https://journalofclinicalcases.com

Journal of Clinical Cases

ISSN 2769-9366

Case Report

A 12 Year Old Boy With 49 Xxxxy Karyotype; A Case Report From Pakistan.

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Abstract

49, XXXXY syndrome is a rare 1; 85,000-100,000 aneuploidic sex chromosome disorders.
Back-ground: Our study comprises of a male patient born to a non-consanguineous family aged 12 years but the mental age is of 6 years. Low birth weight was reported with difficulty swallowing. He has moderately low IQ and has several behavioural problems like aggression, shyness and social awkwardness. He has a history of expressive receptive communication disorder. His developmental milestones were delayed. He has a history of fits leading to collapse.
Methods: Karyotyping using peripheral blood was carried out to check for any possible chromosomal abnormality.
Results: Chromosomal analysis revealed three extra copies of X chromosome in all cells along with an intact Y chromosome i.e. 49, XXXXY.
Conclusion: presence of extra copies of X chromosomes is linked to multiple disorders in the present case. Prenatal amniocentesis would be of great help for early detection of such syndromes in future

Keywords : *49, XXXXY Syndrome, aneuploidy, sex chromosome, Klinefilter syndrome variant.*

INTRODUCTION

49, XXXXY syndrome is an extremely rare 1; 85, 000 to 100, 000 males (1). Fraccaro et al. in 1960 reported it for the first time ever (2). To date 100 such cases has been reported so far (3–6). The case we report here, to the best of our knowledge, is the first such case reported from Pakistan.

MATERIALS AND METHODS

Case History

The reported case was felt different and unusual by the parents. Unfortunately no amniocentesis karyotyping or ultrasound detected abnormalities like facial dysmorphism, hypospadias were not reported. He was delivered by 27 years old primigravida healthy mother. He was the first born to a non-consanguineous couple. Both parents were in good health. The patient had two normal younger sisters. There is no significant family history for possible genetic disorders. Pregnancy remained uneventful, full term and no drugs administration or radiation exposure was reported. At birth baby did not have any abnormal features except for micro-phallus which was not investigated or followed later. Normal Apgar score at birth (8/9) was observed, except difficult suckling. Significant behavioral problems were noted in the case from very early age, such as emotional disturbances with frustration, timidity, shyness and the level of adaptive functioning was much higher than the cognitive level. Parents noted above features and consulted various doctors, went through different basic clinical tests from a very young age. Suddenly at the age of ten years he got severe fits of 3-5 minutes duration, it was controlled on antiepilepsy drugs then and onward till today.

Clinical characteristics

He looked weak, restless and handicapped with saliva dribbling from mouth and had the mental age of 5-6 years old but stature was not short in this particular case. He had, hypertelorism, short neck, narrow shoulders, round face in infancy, flat foot, hyperextensible joints very mild or no radioulnar synostosis detected in this case, hypotonia, less muscle mass generally. Skeletal abnormalities are much

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Received: 25-Mar-2025, Manuscript No. JOCC-4690 **; Editor Assigned:** 28-Mar-2025 **; Reviewed:** 15-APR-2025, QC No. JOCC-4690 **; Published:** 29-Apr-2025, **DOI:** 10.52338/jocc.2025.4690
Citation: Dr. Amara Javaid. A 12 year old boy with 49 XXXXY Karyotype; a case report from Pakistan. Journal of Clinical Cases. 2025 April; 4(1). doi: 10.52338/jocc.2025.4690.
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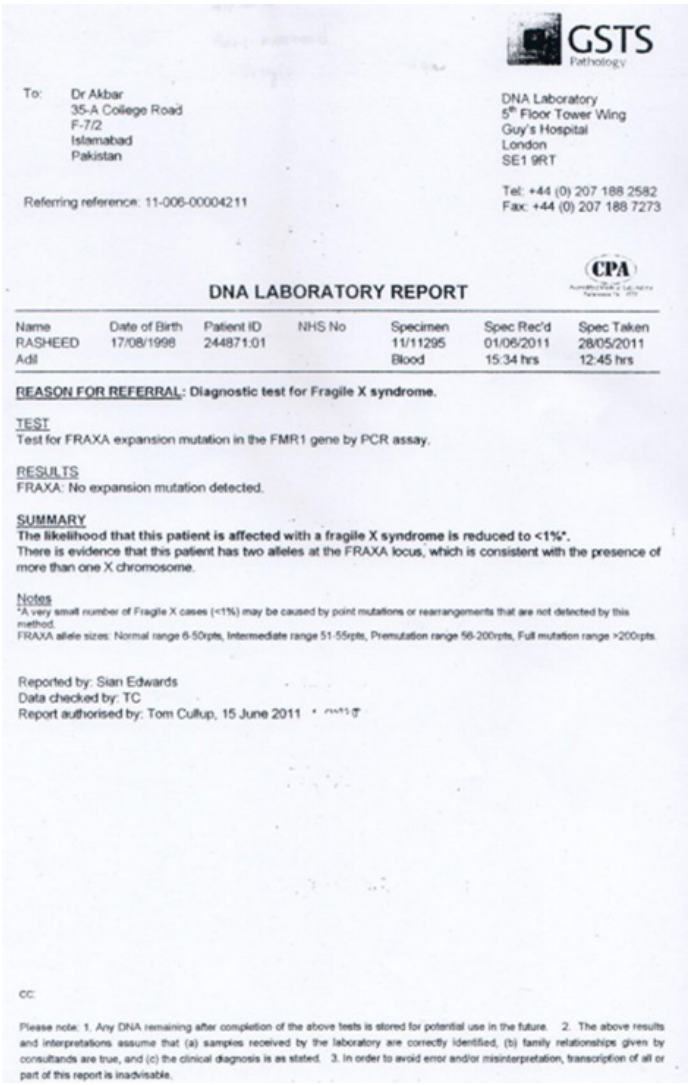
milder and skeletal frame is tall in contrast to some other reported cases. Both testes were smaller around 60% (3.2x1.9cm) of normal size i.e. (5x3cm) or penis was like 5 years old child but ambiguity of genitalia was not observed in our case as reported in other more severely affected cases. Blood testosterone level were moderately lower i.e. 328.4ng/dl, but gynecomastia or ambiguity was not observed in genitalia. Periodic fits were reported. Eye sight was weak with cylindrical number but retina and optic nerve was normal. Renal and Cardiac profile was normal. Facial dysmorphism like flat nose, cleft palate, fifth finger or lower birth weight was not found.

His behavioral pattern was also observed and it was shown that his score in the communication domain was low with a mild to moderate deficit. Expressive sub domain score was moderately low, while his receptive sub domain score was also low too. He had significant weakness in the communication domain. Non-compliance and inappropriate speech was seen. He exhibited abnormal speech form and content. Speech contained significant problems with disarticulation. Problem in mental status involve psychomotor behavioral symptoms. He also exhibited problems with self-control. Aggressive sexual behavior with females was reported. His IQ was much lower than his age fellows and was like 6 years old studying in 3rd grade.

FRAXA Studies

The case was previously referred to Guy's Hospital, London previously, for diagnostic test of Fragile X Syndrome. A Polymerase Chain Reaction (PCR) based test for FRAXA expansion mutation in the fragile X mental retardation 1 (FMR1) gene was conducted **(Figure 1)**. No expansion mutation was detected and hence the likelihood of patient being affected by Fragile X syndrome was as low as less than 1%. However, it was reported that there are two alleles at the FRAXA locus and this is consistent with the presence of more than one X chromosomes. This was the hint we went for karyotyping of this case. This case was then referred for genetic studies to Institute of Biomedical and Genetic Engineering, Islamabad.

Figure 1. FRAXA Expansion mutation in fragile X Mental Retardation (FRX1) gene based upon PCR test showing no expansion mutation but the presence of two alleles at FRAXA locus on X chromosome.



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CPA

DNA LABORATORY REPORT

Name	Date of Birth	Patient ID	NHS No	Specimen	Spec Rec'd	Spec Taken
RASHEED Adil	17/08/1998	244871:01		11/11295 Blood	01/06/2011 15:34 hrs	28/05/2011 12:45 hrs

REASON FOR REFERRAL: Diagnostic test for Fragile X syndrome.

TEST
Test for FRAXA expansion mutation in the FMR1 gene by PCR assay.

RESULTS
FRAXA: No expansion mutation detected.

SUMMARY
The likelihood that this patient is affected with a fragile X syndrome is reduced to <1%*.
There is evidence that this patient has two alleles at the FRAXA locus, which is consistent with the presence of more than one X chromosome.

Notes
*A very small number of Fragile X cases (<1%) may be caused by point mutations or rearrangements that are not detected by this method.
FRAXA allele sizes: Normal range 6-50rpts, Intermediate range 51-55rpts, Premutation range 56-200rpts, Full mutation range >200rpts.

Reported by: Sian Edwards
Data checked by: TC
Report authorised by: Tom Cullup, 15 June 2011

cc:

Please note: 1. Any DNA remaining after completion of the above tests is stored for potential use in the future. 2. The above results and interpretations assume that (a) samples received by the laboratory are correctly identified, (b) family relationships given by consultands are true, and (c) the clinical diagnosis is as stated. 3. In order to avoid error and/or misinterpretation, transcription of all or part of this report is inadvisable.

Cytogenetics

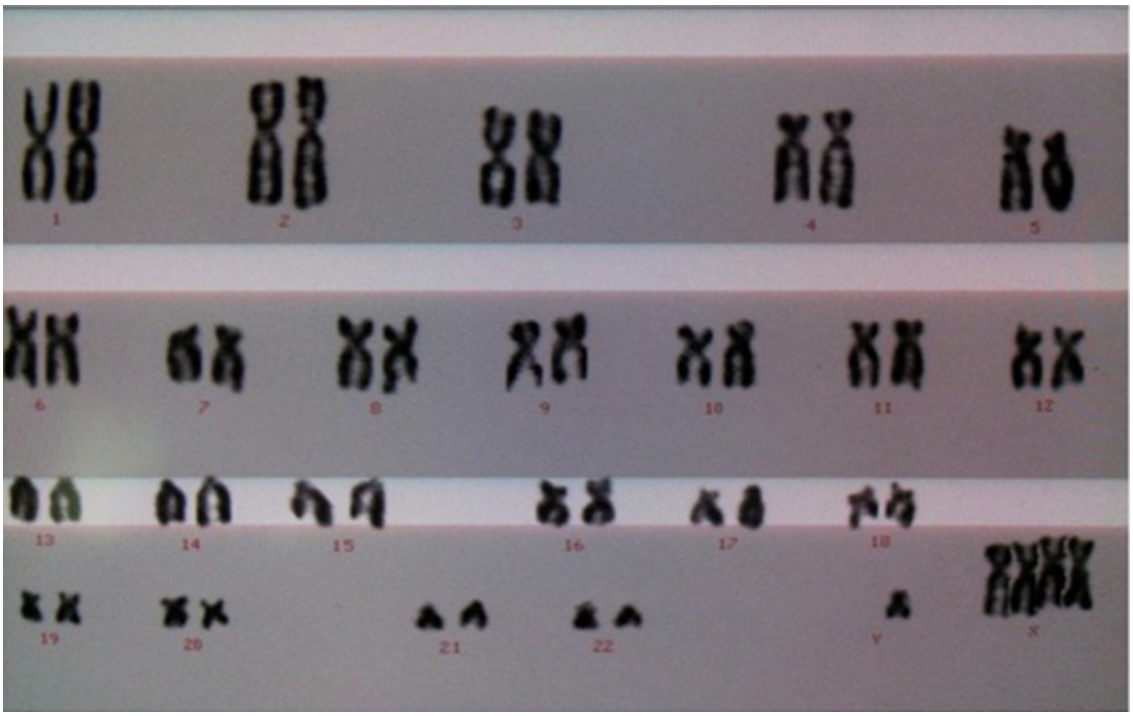
Peripheral blood was cultured using Phytohemagglutinin (PHA) as a mitogenic stimulator, cell growth arrested at 71st hour by adding Colcemid, a colchicine analog. Further hypotonic treatment with Potassium chloride (KCl) and fixation with methanol/ acetic acid leads to the harvesting of the metaphases (7). Slides were prepared, followed by conventional Giemsa staining, and observed under high resolution microscope for chromosomal analysis.

RESULTS

Cytogenetic Studies

A 49, XXXXY karyotype in all cells was demonstrated from metaphase chromosomal preparation of fresh peripheral blood sample obtained after 72 hour culture, followed by conventional Giemsa Staining; there was no evidence of mosiacism. The three extra chromosomes were shown to be X chromosomes (Figure 2).

Figure 2. A peripheral blood karyogram showing the presence of four copies of X chromosome in the patient resulting in 49, XXXXY Syndrome.



DISCUSSION

49,XXXXY occurs in 1/85,000 newborn males. The origin of this particular form of aneuploidy is believed to be a result of consecutive nondisjunction events during maternal meiosis. Typical presentation consists of hypotonia, developmental delay, various dysmorphic features, and severe hypogenitalism. Although initially 49, XXXXY was considered a variant of Klinefelter syndrome; it is currently recognized as a separate clinical entity distinguished by facial features, multiple skeletal and cardiac defects and short stature. Characteristic clinical features of 49, XXXXY syndrome are the triad of mental retardation, radioulnar synostosis, and hypogonadism. There are a range of other associated phenotypic features such as low birth weight, slow growth with retarded bone age, craniofacial anomalies, abnormal genitals, widely spaced nipples, cardiac deformities, and skeletal abnormalities. Facial dysmorphism is characterized by a full round face, hypertelorism, telecanthus, and upslanted palpebral fissures.

The prognosis of these children depends on the extent of severity of the condition while the management mandates a multidisciplinary approach. Though it's a variant of Klinefilter Syndrome (47, XXY), but our patient with 49, XXXXY syndrome had characteristic facial features, particular habitus, multiple skeletal anomalies, genital abnormalities, variable mental impairment and speech problems apart from those seen classically in Klinefelter syndrome. No cardiac defects were seen in this patient. A 49, XXXXY karyotype is thought to arise from maternal non-disjunction during both meiosis I and meiosis II. Typically, an egg has two X chromosomes which must divide in half, so that each egg has one X chromosome. Once this occurs, a sperm

can fertilize the egg and the fetus ends up with 46, XY, which is a normal male chromosomal constitution. If by chance the X chromosomes do not separate properly and they go on to the next cell division and again do not divide properly, when the sperm fertilizes the egg, the fetus can then end up with 4 X chromosomes and 1 Y giving the fetus 49, XXXXY Syndrome. Such successive non-disjunction theoretically produces an egg with four X chromosomes, which, when fertilized by a Y bearing sperm, results in an embryo with 49, XXXXY syndrome. (8, 9)

The diagnosis of 49, XXXXY syndrome is usually ascertained postnatally by the association of mental retardation, variable growth deficiency, Down syndrome-like facial dysmorphy, hypogenitalism and other malformations, especially involving the heart and skeletal system (10). Significant behavioral problems were common in older patients, such as emotional disturbances with low frustration levels, timidity and shyness, and the level of adaptive functioning was much higher than the cognitive level (11).

Aneuploidy above one extra chromosome is usually fatal but because of X-inactivation, which "turns off" all but one X chromosome per cell, the effects of 3 extra chromosomes are reduced. Interestingly, the occurrence of this syndrome does not appear to be related to maternal age. Two prevalent theories have been made to account for the phenotype associated with a 49, XXXXY genotype as well as for other X chromosome aneuploidies: 1) increased dosage of active genes in regions which escape X inactivation, and 2) asynchronous replication of the extra X chromosomes (12, 13). In both cases, the amount and timing of genes expressed on the X chromosome is altered.

CONCLUSION

Prenatal diagnosis of the 49, XXXXY is generally fortuitous. Detailed sonographic findings during the second trimester revealing a small penis and abnormal posturing of the lower extremities are very suggestive of this syndrome (14). A subsequent amniocentesis is indicated to verify the result. The risk of recurrence of this syndrome is very uncertain as this disorder is sporadic in nature. After 12-13 weeks of gestation facial dysmorphisms & hypospadias can be detected by expert sonologist through amniocentesis karyotyping or chronic villous sampling can confirm such abnormality antenataly.

Acknowledgements

We would like to acknowledge Dr. Hani Akbar Rao for referring this case to our Institute for Cytogenetic Analysis.

REFERENCES

1. Visootsak J, Graham JM. Klinefelter syndrome and other sex chromosomal aneuploidies. Orphanet J Rare Dis. 2006; 1: 42.
2. Fraccaro M, Kaijser K, Lindsten J. A child with 49 Chromosomes. Lancet. 1960; 2: 899–902.
3. Kleczkowska A, Fryns JP, van den Berghe H. X-chromosome polysomy in the male. Hum Genet 1988. 80: 16-22.
4. Peet J, Weaver DD, Vance GH. 49, XXXXY: a distinct phenotype. Three new cases and review. J Med Genet. 1998; 35: 420-4.
5. Shanske A, Sachmechi I, Patel DK, Bishnoi A, Rosner F. An adult with 49, XXXXY karyotype: case report and endocrine studies. Am J Med Genet 1998. 80: 103-6.
6. Curfs LGM, Schrepper-Tijdink G, Wiegers A, Borghgraef M, Fryns JP. The 49, XXXXY syndrome: clinical and psychological findings in five patients. J Med Defic Res 1990. 34: 277-82.
7. Dracopoli NC. Current Protocols in Human Genetics, Volume 4, New York: John Wiley & Sons; 1994.
8. Linden MG, Bender BG, Robinson A. Sex chromosome tetrasomy and pentasomy. Pediatrics 1995. 96: 672-82.
9. Leal CA, Belmont JW, Nachtman R, Cantu JM, Medina C. Parental origin of the extra chromosomes in polysomy X. Hum Genet 1994. 94: 423-6.
10. Schluth C, Doray B, Girard-Lemaire F, Kohler M, Langer B, Gasser B, Lindner V, Flori E. Prenatal sonographic diagnosis of the 49, XXXXY syndrome. Prenat Diagn 2002. 22: 1177-80.
11. Jia-Woei Hou. 49, XXXXY syndrome. Chang Gung Med J 2004; 27: 7.
12. Peet J, Weaver DD, Vance GH. 49, XXXXY: a distinct phenotype. Three new cases and review. J Med Genet1998. 35: 420-4.
13. Sarto GE, Otto PG, Kuhn EM, Therman E. What causes the abnormal phenotype in a 49, XXXXY male? Hum Genet 1987. 76: 1-4.
14. Schluth C, Doray B, Girard-Lemaire F, Kohler M, Langer B, Gasser B, Lindner V, Flori E. Prenatal sonographic diagnosis of the 49, XXXXY syndrome. Prenat Diagn 2002. 22: 1177-80.