CASE REPORT

Turner Syndrome with Ring X Chromosome: Do They Have a Distinct Phenotype?

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ABSTRACT

In contrast to classic Turner syndrome, Turner patients with ring X chromosome are associated with distinct dysmorphism and are likely to be mentally impaired. Four Turner patients with ring X chromosome were examined for phenotypic features of Turner syndrome and additional dysmorphism. Both patients 1 and 2 are twins with normal intelligence whereas patients 3 and 4 have mental impairment. With the exception of patient 4, the other three patients only have few Turner characteristics. None of the patients have the distinctive dysmorphism previously reported in Turner syndrome with ring X chromosome. Both twins developed spontaneous puberty. Patients 3 and 4 however had no spontaneous puberty. We postulate that this variation may be related to the ring size, the proportion of 45,X and ring X chromosome in cell lines of various body tissues as well as the ability of these rings to be inactivated as a result of lyonisation.

KEYWORDS: Turner syndrome, ring X chromosome, mental impairment

INTRODUCTION

The incidence of Turner syndrome has been reported as 1:2500 female live births. It is characterized by short stature, delayed puberty, broad chest with widely spaced nipple, webbed neck, cubitus valgus, lymphedema, short 4th and 5th metacarpals, renal and cardiovascular anomalies. Although some studies have suggested a specific cognitive deficiency,[1-3] the incidence of mental retardation does not appear to be higher in Turner syndrome than in the normal population, except for a subgroup of Turner patients with ring X chromosome.[4] In some instances, Turner patients with ring X chromosome have been associated with distinct dysmorphism which include upturned nares, long philtrum, a wide mouth with thin upper lip, strabismus, syndactyly of hands and feet and heart defects.[5] Ring chromosomes are thought to be initiated by two chromosome breakage events occurring at either side of a centromere, followed by fusion of the two broken ends of the centromere containing fragments.[6] Symptoms seen in patients with ring chromosomes are a result of deletion of genes in the telomeric regions of the affected chromosomes.[6] *XIST* is a gene in the X-inactivation centre located on the proximal long arm of the X chromosome which inactivates the abnormal ring X chromosome.[7]

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Four Turner patients with ring X chromosome under follow up at the paediatric endocrine clinic at Universiti Kebangsaan Malaysia Medical Centre were examined for phenotypic features of Turner syndrome and additional dysmorphism described above. The medical records of the four patients were also examined to look for associated features. Cytogenetic analysis by GTG-banding analysis of the cultured peripheral blood and fluorescent *in situ* hybridization (FISH) studies using probes for centromeric X chromosome, centromeric Y

chromosome, *SRY* gene and *XIST* were done to determine the association between phenotype and genotype. All patients had at least 100 cells analysed by FISH analysis. Written informed consent was obtained from all four patients, and ethical approval for this study was obtained from the ethical committee board from Universiti Kebangsaan Malaysia Medical Centre.

Both patients 1 and 2 are twins aged 24 years-old who presented at 13 years of age with short stature. Patient 3 aged 13 years-old and patient 4 aged 24 years-old were both diagnosed with Turner syndrome during evaluation for global developmental delay at 1 year of age and 11 years of age respectively. All 4 patients have short stature. Patients 1, 2 and 3 only have few classic Turner characteristics but patient 4 has more classic Turner characteristics (Table I). Interestingly, lymphedema, neck webbing and epichantic folds, which are thought to reflect *in-utero* oedema, are absent in all these patients. None of the patients have the distinct phenotype described in Turner syndrome with ring X chromosome. Both twins had spontaneous puberty and attained menarche at 13 years of age. However their menses were irregular and both required oestrogen therapy at 20 years of age. Both patients 3 and 4 had no spontaneous puberty and were started on oestrogen therapy since 12 years of age and 13 years of age respectively. High FSH and LH values were demonstrated in all 4 patients suggestive of primary ovarian failure. Both twins have normal intelligence, having completed tertiary education and currently holding occupations as professionals. Patients 3 and 4 however have mental impairment requiring special education.

Cytogenetic analysis by GTG-banding analysis of cultured peripheral blood showed that patients 1, 3 and 4 had mosaicism of 2 cell lines consisting of 45,X/46,X,r(X) with the cell lines containing the ring (X)s present in proportions varying from 24-42%. Patient 2 however had mosaicism of 3 cell lines consisting of 45,X/46,X,r(X)/47,X,+2r(X) whereby 34% of her cell lines had a single ring and only 1% of her cell lines had double rings (Table II). In all 4 patients, the presence of X chromatin and the presence of *XIST* locus from FISH study were evident on the normal X chromosomes and the ring X chromosomes. No signals were found with probes for centromeric Y chromosome and *SRY* gene indicating the absence of Y chromatin in all four patients.

Table I: Phenotypes and clinical features of the patients

Physical features and associated features	Patient 1	Patient 2	Patient 3	Patient 4
Short stature	+	+	+	+
Webbed neck	-	-	-	-
Cubitus valgus	+	+	+	+
Short 4thand 5th metacarpals	+	+	+	+
Scoliosis	-	-	-	-
Low set ears	-	-	-	+
Nail dysplasia	+	+	+	+
Ptosis	-	-	-	-
Hypertelorism	-	-	-	+
Wide spaced nipples	-	-	-	+
Micronagthia	-	-	-	+
Pigmented naevi	+	+	+	+
Hypertension	-	-	-	+
Obese$^{\#}$/overweight*	-	-	-	+*
Cardiac anormalies	-	-	-	-
Renal abnormalities	-	-	-	-
ENT abnormalities	-	-	-	+
Eye abnormalities	-	-	+	-
Thyroid disorders	+	+	-	-
Mental impairment	-	-	+	+
Failure of spontaneous puberty	-	-	+	+
Impaired carbohydrate metabolism	-	-	-	+

Table II: Cytogenetic findings in the patients

No.	Karyotype	% r(X)	Ring size	*XIST* gene
Patient 1	45,X[14]/46,X,r(X)[16]	42%	large	+
Patient 2	45,X[23]/46,X,r(X)[27]/47,X,+2r(X)[1]	35%	large	+
Patient 3	45,X[24]/46,X,r(X)[6]	40%	small	+
Patient 4	45,X[19]/46,X,r(X)[11]	24%	Very small	+

DISCUSSION

Cytogenetic analysis of the G-banded chromosomes revealed large ring (X)s for both our twin patients (Figure 1a and 1b) and small ring (X)s for patients 3 and 4 (Figure 1c and 1d). The large rings seen in our twin patients could have accounted for a milder phenotype due to relatively distal breakpoints which could have preserved critical regions on the ring chromosomes. The presence of *XIST* genes on the X chromosomes in both twin patients also renders these rings to be inactive. In contrast, the small rings seen in patients 3 and 4 may have attributed to

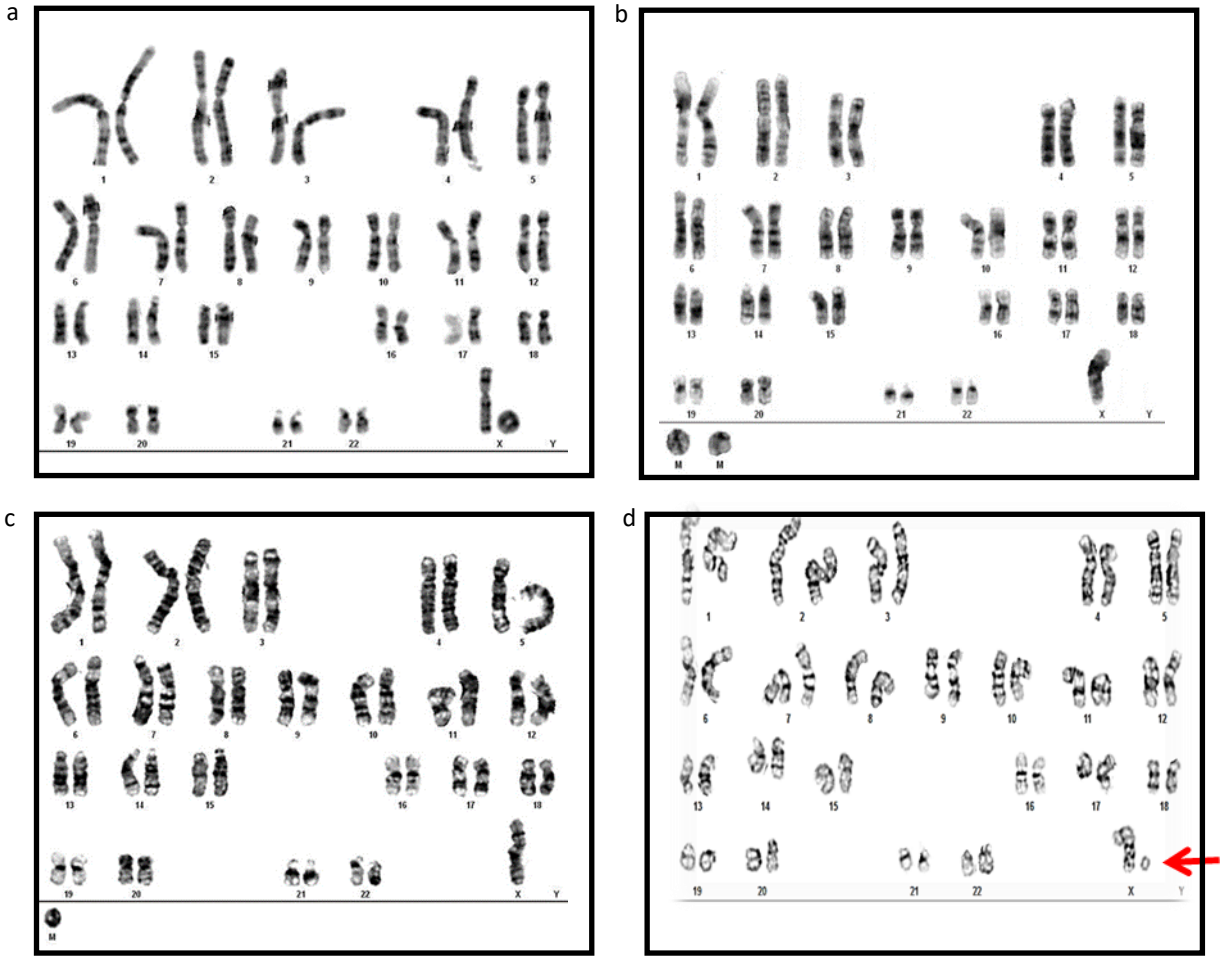

Figure 1 Cytogenetic analysis by GTG-banding analysis. (a) G-banded karyotype of patient 1 showing a large ring (X) in 46,X,r(X) cell line. (b) G-banded karyotype of patient 2 showing 2 large ring(X)s in 47,X,+2r(X) cell line. (c) G-banded karyotype of patient 3 showing a small ring (X) in 46,X,r(X) cell line. (d) G-banded karyotype of patient 4 showing a very small ring (X) (arrow) in 46,X,r(X) cell line.

mental impairment due to proximal breakpoints with deletion of critical regions on the ring X chromosomes, accounting for a more severe phenotype.

Interestingly, both patients 3 and 4 were also found to have *XIST* loci in both ring X chromosomes and monosomy X chromosomes. Similar cases reported previously have found that many of these patients lack expression of the *XIST* gene, which presumably precludes inactivation of the abnormal ring chromosome.[8] Other hypotheses explaining the abnormal phenotypes in patients who have a ring X chromosome with *XIST* include 1) *XIST* being expressed but not fully functional due to missing factors on the ring required for X inactivation, 2) failure of the structurally abnormal chromosome X to undergo conformational changes during X inactivation spreading, and 3) random X inactivation in favour of the normal X during embryogenesis.[9] Replication studies and methylation studies are indirect methods that may be useful to determine the X inactivation status. Other genetic or environmental factor(s) unrelated to X chromosomal abnormalities may also be responsible for mental retardation.

Genetic mosaicism with different proportions of ring X chromosome and monosomy X cell lines can also give rise to clinical variability. On the contrary, we did not see a correlation between the proportion of ring X chromosomes and phenotype in our patients. The level of mosaicism may however differ in various body tissues *ie* brain tissue or skin fibroblast, accounting for different degrees of severity in the phenotype.[10]

CONCLUSIONS

Our case series is consistent with the observation that "classic" Turner characteristics and atypical ring X phenotype may be absent in some Turner patients with ring X chromosome. The ring size was found to be inversely correlated to the severity of the phenotype. Mental impairment associated with the presence of a small ring X cannot be explained solely on the basis of presence or absence of a *XIST* gene, suggesting the involvement of other genetic mechanisms in the process of X inactivation. Further molecular studies of the small ring X chromosomes and further cytogenetic analysis of different tissue samples may lead to a better understanding of the genetic mechanisms involved and how it relates to the patients' clinical features.

REFERENCES

1. Bender B, Puck M. Salbenblatt J, Robinson A. Cognitive development of unselected girls with complete and partial X monosomy. *Pediatrics*. 73,175-82 (1984)
2. McCauley E, Kay T, Ito J, Treder R. The Turner syndrome: cognitive deficits, affective discrimination and behavior problems. Child Develop 58: 468-478 (1987)
3. Romans SM, Stefanatos G, Roeltgen DP, Kushner H, Ross JL. The transition to young- adulthood in Ullrich- Turner syndrome: neurodevelopmental changes. Am J Med Genet 79:140-147 (1998)
4. Van Dyke D, Wiktor A, Paliner C et al. Ulrich-Turner syndrome with a small ring X chromosome and presence of mental retardation. *Am. J. Med. Genet*. 43(6),996-1005 (1992)
5. Grompe M, Rao N, Elder FFB et al. 45X/46,X,1r (X) can have a distinct phenotype different from Ullrich – Turner syndrome. *Am. J. Hum. Genet*. 42,39(1992)
6. Gardner RJM, Sutherland GR, and Shaffer LG. Chromosomal Abnormalities and Genetic Counseling, Oxford University Press, New York, USA, 4th ed. (2011)
7. Schinzel A. Catalogue of Unbalanced Chromosome Aberrations in Man, De Gruyter, Berlin, NY, USA,2nd ed. (2001)
8. Migeon BR, Luo S, Stasiowski BA et al. Deficient transcription of XIST from tiny ring X chromosomes in females with severe phenotypes. *Proc. Natl. Acad. Sci. USA*. 90, 12025-9 (1993)
9. Leppig KA, Disteche CM. Ring X and other structural X chromosome abnormalities : X inactivation and phenotype. *Seminars in Reproductive medicine*. 19(2), 147-57 (2001)
10. Eduardo SC, Donna FJ and G. Shashidhar Pai. An atypical Turner Syndrome patient with ring X chromosome mosaicism. *Annals of Clinical and Laboratory Science*. 25(1), 60-65 (1995)