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ORIGINAL ARTICLE

Clinical Features of Girls with Turner Syndrome in a Single Centre in Malaysia*

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Abstract

Objectives. Diagnosis of Turner syndrome in Malaysia is often late. This may be due to a lack of awareness of the wide clinical variability in this condition. In our study, we aim to examine the clinical features of all our Turner patients during the study period and at presentation.

Methodology. This was a cross-sectional study. Thirty-four (34) Turner patients were examined for Turner-specific clinical features. The karyotype, clinical features at presentation, age at diagnosis and physiologic features were retrieved from their medical records.

Results. Patients with 45,X presented at a median age of 1 month old with predominantly lymphoedema and webbed neck. Patients with chromosome mosaicism or structural X abnormalities presented at a median age of 11 years old with a broader clinical spectrum, short stature being the most common presenting clinical feature. Cubitus valgus deformity, nail dysplasia and short 4th/5th metacarpals or metatarsals were common clinical features occurring in 85.3%-94.1% of all Turner patients. Almost all patients aged ≥2 years were short irrespective of karyotype.

Conclusion. Although short stature is a universal finding in Turner patients, it is usually unrecognised till late. Unlike the 45,X karyotype, non-classic Turner syndrome has clinical features which may be subtle and difficult to discern. Our findings underscore the importance of proper serial anthropometric measurements in children. Awareness for the wide spectrum of presenting features and careful examination for Turner specific clinical features is crucial in all short girls to prevent a delay in diagnosis.

Key words: Turner syndrome, short stature, webbed neck, lymphoedema, karyotype

INTRODUCTION

Turner syndrome occurs in approximately 1 in 2500 female live births.[1] This syndrome is usually diagnosed in females with characteristic features with an absence of one X chromosome in their karyotype (45,X). However, studies have shown that 45,X karyotype accounts for only 45-50% of all cases of Turner syndrome.[2] Up to 55% of Turner syndrome have other karyotypes including 46,X,i(X)(q10), 46,X,r(X), 45,X/46,XX, 46,X,del(Xp), and 46XY.[2]

Clinical features of classic Turner syndrome with 45,X include short stature in the majority, delayed puberty and infertility in 60-90%, left- sided cardiac anomalies in 50% and renal defects in one-third of cases.[3-5] Other clinical features seen in these patients are short webbed neck, low-set ears, multiple pigmented naevi, oedema of hands and feet, short metacarpals or metatarsals and cubitus valgus deformity. Studies have shown that cardiovascular malformations are more common in classic Turner with 45,X karyotype compared to non-classic Turner with chromosome mosaicism or structural X abnormalities.[4,5-7]

Even though the karyotype of a patient with Turner syndrome does not reliably determine its phenotype or clinical features, patients with mosaic 45,X or structural X chromosomal abnormalities may have less or subtle clinical features compared with patients with 45,X. For instance, normal puberty and fertility are more commonly reported in mosaic Turner patients.[8] Amongst Turner patients with structural X chromosomal abnormalities, ring X-chromosome may also convey a distinct phenotype. Notably these patients may have severe mental retardation, growth retardation and multiple congenital anomalies, which are usually not found in the 45,X patients.[9,10] On a different note, Turner patients with presence of SRY or other Y-chromatin harbor a risk of developing gonadoblastoma in the streak gonads.[11] Management include prophylactic excision of the abnormal gonads.

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Human growth hormone has been shown to be effective in improving the growth of Turner syndrome patients to prevent short adult stature. Treatment has to be initiated early to achieve a satisfactory outcome. Unfortunately, Turner syndrome is often diagnosed late due to lack of awareness of the variability in clinical features and karyotypes. Hence, the aim of our study is to compare the age at diagnosis between 45,X Turner syndrome and the non-classic Turner syndrome and to evaluate the association between age at diagnosis and karyotype. We also aim to evaluate the association between clinical features at presentation and karyotype. These Turner patients are also examined thoroughly for clinical features of Turner syndrome and the association between clinical and physiologic features of Turner syndrome and karyotype are evaluated. We hope that this knowledge may help to heighten awareness and enhance early diagnosis of Turner syndrome so that counseling and appropriate management may be instituted as soon as possible.

Table 1. Classification of Turner Syndrome (n=34) based on karyotype

	Karyotype	N(%)
1. Group A		
Monosomy X	45,X	16 (47.1%)
2. Group B		
X mosaicism	45,X/46,X+1Mar (n=3)* 45,X/46,X+2Mar (n=1)* 45,X/46,XX (n=3)	7 (20.6%)
Y mosaicism	45,X/46,XY (n=2) 45,X/47,XYY (n=1) 45,X/46,X+Mar.ish dic(Y;Y) (n=1)	4 (11.8%)
Ring X	45,X/46,X, r(X) (n=3) 45,X/46,X, r(X)/ 47,X, +2r(X) (n=1)	4 (11.8%)
Isochromosome Xq	46,X,i(Xq) (n=2)	2 (5.9%)
Isochromosome Xp	45,X/46,X,i(Xp) (n=1)	1 (2.9%)
	Total	34 (100%)

* Lymphocytes examined by fluorescent in situ hybridization were negative for SRY gene probe and positive for X pericentromeric probe.

METHODOLOGY

We conducted a cross-sectional study over a 1 year period from 2015 to 2016 in Universiti Kebangsaan Malaysia Medical Centre (UKMMC). All karyotype proven Turner patients who were on active follow up in the paediatric endocrine clinic and aged more than 6 months were selected for the study. A total of 34 patients were included in the study. In all cases, Turner syndrome was diagnosed based on karyotype findings using G-banding technique on at least 30 cells performed by the cytogenetic unit at PPUKM. FISH studies using centromeric X, centromeric Y and SRY gene probes were carried out on at least 100 nuclei in selected cases, i.e., in patients with Turner phenotype where karyotype was found to be normal, in patients with detectable marker chromosomes and in patients with detectable Y chromosome.

All patients were classified into 2 groups based on their karyotype. Sixteen patients (47.1%) were in Group A, i.e., 45,X and 18 patients (52.9%) were in Group B, i.e., chromosome mosacism with more than one cell line or structural abnormality of the X chromosome. Table 1 shows the karyotype distribution of the study group. The median age was 14.7 years (11-20.4 years) in Group A and 17.3 years (12.5-22.1 years) in Group B (Table 2).

Throughout the study, these patients underwent thorough clinical examination by the same researcher during their routine clinic visits. This clinical examination included all clinical features of Turner syndrome as stated in Table 3, anthropometric measurements and pubertal staging by method of Tanner. For patients aged more than 2 years and who can stand properly as instructed, height was measured using the Harpenden stadiometer. Patients younger than 2 year or those who could not stand properly as instructed, length was measured using an infantometer. Short stature was defined as height or length less than 3rd percentile on the NCHS (National Child Health Statistics) growth chart and below the target height range for the mid parental height in patients aged ≥2 years. For Turner patients who had been started on growth hormone therapy, their pre-treatment heights were obtained from their respective medical records. Short stature was only determined in 14 patients in group A and 18 patients in group B aged ≥2 years.

The plasma FSH values and pubertal staging of all subjects were reviewed from their medical records. Delayed puberty was defined by presence of exaggerated rise in plasma FSH >10 IU/L and the absence of clinical signs of spontaneous puberty (Tanner stage 2 breast development) by 12 years of age. Delayed puberty was only determined in 11 patients in group A and 15 patients in group B who were aged ≥12 years. Arrested puberty was defined by a lack of pubertal progression over one year or more.

Other physiologic features, i.e., cardiac abnormalities, mental retardation, hearing abnormalities, thyroid disorders, impaired carbohydrate metabolism and renal abnormalities were obtained from medical records. The presence of cardiac abnormalities was confirmed by echocardiography. The presence of hearing and thyroid abnormalities were confirmed by audiology assessment and abnormal thyroid function tests. All subjects in the study had undergone echocardiography, audiology assessment, renal ultrasound and thyroid function screening at diagnosis and/or during follow up.

Impaired carbohydrate metabolism was confirmed by HbA1c and fasting blood glucose (FBG) before and during growth hormone therapy. For Turner patients who were not on growth hormone treatment, HbA1c and FBG were performed by 10 years of age. Patients who had an abnormal HbA1c or FBG underwent an oral glucose tolerance test (OGTT). Impaired carbohydrate metabolism was defined as presence of impaired fasting glucose, impaired glucose tolerance or diabetes mellitus. Impaired fasting glucose was defined by FBG level of 5.6-6.9 mmol/L and impaired glucose tolerance was defined by a 2- hour postload glucose of 7.8 to <11.1 mmol/L during an OGTT.[12] Diabetes mellitus was defined by a FBG of ≥7.0 mmol/L or 2 hour postload glucose of ≥11.1 mmol/L during an OGTT.[13] Only 14 patients in Group A and 16 patients in Group B underwent screening for impaired carbohydrate metabolism.

Table 2. Age at diagnosis and clinical features at presentation

	Group A N=16	Group B N=18	OR (95% CI)	*P* value
*Current age (years)	14.7 (11.0- 20.4)	17.3 (12.5-22.1)		0.32
Age at diagnosis				
<12 months old	11 (68.8%)	4 (22.2%)	7.7 (1.66 to 35.69)	0.009
1-12years	5 (31.3%)	8 (44.4%)	0.57(0.14 to 2.32)	0.43
≥13years	0 (0%)	6 (33.3%)	0.06(0.003 to 1.14)	0.06
*Overall age at diagnosis	1 month (0- 4.3 years)	11 years (0.75-13.4 years)		0.005
Clinical Features at Presentation				
Lymphoedema	9 (56.3%)	1 (5.6%)	21.86 (2.31 to 206.46)	0.007
Webbed neck	6 (37.5%)	0 (0%)	22.91 (1.17 to 448.48)	0.04
Short stature	4 (25%)	8 (44.4%)	0.42 (0.10 to 1.80)	0.24
Delayed/arrested puberty	0 (0%)	4 (22.2%)	0.10 (0.005 to 1.973)	0.13
Developmental delay	0 (0%)	3 (16.7%)	0.13 (0.006 to 2.815)	0.2
Clitoromegaly	0 (0%)	1 (5.6%)	0.35 (0.01 to 9.31)	0.53
Spinal bifida	0 (0%)	1 (5.6%)	0.35 (0.01 to 9.31)	0.53
Hearing deficits	1 (6.3%)	0 (0%)	3.58 (0.14 to 94.32)	0.44

* Age is in median with IQR (Q1-Q3)

Table 3. Clinical features detected during the study and physiologic features of the study group

Clinical features	Group A (N=16) n(%)	Group B (N=18) n(%)	OR (95% CI)	*P* value
Webbed neck	11 (68.8%)	3 (16.7%)	11.0 (2.16 to 56.10)	0.004
Short neck	15 (93.8%)	7 (38.9%)	23.57 (2.52 to 220.34)	0.006
Edema of hands/feet	9 (56.3%)	3 (16.7%)	6.43 (1.32 to 31.37)	0.02
Ptosis	6 (37.5%)	3 (16.7%)	3.00 (0.61 to 14.86)	0.18
Low set ears	13 (81.3%)	10 (55.6%)	3.47 (0.73 to 16.53)	0.19
Scoliosis	5 (31.3%)	3 (16.7%)	2.27 (0.45 to 11.59)	0.32
Hypertelorism	8 (50%)	7 (38.9%)	1.57 (0.40 to 6.14)	0.52
Pigmented naevi	10 (62.5%)	13 (72.2%)	0.64 (0.15 to 2.72)	0.55
* Short stature	14 (100%)	17 (94.4%)	2.49 (0.09 to 65.76)	0.59
Nail dysplasia	15 (93.8%)	16 (88.9%)	1.88 (0.15 to 22.88)	0.62
Short 4th/5th metacarpals or metatarsals	14 (87.5%)	15 (83.3%)	1.40 (0.20 to 9.66)	0.73
Micrognathia	8 (50%)	8 (44.4%)	1.25 (0.32 to 4.83)	0.75
Widely spaced nipples	12 (75%)	14 (77.8%)	0.86 (0.18 to 4.19)	0.85
Cubitus valgus	15 (93.8%)	17 (94.4%)	0.88 (0.05 to 15.37)	0.93
Physiologic features				
Cardiac abnormalities	8 (50%)	2 (11%)	8 (1.38 to 46.81)	0.02
Mental retardation	0 (0%)	6 (33.3%)	0.058 (0.003 to 1.135)	0.06
# Delayed puberty	11 (100%)	11 (73.3%)	9.0(0.43 to 187.02)	0.16
Hearing abnormalities	7 (43.8%)	5 (27.8%)	2.02(0.49 to 8.43)	0.33
Thyroid disorders	0 (0%)	3 (16.7%)	0.13 (0.006 to 2.82)	0.2
Renal abnormalities	1 (6.3%)	0 (0%)	3.58 (0.14 to 94.31)	0.44
** Impaired carbohydrate metabolism	1 (7.1%)	2 (12.5%)	0.54 (0.044 to 6.668)	0.63

* Short stature was only determined in patients aged ≥2 years old (14 patients in Group A and 18 patients in Group B)
# Delayed puberty was only determined in 11 patients in Group A and 15 patients in Group B who were aged ≥12 years
** Impaired carbohydrate metabolism was only screened for 14 patients in Group A and 16 patients in Group B

As an IQ assessment was not carried out in our study to ascertain the degree of intellectual impairment, mental retardation was defined by significant developmental delay or intellectual impairment in need of special education. To identify potential delays in the diagnosis of Turner syndrome, information on the age at diagnosis and clinical features at presentation were retrieved from the medical records.

This study had been approved by the ethics committee of UKMMC (Project code number FF-2015-337). Written informed consent had been obtained from the patients.

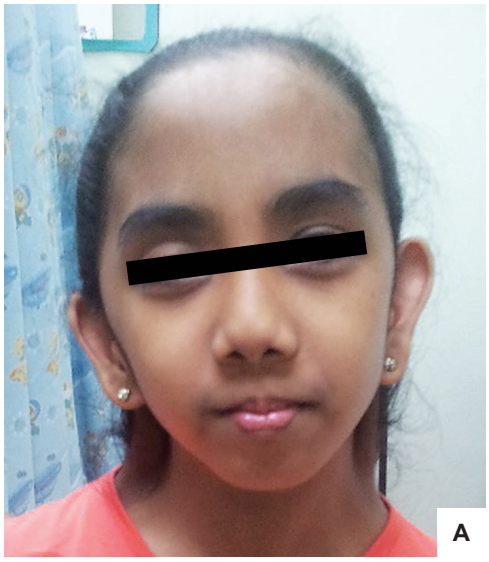
Statistical analysis

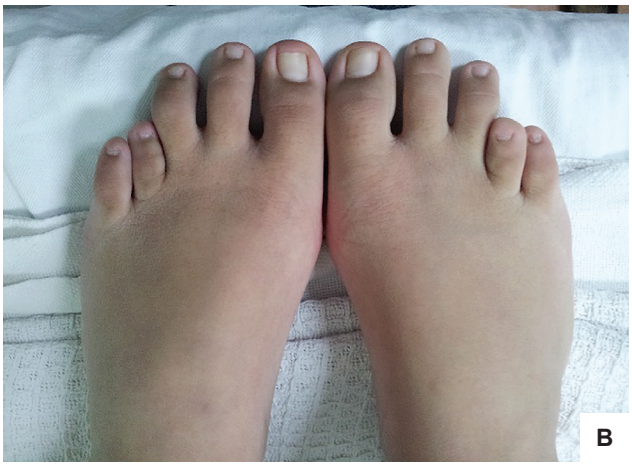
Categorical data was expressed as frequency and percentage. Numerical values were expressed as median and inter-quartile range. Group medians were compared using Mann- Whitney U test. Categorical variables were compared using Chi Square test and Fisher's exact test. All statistical analyses were performed using IBM SPSS (Version 25). A p value <0.05 was considered statistically significant.

RESULTS

Age at diagnosis and clinical features at presentation

The median age at presentation was 1 month (0-4.3 years) in Group A and 11 years (0.75-13.4 years) in Group B. In Group A, 68.8% of the patients presented during infancy compared to 22.2% in Group B (OR 7.7, 95% CI 1.66 to 35.69, p=0.009). In Group A, the predominant clinical features at presentation were lymphoedema and webbed neck. These features were significantly more common in Group A than Group B (56.3% vs 5.6% for lymphedema and 37.5% vs 0% for webbed neck). The majority of patients in Group B (77.7%) presented later after 1 year of age. Out of the patients in Group B who presented beyond infancy, 42.9% were of ages ≥13 years. The initial presentation for Group B was more varied, with short stature being the commonest (44.4%), followed by delayed/ arrested puberty (22.2%) and developmental delay (16.7%). Lymphedema (5.6%) and webbed neck (0%) were uncommon presentation (Table 2).





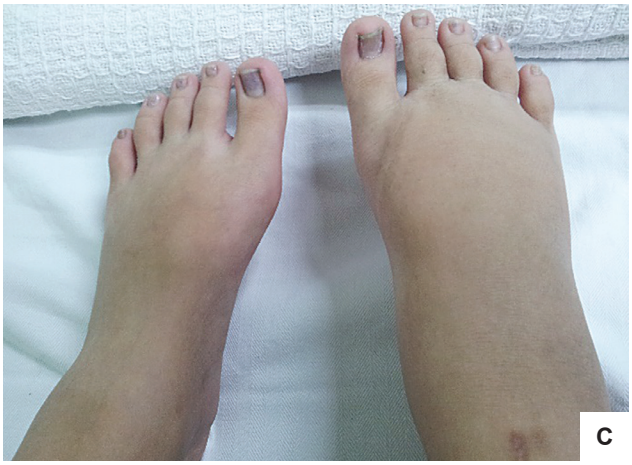
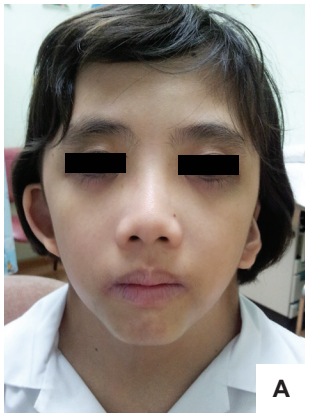


Figure 1. (A) Low set ears, micrognathia and short webbed neck in a 12-year-old with 45,X karyotype. **(B)** Short 4th and 5th metatarsals and hypoplastic nails in a 16-year-old girl with 45,X karyotype. **(C)** Right foot lymphoedema, bilateral hyperconvex and hypoplastic nails in a 11-year-old girl with 45,X karyotype.



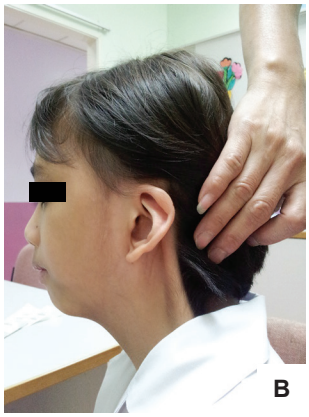


Figure 2 (A & B). Low set ears, hypertelorism, micrognathia, short webbed neck, left eye strabismus, pigmented nevus depicted in a 14-year-old girl with 45,X/47,XYY karyotype.

Figure 3. 24-year-old girl with 45,X/46,X,r(X) karyotype untreated with growth hormone showing cubitus valgus and short stature with a final height 19 cm below the mid-parental height which is indicated by the level of the Harpenden stadiometer head-block.

Two patients in Group B had unusual presentation. One of them had presented with spinal bifida, Arnold Chiari malformation and communicating hydrocephalus at birth. Clinical features of Turner syndrome were also present, i.e., oedema of hands and feet, nail dysplasia, low set ears and scoliosis. G-banded chromosome karyotyping showed 45,X/46,X,i(Xp). Another patient had presented with mild clitoromegaly at birth. Karyotyping revealed 45,X/46,XY. She subsequently underwent prophylactic gonadectomy at 1 year of age. Histopathologic Examination (HPE) of the gonads showed immature semiferous tubules with sertoli cells but no malignant cells.

Clinical features detected during the study

Clinical features of Turner syndrome as listed in Table 3 were more commonly detected in Group A than Group B. Short neck (OR 23.57, 95% CI 2.52 - 220.34, *p*=0.006), webbed neck (OR 11.0, 95%CI 2.16 - 56.10, *p*=0.004) and edema of hands/feet (OR 6.43, 95% CI 1.32 to 31.37, *p*=0.02) were significantly more common in Group A than Group B. Short stature was present in 100% of patients in Group A compared to 94.4% in Group B (Only one patient in Group B did not have short stature). There was no statistical significant difference between both the groups (*p*=0.59). Cubitus valgus deformity, nail dysplasia and short 4th/5th metacarpals or metatarsals were also common clinical features in both Group A and Group B, occurring in 85.3-94.1% of all the Turner patients. Again there was no statistical significant difference between the groups (Table 3). Figures 1 to 3 illustrate the clinical features detected by clinical examination during the study.

Physiologic features

The prevalence of cardiac abnormalities in our study was 29.4%. Cardiac abnormalities were significantly more common in Group A compared to Group B (OR 8, 95% CI 1.38 to 46.81, *p*=0.02) (Table 3). The commonest cardiac abnormality was coarctation of aorta, which accounted for seven out of the eight patients in Group A and one out of the two patients in Group B with cardiac abnormalities. Other cardiac abnormalities detected were aortic stenosis in one patient in Group A and hypoplastic aortic arch in one patient in Group B. Amongst the ten patients with cardiac abnormalities, nine (90%) had neck webbing and six (60%) had edema of the hands or feet, suggesting a coexistence between aortic arch structural abnormalities and lymphoedema.

Delayed puberty, hearing abnormalities and renal abnormalities were more common in Group A than Group B. However, the differences were not statistically significant. Delayed puberty was diagnosed in 100% group A and 73.3% group B patients who were ≥12 years of age (*p*=0.16) (Table 3). Four out of fifteen (26.7%) patients in group B had spontaneous onset of puberty, whereby two had 45,X/46,XX mosaicism and two had ring X-chromosome. All the subjects in the study group, including the four patients with spontaneous puberty had elevated plasma FSH >10IU/L. Out of these four, three had spontaneous menarche but developed secondary amenorrhoea, requiring hormonal replacement therapy.

None (0%) of the patients in Group A had mental retardation whereas six out of eighteen (33.3%) in Group B had mental retardation (Table 3). Amongst patients with mental retardation, three had karyotype 45,X/46,X+Mar, two had karyotype 45,X/46,X,r(X) and one had karyotype 45,X/46,X,i(Xp). Three patients in Group B had subclinical hypothyroidism secondary to autoimmune thyroiditis, and none in Group A. Two out of the three patients required thyroxine replacement. One patient in group A had dysplastic left kidney, and none in group B. None of our patients had horseshoe kidney. One patient in Group A had impaired fasting glucose. In Group B, one patient had diabetes mellitus on gliclazide and one had impaired glucose tolerance. Two out of the three patients with impaired carbohydrate metabolism were overweight. Impaired carbohydrate metabolism did not occur during growth hormone therapy.

DISCUSSION

Monosomy X or 45,X karyotype accounted for 47.1% of our cohort of Turner syndrome. This figure is consistent with other reports whereby monosomy X makes up 45% to 50%. of the karyotype of girls with Turner syndrome.[2] However, in contrast to other studies where isochromosome Xq forms the majority of patients in the non-classic Turner group,[2] our study showed that isochromosome Xq was uncommon and accounted for only two out of eighteen (11.1%) of our non- classic Turner group. This discrepancy might have been due to the small sample size of our cohort.

Short stature was the universal clinical feature seen in both groups. Patients with 45,X tended to present early in life at the median age of 1 month. Lymphoedema and webbed neck were the prominent clinical features leading to early presentation in this group before short stature became apparent. Webbed neck and lymphoedema were rare presenting features at diagnosis (Table 2) and uncommon clinical features in group B (Table 3). This might have been a reason for late diagnosis in these patients until peripubertal age when short stature became obvious or when delayed puberty set in which prompted medical consultation.

In addition to short stature, cubitus valgus deformity, nail dysplasia and short 4th / 5th metacarpals or metatarsals were common physical features across both groups. These characteristics may however be subtle and not easily discernible clinically. Unrecognised short stature and the failure to detect subtle clinical features in Turner syndrome could have led to late diagnosis of patients in Group B at median age of 11 years. It is noteworthy that 33.3% of patients in Group B presented at the age of ≥13 years, hence would miss the opportunity for height restoration with early growth hormone therapy.

The clinical features of short stature and skeletal abnormalities seen in 45,X is due to haploinsufficiency of the *SHOX* gene that has escaped X inactivation and is located in the terminal pseudoautosomal region Xp22.3.[13,14] It has been inferred that the lymphogenic genes residing at Xp11.3 could be responsible for the lymphoedema and webbed neck phenotype seen in Turner syndrome.[14,15] *USP9X (DFRX)*, a gonadal dysgenesis gene which maps to Xp11.4, is implicated in ovarian failure.[14] The diaphanous gene *(DIAPH2)* located on the Xq arm is required for normal ovarian function.[15] The smaller proportion of abnormal cells bearing the 45,X karyotype seen in our mosaic patients in group B could explain the lower prevalence of clinical features in group B compared to group A. This notion is however controversial as the karyotype of these patients is only performed on cultured lymphocytes from peripheral blood, and does not take into account the karyotype of body tissues, e.g., skin, brain, heart and ovaries which might be different.

The prevalence of cardiac abnormalities in Turner syndrome reported by other authors ranges from 20% to 50%, with biscupid aortic valve and coarctation of aorta as the leading causes.[4,6,16] Correlation between cardiac abnormalities and karyotype has been suggested in some

studies.[6,8,17] The largest patient series by Mazzanti et al., on 594 Turner patients showed that patients with 45,X were more likely to be associated with neck webbing and more serious cardiac abnormalities especially coarctation of aorta and partial anomalous pulmonary venous return.[6] Patients with structural X abnormalities were more likely to have bicuspid aortic valve and aortic valve disease.[6] In our study cohort, the prevalence of cardiac abnormalities was 29.4%. Coarctation of aorta was the predominant cardiac defect in our Turner patients with 45,X, comprising 87.5% of total cardiac defects in this group. Only two of the patients in our non-classic Turner group had cardiac abnormalities, comprising of coartation of aorta in one patient and hypoplastic aortic arch in another. The coexistence of webbed neck and congenital heart disease which has been reported by other authors[6,17] was also implicated in our study. It has been postulated that aberrant fetal lymphatic drainage could have caused disturbances to intracardiac blood flow and led to left sided cardiac abnormalities.[18]

Spontaneous puberty is reportedly more common in 45, X mosaicism than monosomy X. For instance, spontaneous puberty has been documented in 6% of patients with monosomy X compared to 54% of patients with 45X/46XX karyotype.[9] In our study, none of the patients with 45,X had spontaneous puberty. Spontaneous puberty onset however occurred in 26.7% of our patients with 45,X mosaicism, consisting of two patients with 45,X/46,XX, and 2 others with large ring X chromosomes. Large ring chromosomes have relatively distal break points which could preserve the critical regions where the ovarian failure genes map. There have been few cases of patients with large ring chromosome reported to be fertile and transmitted their r(X) to their offsprings.[19-21]

Most Turner patients have normal intelligence, with only specific deficits in visuospatial, psychomotor, social and nonverbal problem solving skills. The occurrence of mental retardation is greatest amongst Turner patients with ring chromosomes and marker chromosomes.[9,10,22,23] In our study, mental retardation was found in two out of four (50%) patients with ring X chromosomes and three out of four patients (75%) with marker chromosomes. The more severe phenotype could be a result of deletions in critical regions in the small ring Xs and marker chromosomes as well as failure of X inactivation. Mental retardation was also a feature in one patient with 45,X/46,X,i(Xp). The developmental delay found in this patient could be explained by the underlying Arnold Chiari malformation associated with hydrocephalus and spinal dysraphism.

The majority of our patients with non-classic Turner syndrome were diagnosis late in life at the median age of 11years. Even though short stature, cubitus valgus deformity, nail dysplasia and short 4th/ 5th metacarpals or metatarsals were very common clinical features in both 45,X and non- classic Turner syndrome, under recognition of these features had led to delayed diagnosis. This suggests an inadequacy in our community based health screening programme in detecting children with short stature as well as poor awareness among clinicians of the broad clinical spectrum and subtle phenotype that can be seen in non- classic Turner syndrome.

In a study by Sävendahl and Davenport,[24] lymphoedema was an important feature which led to the diagnosis in most of the girls diagnosed in infancy. Girls who were diagnosed during childhood or adolescence were found to have Turner-specific features and/or a history of lymphoedema. The diagnosis was however delayed an average of 5.3 years after faltering of their heights below the 5th centile. Screening guidelines were proposed following their study whereby girls with at least one of the following features, i.e., unexplained short stature (height below the 5th percentile); peripheral lymphoedema; webbed neck; delayed puberty (no signs of puberty by age 12.5 years) and coarctation of aorta required karyotype analysis for Turner syndrome.[24] It was also proposed that girls with at least two of the following features, i.e., nail dysplasia, short 4th metacarpal bone, strabismus and high arched palate) to be screened for Turner syndrome.[24]

Limitations in our study include a small study population sample size from a single centre. The assessment of clinical features during the study was by one single investigator and this may constitute bias in identification of subtle features. Knowledge of the patients' karyotype could also have caused bias. This study is however the first study in Malaysia which examined the age at diagnosis, presentation, clinical features and karyotype of patients with Turner syndrome.

CONCLUSION

Turner syndrome with monosomy X may be diagnosed early due to their association with webbed neck and lymphoedema. However, Turner patients with mosaic 45,X or structural X chromosomal abnormalities often present late. They lack the obvious clinical features of short webbed neck and lymphoedema. They can present with a wider clinical spectrum and have more subtle clinical features. We recommend accurate height measurement and careful detailed examination of all girls with clinical features suspicious of Turner syndrome. Karyotyping with or without florescent in-situ hybridization (FISH) should be performed to confirm the diagnosis so that appropriate management may be instituted early to prevent morbidities such as short stature, delayed/absent puberty, osteopenia and psychosocial issues.

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