal abnormalities obtained by standard 30 lymphocytes karyotype and detection of *SRY* gene. The clinical spectrum includes birth weight, height or length at presentation, typical dysmorphic features, and systemic involvement concerning cardiac, renal, ophthalmological, hearing, reproductive, autoimmune, and intellectual. Clinical examination performed by Paediatric Endocrinologist, as a part of routine care. The following data on systemic involvement was extracted from imaging studies, biochemical investigations, and ophthalmological and hearing assessments. Details of individual patient management were obtained directly from the database.

Results

Presentation

Forty-five girls (n=45) with Turner Syndrome were analyzed. A majority (46.5%) were diagnosed between 5 years and 12 years of age (Table 1). The mean age of diagnosis is 8.0 years. 75.5% of girls were diagnosed after 5 years of age and only 24.5% were diagnosed before the age of 5 years. Two girls were diagnosed prenatally.

Table 1: Different chromosomal anomalies found in karyotypes of the Turner cohort.

Chromosomal Abnormalities	Number (%)	Description
45,XO	25 (55.5)	Monosomy X
45,XO/46,XX	7 (15.5)	Mosaicism
45,XO/46,XY	3 (7)	Mix gonadal dysgenesis
45,x/46xi(x)/47xxx	1 (2.2)	Mosaicism with 'Triple X'
45X INV(9) (p11q1B)(12)/46xy INV(9)(p11q13)(9)	1 (2.2)	
45,x[44]/46,xx,r(x)[3]	1 (2.2)	Ring Chromosome
46x,i(x)(q10:q10)	1 (2.2)	Isochromosome
46,i(X)(q10)(30)/45,X[14]	1 (2.2)	
46,x,i(x)(q10)[18/45,x[12]	1 (2.2)	
45,x, 46,xi	1 (2.2)	
45,x(40)/46,x,i(x)(I)	1 (2.2)	
46xx del(x)q21.3->27terminal deletion on the long arm on x h	1 (2.2)	Deletion
45,x/46,x+mar(11)	1 (2.2)	mar Chromosome
Total	**45**	

Even though 24.5% were diagnosed as less than 5 years of age, only 20% presented to Paediatric Endocrinology services before the age of 5 years. Seventeen patients (37.8%) presented to the Paediatric Endocrinology service after 12 years of age.

The majority (67%) of girls initially presented with short stature and 13% of them presented with dysmorphic features suggestive of the Turner phenotype. The rest of them presented with neonatal lymphedema (4.5%), typical cardiac lesions (4.5%), and antenatal diagnosis (4.5%), autoimmune hypothyroidism (4.5%). One patient (2%) presented with failure to thrive (Figure 1).

Half of the girls (n=23) were referred by Paediatricians from tertiary care hospitals as well as from local hospitals. Pediatric Cardiologists referred 17% (n=8). The rest of the patients were referred a by Neonatologist, Ophthalmologist, Developmental Paediatrician, Adult Endocrinologist, General Practitioner, and by the school medical inspection. Five percent of them (n=2) self-referred (Figure 2).

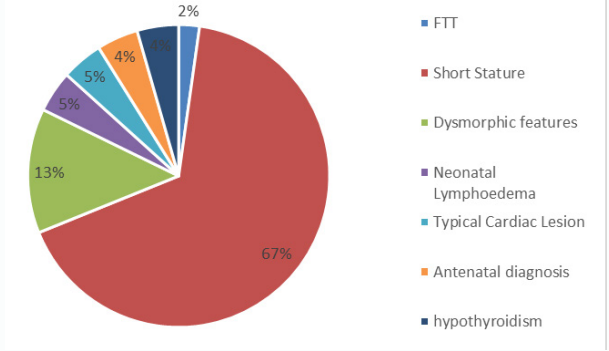

Figure 1: Initial presentation leading to a diagnosis of TS.

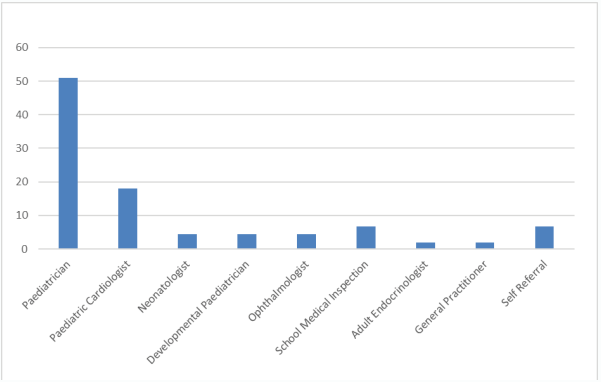

Figure 2: Clinicians who referred girls with TS to endocrinology service.

Type and frequency of chromosomal abnormalities

Chromosomal analysis showed 45, XO is the commonest karyotype found in more than half of the girls (55.5%). Rest showed variable abnormalities including mosaicism, deletions, ring chromosomes, and, isochromosomes. Y chromosome material was detected in 3 patients (Table 1).

Clinical spectrum:

Growth and skeletal abnormalities: Majority of patients (60%) of patients born with a low birth weight according to WHO classification

[5]. Table 2 shows the distribution of birthweight of patients with Turner syndrome.

Short stature was evident in almost all the patients. (Except in 4 patients presented in infancy). Thirty percent of them had a height between the 50th to 75th centile according to the Turner growth chart and 27% had a height the between 9th to 25th centile (Figure 3). Two (4.5%) had scoliosis which required surgical correction. Among 45 girls 31 (68.8%) are currently on Growth Hormone (GH) treatment. Eight girls (17.7%) presented after the age of 14 with advanced bone age and growth hormone treatment not commenced. Four (8.8%) girls less than 2 years of age were within the mid-parental height range and had, not commenced GH therapy yet. One patient refused GH therapy despite fulfilling the criteria for treatment. Interestingly, one patient presented at 15 years with significantly delayed bone age and, commenced on GH therapy due to concomitant severe GH deficiency confirmed by GH provocation test.

Table 2: Birthweight of babies with Turner Syndrome.

Birth Weight (Kg)	Number of Patients	Percentage %
<2	9	20
2-2.5	18	40
2.5-3.00	14	31
>3.00	4	9

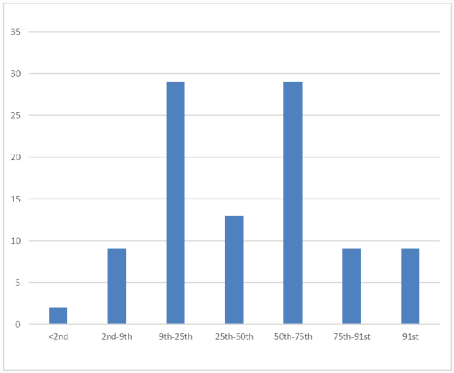

Figure 3: Height percentiles according to Turner specific growth chart.

Phenotype: Typical physical features and organ involvement seen in the majority of girls with TS are shown in Tables 3 and 4. History of neonatal lymphedema found in 27% (n=12).

Cardiac manifestations: Nearly half of the patients had cardiac lesions (48%). The commonest manifestation was bicuspid aortic valves (18%). Coarctation of the aorta was detected in 9%. All were normotensive during follow-up. Patients were followed up with interval echocardiograms for aortic root dilation, but none of them were positive. All were normotensive during follow-up.

Renal: Renal anomalies were detected in 8 patients (18%), consisting of horseshoe kidneys, duplex systems, hypoplastic kidneys, renal cysts, and hydronephrosis.

Reproductive system: Pelvic ultrasonographic results were available in 41 girls. Among them, 27% (n=11/41) had normal uterus and ovaries. The rest of them (73%) had streaky ovaries or ovaries not visualized by ultrasonography. Thirty four percent (n=14/41) had a small tubular uterus. In 16 (36%) patients' biochemistry was suggestive of hypogonadotropic hypogonadism.

Out of 12 girls (n=12/45) in pubertal age, 9 girls were commenced on hormone replacement with oral Estradiol valerate. In contrast, one girl achieved spontaneous menarche.

Table 3: Frequency of typical clinical features in patients with Turner Syndrome.

Clinical Features	Number of Patients	Percentage %
Webbed neck	28	64
Wide carrying angle	27	61
Shield shaped chest	32	72
Low posterior hairline	21	73
Clinodactyly	8	17
Hyperconvex nails	5	11
Short 4th metacarpal	5	11

Table 4: Frequency of different organ involvement in patients with Turner Syndrome.

Abnormalities	Number (%)
Cardiac	
Bicuspid Aortic Valve	8 (18)
Coarctation of Aorta	4 (9)
Partial Anomalous Pulmonary Venous Drainage	4 (9)
Patent Ductus Arteriosus	2 (4.5)
Trivial mitral Regurgitation/Aortic Regurgitation	2 (1)
Peri membranous Ventricular Septal Defects	1 (2)
Tetralogy of Fallot with Pulmonary Atresia	1 (2)
Mal-aligned Fenestrated Intra-atrial Septum	1 (2)
Normal Echocardiogram	22 (52)
Renal	
Hydronephrosis	3 (7)
Renal cysts	2 (4.5)
Horseshoe kidney	1 (2)
Duplex system	1 (2)
Hypoplastic kidney	1 (2)
No abnormality	36 (82)
Ophthalmology	
Refractory errors	6 (14)
Squints	4 (9)
Ptosis	1 (2)
Reduced contrast severity of vision	1 (2)
No abnormality	32 (73)

Three girls (6.6%) underwent bilateral gonadectomy due to the detection of Y chromosomal material. One patient was diagnosed with mixed gonadal dysgenesis. Clitoromegaly was noted in three (6.6%).

Hearing: History of recurrent otitis media reported in 8 (18%). All of them underwent hearing assessment as per routine surveillance and 10 (23%) were diagnosed with hearing impairment. Nine (20%) had mild to moderate conductive hearing impairment and one (2.5%) patient had moderate Sensorineural Hearing Loss (SNHL).

Ophthalmology: Ophthalmological assessment detected 12 (27%) patients with visual defects. that 14% of patients had refractory errors, 9% had squints and one patient had reduced contrast severity of vision.

Autoimmune: Autoimmune hypothyroidism was diagnosed in five (11%) girls with positive antithyroglobulin and thyroid peroxidase antibodies. Ultrasound thyroid showed features of autoimmune thyroiditis.

All of them had annual HbA1c (glycosylated hemoglobin levels) within normal limits. Only one (2.5%) had abnormal liver functions without clinical features of autoimmune hepatitis and was under regular monitoring.

IQ/ School performance/development: Below-average school performances were reported in 3 (7%) and others had average school

performance. However, a standard IQ assessment was not performed for each patient.

Discussion

Diagnosing TS at early age and referral is important in every aspect of management. To obtain optimum adult height growth hormone therapy it should commence before the age of 5 years. Antenatal detection of TS is possible with certain ultrasound findings like increased nuchal translucency, presence of cystic hygroma, specific cardiac anomalies, renal anomalies, and growth retardation. Maternal serum biomarkers and maternal plasma DNA sequencing, detection of chromosomal abnormalities in chorionic villous sampling, and amniocentesis help to diagnose TS [2]. However, antenatal diagnosis in the present study is low (4.5%) compared to recent data published in the United Kingdom (UK) which was 29% [6].

In the present study, the majority were diagnosed after 5 years of age and about 29% after the age of 12 years delaying the commencement of GH therapy and hence affecting the final adult height even with GH therapy. This correlates with the data published in a Belgian study group in 2005 [7]. However, the mean age at diagnosis in the present study is 8.0 years and it is slightly higher than Belgian (6.6 years) and UK data (5.89 years) [6,7].

Despite having a high probability of spontaneous abortion, 45, X monosomy is the commonest chromosomal abnormality seen and associated with the most abnormal phenotype [8]. Mosaicism 45, XO/46, XX and 45, XO/46, XY were found in 15% and 7.5% respectively. This is similar to the study published in Sri Lanka and is similar the review article published in 2016 [9,10]. Mosaicism may be limited to tissues that do not include peripheral blood, making its diagnosis difficult unless studying the affected tissue [10]. One patient with a typical phenotype was excluded from the present study due to a normal Karyotype suggesting tissue mosaicism.

The rest of the karyotypes displayed deletions, isochromosome, and es, ring chromosomes.

Patients with mosaic 46, XX karyotype or isochromosome Xq results in milder phenotype, while patients with mosaicism for 46, XY cell line or structural rearrangement of the Y chromosome mostly have masculinized external genitalia and are at increased risk for having gonadoblastoma and other gonadal tumors [11]. In this series, three patients were found to have clitoromegaly and 45, XO/ 46, XY and underwent gonadectomy. One out of them was diagnosed as mixed gonadal dysgenesis on histology and one had gonadoblastoma *in situ*.

Congenital lymphoedema of the hands, feet, and neck region is a key diagnostic indicator (present in more than 60% of TS), most commonly seen in infants but can occur and recur at any age [8,12]. Lymphoedema occurs as a result of lymphatic hypoplasia or aplasia of the lymphatic tracts, which results in stasis of lymph fluid and swelling. Phenotypic features of TS are believed to result from in-utero edema. Cervical lymphatic system distension manifests as a webbed neck and a low posterior hairline and increased nuchal translucency on ultrasound scan. Epicanthic folds are manifestations of in-utero facial oedema. Swollen hands and feet, deep digital skin fold creases, and small dysplastic toenails are manifestations of peripheral oedema. Prenatal lethality in TS is believed to be due to an underlying lymphatic abnormality, resulting in fluid imbalance and hydrops fetalis [12]. However, in this series, 5% of patients had a history of lymphedema and one patient had recurrent lymphoedema that required surgical intervention.

Genetic analyses have identified the Short Stature Homeobox (SHOX) gene as being a candidate gene for short stature and other skeletal abnormalities associated with TS including high-arched palate, abnormal auricular development, cubitus valgus, genu valgum, Madelung deformity and short metacarpals [13].

A decrease in growth velocity occurs in some patients as early as 18 months of age, some may have a significant decrease in linear growth rate by third or fourth grade, and some present only when the normal pubertal growth spurt fails to occur [4]. According to the literature, short stature is found in 98% of women diagnosed with TS [14]. In this series 90% (n=36) of patients were short (<3rd centile in standard growth chart) but the other 4 patients presented during infancy and are currently under growth monitoring.

In this cohort, major dysmorphic features webbed neck, low posterior hairline, cubitus valgus, shield chest found in more than 60% of children. In literature, the presence of these features is slightly low. Webbed neck 25%, low posterior hairline 42%, cubitus valgus 47%. In the current study short 4th metacarpal bones were found in 12.5% of patients whereas in published data it is high as 37%. Nail abnormalities were found in 10% and 13% respectively in the present study and published data.

Congenital heart defect occurs in approximately 50% of patients with TS and left-sided obstructive defects predominate, especially Bicuspid Aortic Valve (BAV) and Coarctation of the Aorta (COA) [8,15]. Recent imaging studies revealed prevalence of COA and BAV in large groups of girls and women with TS, approximately 11% have coarctation and 16% have BAV. In present study almost half of the patients had heart defects and 9% and 18% had COA and BAV respectively. COA and BAV are each almost 4-fold more frequent in patients with webbed necks. COA may not be detected in infancy, but may be first diagnosed in older children or adults. BAV is at risk for infective endocarditis, and over time can develop aortic stenosis or regurgitation. It is also associated with aortic wall abnormalities including ascending aortic dilation, aneurysm formation, and aortic dissection necessitating the regular follow up even without congenital malformations [2]. In this series 9% of patients had Partial Anomalous Pulmonary Venous Drainage (PAPVD), whereas in literature it approximately affects 13% in TS *vs.* less than 1% in the general population. PAPVC in TS frequently involves the left upper pulmonary vein, which is less common than the typical right-sided presentation in the general population and makes echocardiographic detection more challenging. In the present study cardiovascular abnormalities assessed only by echocardiography. However, clinical use of Cardiac Magnetic Resonance imaging (CMR) in patients with TS over recent years has allowed for characterization of disease not always possible with standard imaging modalities [16]. Hypertension affects about 25% of girls and a larger percentage of adults with TS [2,3]. In contrast, none of the patients in this series were found to have hypertension.

Congenital malformations of the urinary system are present in 30% to 40% of patients with TS. Most frequently found ultrasound abnormalities were collecting-system malformations (20%), followed by horseshoe kidneys (10%), malrotation, and other positional abnormalities (5%). However, in the present study, only 16% of patients had ultrasonically detectable renal anomalies. If an intravenous pyelogram is also performed as screening, even more abnormalities will be identified, but these tend to be clinically insignificant [2].

Nearly, 85% of patients with a Karyotype 45, X have a total loss of germinal cells at birth, 10% to 15% of them have enough germinal cells to develop a pubertal response and 5% of them have enough germinal cells to allow for pubertal development and spontaneous menstrual cycles, with premature menopause at around 30 years of age. Only 1% to 2% of women with TS will undergo natural pregnancy but with a greater risk of loss [10]. A longitudinally followed-up Turner cohort showed 76% of the patients with mosaic Turner syndrome had two detectable ovaries and larger ovarian volumes, compared to girls with 45, X karyotypes, of whom only 26% had ovaries detected by ultrasonography [17,18]. In the current study, 73% of them had streaky, small ovaries or ovaries that could not be identified.

Uterine development is altered in girls with Turner Syndrome. Even though with time had increased uterine size, these measurements were significantly lower than those from the control group [18]. In our cohort, 34% had small size uterus.

A wide range of eye disorders has been detected in patients with TS. In a recent cross-sectional study, out of 82 patients with TS eye disorders were diagnosed in 52%. Defects related to impaired vision were the most common (44%), followed by strabismus (21%), changes in the posterior eye segment (6%), red-green colour deficiency (5%), changes in the anterior eye segment (5%), and nystagmus (4%). Amblyopia was diagnosed in 13 patients (16%) [19,20]. In contrast, this series showed eye abnormalities in 27% of patients, and problems with visual acuity and squints were the commonest.

Otitis media is common during childhood and lead to conductive hearing loss, frequent tympanostomy tube insertions, and antibiotic treatment [21]. The high prevalence of otitis media seems to result from the abnormally horizontal orientation of the eustachian tube, which results in poor drainage and inadequate ventilation of the middle ear space. The shorter length of the eustachian tube may allow more nasopharyngeal microorganisms to reach the middle ear. In our study, 20% of patients had a conductive hearing impairment and only 2.5% had sensorineural deafness. The most commonly mid-frequency Sensorineural Hearing Loss (SNHL) in TS begins in the second or third decade, even though it has been reported in children younger than 10 years. With aging, the SNHL develops into a high-frequency hearing loss [22]. There is an increased risk for ear and hearing problems in all women with Turner syndrome, but it is more common in karyotype 45, X, and 46, X, i (Xq) [21].

Individuals with Turner Syndrome (TS) are prone to develop autoimmune conditions such as coeliac disease, thyroiditis, autoimmune hepatitis, and Type 1 Diabetes (T1DM). The prevalence increases with age and it is estimated 50% of middle-aged patients with TS, suffer from Hashimoto's thyroiditis [23]. The underlying pathophysiological mechanism leading to the increased risk of morbidity secondary to autoimmune hyperreactivity is unknown [20]. In our cohort, 11% of patients had autoimmune hypothyroidism with positive antithyroglobulin and thyroid peroxidase antibodies. A Danish cohort of patients aged (6 - 60) years, showed a prevalence of anti-TPO of 48% in TS in comparison with an estimated prevalence of 13% in the general population [20]. This revealed prevalence of hypothyroidism in one of every five TS patients confirms autoimmune thyroiditis as a significantly increase morbidity in both paediatric and adult TS populations [23]. The current finding of anti-TPO in 94% of the hypothyroid TS patients indicates a causative relationship between autoimmune reactivity and hypothyroidism in TS. Screening for diabetes and autoimmune hepatitis negative at present in this series but annual screening is recommended.

The majority of individuals with TS have normal intelligence, although patients with a small ring X-chromosome clearly have an increased risk of mental retardation. The specific neuropsychological deficits include four interacting areas of functioning: visual-spatial organization deficits (e.g., difficulty with direction sense), difficulty with social cognition (e.g., failure to appreciate subtle social cues), difficulty with problem-solving (e.g., mathematics), and motor deficits. Some of these deficits may be improved by hormonal therapy at the time of puberty. A higher-than-expected rate of attention deficit disorder diagnoses (24%) is reported in school-age girls [5]. In contrast, in our study, 7% of patients had below-average school performance but were not associated with the presence of ring chromosomes. It is important to perform a standard IQ assessment to explore this field.

Conclusion

Our study concludes that only 25% of TS patients were diagnosed before the age of 5 years and only 20% were referred to Paediatric Endocrinology services before the age of 5 years. Short stature is the main clinical presentation that led to the diagnosis TS. Delays in the evaluation of short stature and lack of awareness of the clinical spectrum of TS may have contributed to potential delays in diagnosis and referral.

Limitations

We do not have data on systematic IQ assessment in this cohort and future studies will include such data.

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