

Triple X syndrome and various abnormality of 3q in Iraqi women: a case report

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Abstract:

Triple X syndrome 47XXX is a sex chromosome abnormality characterized by presence of an extra X chromosome. Most of the girls born with triple X chromosomes have no signs or symptoms at birth. The condition often remains undiagnosed until adulthood when the genetic defect is discovered on investigation for other reasons as in this case of a 52 year old lady who diagnosed with systemic lupus erythematosus (SLE). The chromosomal analysis for peripheral blood cells by using G-banding technique revealed trisomy X and various abnormality of 3q karyotype. Chromosomal analysis was also done for two daughters and one son of the patient that showed normal karyotype. In conclusion our findings provide additional support for the hypothesis that X-chromosome polysomy may confer increased susceptibility to SLE. The association of SLE with chromosomal abnormality of 3q found in our patient needs further studies to uncover the role of genes affected by this aberration in SLE.

Key words : Triple X syndrome , trisomy X , chromosomal abnormality.

Introduction:

Triple X syndrome (trisomy X, 47,XXX), first described by Jacobs 1959, is a sex chromosomal abnormality (SCA) condition with female phenotype (1). Triple X syndrome is not extremely rare as the majority of cases go undiagnosed. 47,XXX karyotype is present in about 1/1000 female births and is usually diagnosed incidentally, mostly at prenatal diagnosis (2). Triple X syndrome results from errors in the process of maternal or paternal meiosis that can lead to X chromosome trisomy (nondisjunction of chromosomes during meiotic divisions of X chromosome). The extra X chromosome is very rarely of paternal origin (3). The non-mosaic 47,XXX karyotype is the most frequent. Mosaicism occurs in approximately 10% of cases and can occur in various combinations such as 47,XXX/46,XX or 47,XXX/48,XXXX or 45,X/47,XXX. Mosaicism can change the effects of triple X (4).

Triple X affects individual girls and women differently. Some are scarcely affected, if at all, while others can have obvious and significant problems. The majority of females

with triple-X syndrome appear normal at birth, and without specific congenital malformations or identifying physical characteristics (5). The physical features are subtle and variable and include tall stature, short head circumference, an increased risk for speech delay, mild learning disabilities and poor motor coordination. Behavioural problems have been reported but are not fully confirmed (5).

Female patients with triple-X syndrome may be fertile and can expect to have healthy children. In patients with a 47,XXX cell line there appears to be an increased risk of a cytogenetically abnormal child but the extent of this risk cannot yet be determined; it is probably lower in the non-mosaic 47,XXX patient than the mosaic 46,XX/47,XXX one. The extra X chromosome is not usually passed on to their children (4).

Systemic lupus erythematosus (SLE) is a prototype autoimmune disease with a strong genetic component, characterized by hyperactive T and B cells, autoantibody production, immune complex deposition and multi-organ damage (6). It occurs more commonly in females than in males and the reason is not completely understood (7).

There are very few descriptions of SLE in females with X-chromosome polysomy (8-11). We describe a 52-year old lady with triple X and various abnormality of 3q diagnosed with SLE.

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Case Report :

A 52 year old lady diagnosed with SLE in (1999) and treated with prednisolone was referred to Iraqi center for cancer and medical genetic research for chromosomal analysis as a member of group in a research to study chromosomal aberrations in Systemic lupus erythematosus. Her physical features and mentality are normal .She had a normal menstrual history. The patient was married and has four sons (three females and one male). Cytogenetic study on peripheral blood cells was performed by short term culture technique (12) in Iraqi center for cancer and medical genetics research. Briefly, stimulated peripheral blood cells with Phytohaemagglutinin (PHA) were cultured for 72 hour (short term culture technique) at 37 °C . Cells were exposed to colcemid (0.2 µg/ml) in last 30 minute of culturing time at 37 °C and harvested for

chromosome analysis on G-banded metaphases. Karyotype designation followed the International System for Human Cytogenetic Nomenclature (ISCN, 2013) (13).

Cytogenetic analysis showed : 47XXX, add(X)(q28-qter)[20], 47XXX, add(X)(q28-qter), dup(3)(q24-q26)[5] , 47XXX, add(X)(q28-qter), inv(3)(q25-q29)[4] , 47XXX, add(X)(q28-qter), -21 [1] . The number of cells that were analyzed is given in square brackets after the karyotype. The karyotype revealed trisomy X in all metaphases studied and various abnormality of 3q (table 1, figure 1, 2). Chromosomal analysis was also done for three of the patient sons (two females, one male). There was nothing unusual about their physical features and mentality. Cytogenetic analysis showed normal karyotype. Their results are illustrated in table 1.

Table (1). Age , sex and karyotype results .

Patient no.	Age	Gender	Number of cells analyzed	Karyotype
1	52	Female (mother)	30	47XXX, add(X)(q28-qter)[20], 47XXX, add(X)(q28-qter), dup(3)(q24-q26)[5] , 47XXX, add(X)(q28-qter), inv(3)(q25-q29)[4] , 47XXX, add(X)(q28-qter) , -21 [1] .
2	23	Male	12	46XY
3	22	Female	15	46XX
4	16	Female	11	46XX

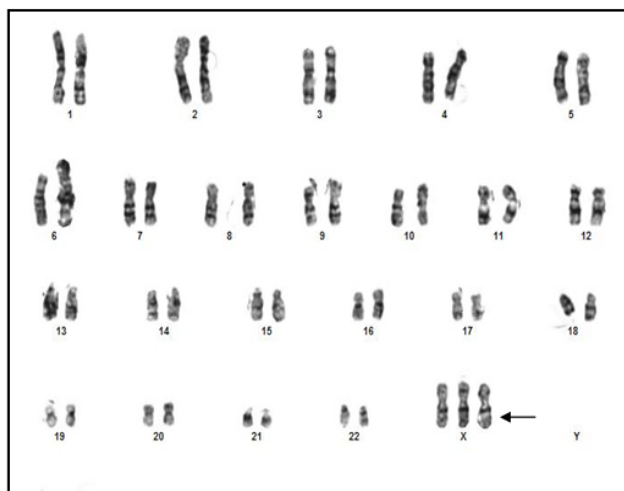
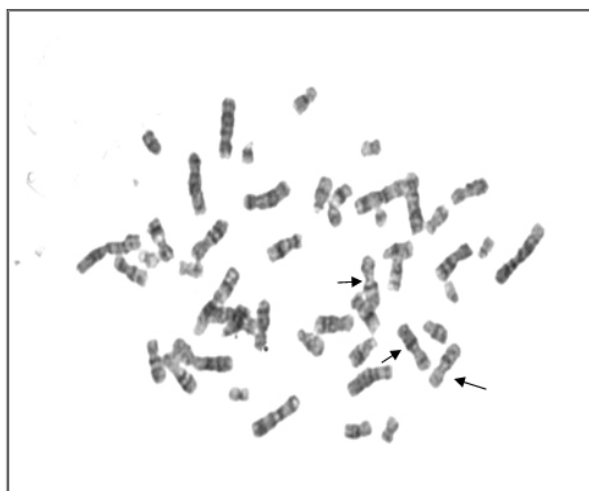


Figure (1) (a) G-banding metaphase cell of the peripheral blood revealed chromosomal abnormality: trisomy X , add(X)(q28-qter) (→) under (1000X) magnification . (b) karyotype of the peripheral blood cell : 47XXX, add(X)(q28-qter).

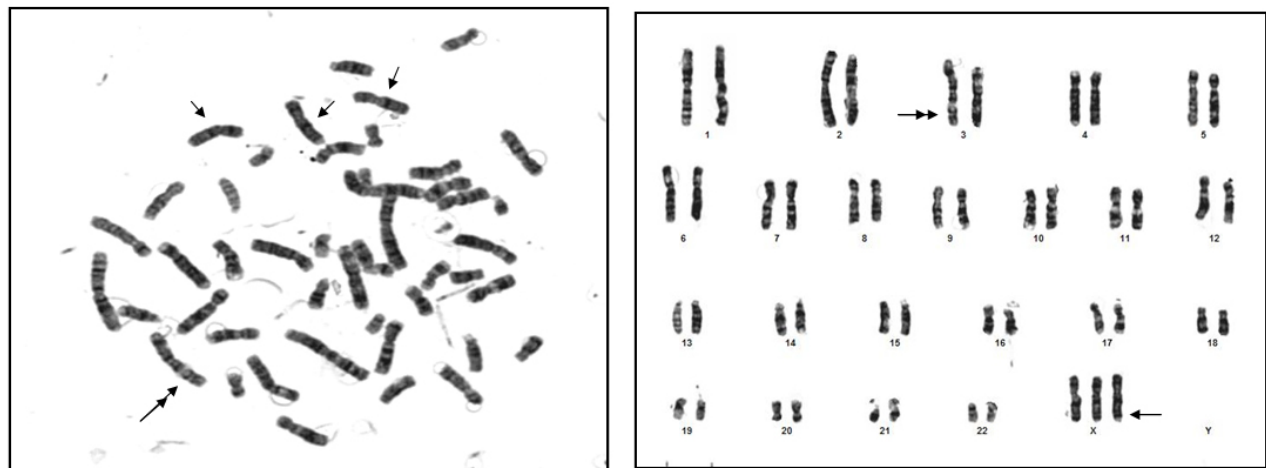


Figure (2) (a) G-banding metaphase cell of the peripheral blood revealed chromosomal abnormality : trisomy X , add(X)(q28-qter) (→), dup(3)(q24-q26) (→→) under (1000X) magnification . (b) karyotype of the peripheral blood cell : 47XXX, add(X)(q28-qter).

Discussion:

The result of our study revealed that the patient karyotype shows trisomy X in all analyzed cells and 30% of those cells showed various abnormality of the long arm of chromosome 3 (3q). The chromosomal analysis for 3 out of 4 of her sons showed normal karyotype for all of them. Although no direct studies of fertility in triple X have been carried out, most women with triple X have normal Sexual development and fertility and several triple X women give birth to chromosomally and physically normal children (3,4).

Chromosomal analysis revealed an Intrachromosomal duplications of X q28-qter in the triple X patient result in partial tetrasomy of X q28-qter. Prevalence of Xq duplications is presently unknown . Few studies reporting cases with Xq duplications (14). Duplications of the distal long arm of the X chromosome are rare and carrier females are usually phenotypically normal (15) .The majority of Xq duplications are inherited and transmitted in families through non-manifesting mothers. Most heterozygous females show extreme to complete skewing of X chromosome inactivation and thus are a symptomatic (16).

The lady with triple X syndrome also shows various abnormality of the long arm of chromosome 3(3q). Duplication of the long arm of chromosome 3, dup(3)(q24-q26) was found in 17% of analyzed cells, and inversion of the long arm of chromosome 3 , inv(3)(q25-q29) was found in 13% of analyzed cells. The chromosomal abnormality of 3q found in our patient was described previously (17). Inverted duplications are a kind of genetic lesions that can appear either as mosaic, or non-mosaic, depending on the time that they

are formed (18) .The duplication of chromosome 3q is a rare disorder with varying chromosomal breakpoints and consequently symptoms (17). Inverted duplications of 3q with aberrations in another chromosome may not show the effects of a 'pure' duplication.

The lady in our report is notable in that she has SLE in association with X-chromosome trisomy and various abnormality of 3q karyotype. Systemic lupus erythematosus (SLE) occurs more commonly in females than in males (7). Recent reports demonstrate excess Klinefelter's among men with SLE and a possible under representation of Turner's syndrome among women with SLE (19). It might be possible that X-chromosome polysomy confer further increased risk for lupus. These data suggest that risk of SLE is related to a gene dose effect for the X chromosome (8).

Genetic and environmental factors contribute in the pathogenesis of SLE. Numerous disease susceptibility loci have been identified in human (20,21). Identification and Characterization of one of these genetic loci has found on chromosome 3 (22). Genetic predisposition to SLE is caused by epistatic interactions between several genes spread throughout the genome and organized in susceptibility and modifier/suppressor loci. These genes may regulate different pathogenic aspects of SLE , influence the severity of the clinical manifestations and affect the outcome of the disease (22).

In conclusion diagnosis of patients with trisomy X remains difficult because of phenotypic variability of patients with trisomy X and specific clinical criteria used to identify this condition are not available .Research on triple X syndrome may yield more insight into physical ,clinical , developmental and psychological characteristics. Our findings provide addition-

al support for the hypothesis that X-chromosome polysomy may confer increased susceptibility to SLE. The association of SLE with chromosomal abnormalities of 3q found in our

patient need further studies to uncover the role of genes affected by this aberration in SLE.

References:

- Jacobs, P.A.; Baikie, A.G.; Brown, W.M.; Macgregor, T.N.; Maclean, N.; Harnden, D.G.(1959). Evidence for the existence of the human "super female". *Lancet*, 2(7100):423-425.
- Otter, M.; Schrander-Stumpel, C.T.R.M. and Curfs, L.M.G.(2010) Triple X syndrome: a review of the literature. *European Journal of Human Genetics* (2010) 18, 265–271.
- Afshan, A. (2012). Triple X Syndrome. *J Pak Med Assoc*, 62(4): 392-394.
- Tartaglia, N.R.; Howell, S.; Sutherland, A.; Wilson, R. and Wilson, L. (2010). Review of trisomy X (47,XXX). *Orphanet Journal of Rare Diseases*, 5:8.
- Butnariu, L.; Rusu, C.; Caba, L.; Pânzaru, M.; Braha, E.; Grănescu, M.; Popescu, R.; Bujoranu, C. and Gorduza, E.V.(2013). Genotype-phenotype correlation in trisomy X: a retrospective study of a selected group of 36 patients and review of literature. *Rev Med Chir Soc Med Nat Iasi*, 117(3):714-21.
- Cui, Y.; Sheng, Y. and Zhang X.(2013). Genetic susceptibility to SLE: Recent progress from GWAS. *J Autoimmun*, 41:25–33.
- Hewagamaa, A.; Gorelika, G.; Patela, D.; Liyanarachchia, P.; McCunea, W.J.; Somersa, E.; Gonzalez-Riveraa, T.; the Michigan Lupus Cohort, Strickland, F. and Richardson, B.(2013). Overexpression of X-Linked Genes in T Cells From Women With Lupus. *J Autoimmun*, 41: 60–71.
- Slae, M.; Heshin-Bekenstein, M.; Simckes, A.; Heimer, G.; Engelhard, D. and Eisenstein, E.M. (2014). Female polysomy-X and systemic lupus erythematosus. *Seminars in Arthritis and Rheumatism*, 43:508–512.
- Kurosawa, S.; Kimura, O. and Sagawa, A. (1991) Systemic lupus erythematosus in a patient with the 47,XXX karyotype. *Arthritis Rheum*, 34:371–372.
- Alvaro-Gracia, J.M.; Humbria, A.; Garcia-Vicuna, R.; Ariza, A.; Garcia-Vadillo, A, Laffon A.(1989). Systemic lupus erythematosus and tetrasomy-X. *J Rheumatol*, 16:1486–1488.
- Lenoble, L. and Kaplan, G.(1987). Systemic lupus erythematosus in a woman with primary 47XXX hypogonadism. *RevMed Interne*, 8:430–432.
- Yaseen, N.Y.; Humadi, A.A.; Tawfiq, M.S. and Estivan, A.G. (1998). Cytogenetic Studies on patients with chronic Myelocytic leukemia. *Med. J. Tikrit Univ*, 4:5-9.
- ISCN (2013). An International System for Human Cytogenetic Nomenclature. Shaffer, L.G.; McGowan–Jordan, J. and Schmid, M. (eds.) Karger, S. Publisher, Inc. USA.
- Sanlaville, D.; Schluth-Bolard, C. and Turleau C. (2009). Distal Xq duplication and functional Xq disomy. *Orphanet Journal of Rare Diseases*, 4:4.
- Stankiewicz, P.; Thiele, H.; Schlicker, M.; Cseke-Friedrich, A.; Bartel-Friedrich, S.; Yatsenko, S.A.; Lupski, J.R. and Hansmann, I.(2005). Duplication of Xq26.2-q27.1, including SOX3, in a mother and daughter with short stature and dyslalia. *Am J Med Genet A*, 138(1):11-7.
- Zhang, A.; Weaver, D.D. and Palmer C.G. (1997). Molecular cytogenetic identification of four X chromosome duplications. *Am J Med Genet*, 68:29-38.
- Carreira, I.M.; Melo, J.B.; Rodrigues, C.; Backx, L.; Vermeesch, J.; Weise, A.; Kosyakova, N.; Oliveira G. and Matoso, E. (2009). Molecular cytogenetic characterisation of a mosaic add(12)(p13.3) with an inv dup(3)(q26.31 → qter) detected in an autistic boy. *Molecular Cytogenetics*, 2:16.
- Daniel, A.; St Heaps, L.; Sylvester, D.; Diaz, S. and Peters, G. (2008). Two mosaic terminal inverted duplications arising post-zygotically: Evidence for possible formation of neo-telomeres. *Cell Chromosome*, 7:1.
- Sawalha, A.H.; Harley J.B. and Scofield, R.H.(2009). Autoimmunity and Klinefelter's syndrome: when men have two X chromosomes. *J Autoimmun*, 33: 31–34.
- Fairhurst, A. M.; Wandstrat, A. E and Wakeland, E. K. (2006). Systemic lupus erythematosus: multiple immunological phenotypes in a complex genetic disease. *Adv. Immunol.* 92: 1–69.
- Rhodes, B.; and Vyse, T. J. (2008). The genetics of SLE: an update in the light of genome-wide association studies. *Rheumatology (Oxford)*, 47: 1603–1611.
- Carlucci, F.; Fossati-Jimack, L.; Dumitriu, I.E.; Heidari, Y.; Walport, M.J.; Szajna, M.; Baruah, P.; Garden, O.A.; Cook, H.T. and Marina Botto, M.(2010). Identification and Characterization of a Lupus Suppressor 129 Locus on Chromosome 3. *J Immunol*, 184:6256-6265.

متلازمة ثلاثي كروموسوم X مع تغيرات مختلفة في الذراع الطويل لكروموسوم 3 (3q) لدى امرأة عراقية : تقرير حالة

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الخلاصة:

متلازمة ثلاثي كروموسوم (47XXX) هي شذوذ في الكروموسوم الجنسي تتميز بوجود كروموسوم X اضافي. معظم الفتيات المولودات بهذه المتلازمة ليس لديهم اعراض او علامات عند الولادة وغالبا ما تبقى غير مشخصة حتى سن البلوغ حينما يتم اكتشاف الخلل الوراثي عند اجراء فحوصات لاسباب اخرى كما في حالة السيدة ذات عمر 52 سنة التي شخصت بداء الذئب الاحمراري. تم اجراء التحليل الكروموسومي لخلايا الدم المحيطي باستخدام تقنية التحزيم بالكمزا. اظهر تحليل الهيئة الكروموسومية وجود ثلاث نسخ من كروموسوم X مع تغيرات مختلفة في الذراع الطويل لكروموسوم 3 (3q). تم اجراء تحليل الكروموسومات لابنتان وابن واحد من ابناء السيدة واظهروا هيئة كروموسومية طبيعية. يستنتج ان النتائج التي توصلنا اليها تقدم المزيد من الدعم لفرضية ان تعدد كروموسوم X قد تزيد الاستعداد للاصابة بداء الذئب الاحمراري. ارتباط داء الذئب الاحمراري مع التغيرات في الذراع الطويل لكروموسوم 3 (3q) التي وجدت لدى المريضة يحتاج الى المزيد من الدراسات للكشف عن دور الجينات المعطوبة نتيجة لهذه التغيرات في داء الذئب الاحمراري.