Case Report

www.ijrhs.com
ISSN (o):2321–7251

A case report of rare sex chromosomal aneuploidy: 48,XXXY/49,XXXXY

Rao Swathi S [1], Arumugam Meenakshi [2], Shetty Prashanth D [3], Shenoy Vijaya D [4]

1. MBBS, DNB(Paediatrics), Senior Resident, Department of Paediatrics. 2. MSc Biotechnology, Lecturer/Research Associate, Diagnostic Centre for Cytogenetics and Molecular genetics. 3. PhD, Professor/ Coordinator, Diagnostic Centre for Cytogenetics and Molecular genetics. 4. MBBS, DCH, MD(Paediatrics),Professor/Head of the Department, Department of Paediatrics.

Corresponding Author: Dr Swathi S Rao, 23-13/23(1), Shivakripa, Koragappa Compound, 3 rd Cross Kapikad, Ullal, Mangalore-575020. Email: swathiyrao@yahoo.com

Abstract:

The sex chromosome aneuploidy 49,XXXXY is a rare syndrome characterized by mental retardation, severe speech impairment, multiple skeletal defects, genital abnormalities and subtle dysmorphic features. The incidence of 48,XXXY/49,XXXXY is very rare and to our knowledge only few reports of mosaicism have been reported so far but with different cell line proportions. We describe a case with 48,XXXY[16]/49,XXXXY[4] mosaicism in a four year old boy with microcephaly, short stature, expressive speech delay, and clinodactyly. Karyotyping showed mosaicism with 48XXXY[16]/49XXXXY[4] and was confirmed by FISH analysis.

Key words: Short stature; Expressive speech delay; Sex chromosomal aneuploidy

Key Messages:

Males with subtle dysmorphism and expressive speech delay are candidates for chromosome analysis to rule out underlying sex chromosomal aneuploidy disorders. 48,XXXY/49,XXXXY syndrome should be considered as a distinct clinical entity and not just a variant of Klinefelter syndrome.

Introduction:

The most common sex chromosomal aneuploidy in males is Klinefelter syndrome, with the prevalence of 1:600 males. About 20% are variants which include 48,XXYY, 48,XXXY, 49,XXXXY syndromes and mosaicism[1,2]. The incidence of 48,XXXY and 49,XXXXY is estimated to be 1:50,000 and 1:100,000 male births respectively while occurrence of mosaicism is very rare and only few reports have been reported so far but with different cell line proportions[2]. Mosaics with three or more different chromosomal lines are very rare. We describe a case with 48,XXXY[16]/49,XXXXY[4] mosaicism in a four year old boy with short stature and subtle dysmorphism.

Case History:

A four year old phenotypically male, was referred for evaluation of his speech delay. He was the second born child to a non-consanguineous couple, the mother and father being 26 and 30 year old respectively. The child has an elder sibling who is a seven year old phenotypically normal boy. The child was born by a full term vaginal delivery with normal Apgar score and birth weight of 2300g. He had global developmental delay, the developmental age being two years six months in gross motor domain and one year six months in fine motor domain. He was presently able to speak only two words with meaning the developmental age being one year. The child used sign language and points to indicate his needs. However his interaction with his sibling, parents and peers was normal.

On examination the patient had several minor congenital anomalies: microcephaly, hypertelorism, epicanthal folds, upward slant to the palpebral fissures, dysplastic ears with cleft of helix (Fig 1A), micrognathia, high arched palate, thin upper lip, clinodactyly of fifth finger bilaterally (Fig1B), prominent elbows with cubitus varus (Fig1C), microphallus (stretched penile length of 2.5 cm) and small testis (1ml). His height and weight were less than the third centile for age. He had normal vision and his fundi were normal.

Radiographs of the left wrist showed bone age of one year (Fig 1D). Abdominal ultrasound and echocardiography were normal. Audiometry done revealed normal hearing bilaterally. His thyroid function tests and growth hormone assay were normal.

Chromosomal analysis of boy was carried out on peripheral blood lymphocyte cultures by the standard conventional GTG banding technique. Twenty well spread metaphase chromosomes were analyzed microscopically and showed mosaicism with 48XXXY[16]/49XXXXY[4] (Fig 2).

Fluorescence in situ hybridization (FISH) analysis of 200 interphase nuclei, using CEB probes for chromosomes X and Y indicated a line proportion of 80.5% for 48,XXXY and 19.5% for 49,XXXXY (Fig 3). This result confirmed the presence of 48,XXXY/49,XXXXY mosaicism.[FISH result – 48,XXXY- 161(80.5%), 49,XXXXY- 39(19.5%)]. Analysis of the karyotyping and FISH results were performed using GeneASIS 7.2 software (Applied Spectral Imaging) and reported based on International System for Human Cytogenetic Nomenclature (ISCN)-2013.

Discussion:

49,XXXXY is a rare sex chromosome aneuploidy syndrome characterized by mental retardation, severe speech impairment, craniofacial abnormalities, multiple skeletal defects and genital abnormalities. These patients have also subtle dysmorphic features such as strabismus, microcephaly, epicanthal folds, hypertelorism and cleft palate. In 1960, the 49,XXXXY chromosomal constitution and clinical findings were described by Fraccaro et al [5,6]. These individuals differ significantly from Klinefelter syndrome and have features which overlap with many other chromosomal syndromes.

In this paper we describe a young boy with 48,XXXY/49,XXXXY mosaicism with Fraccaro syndrome phenotype. He also had global developmental delay with severe delay in speech which is well documented in cases of excess X chromosome material. The most significant effect of the additional X chromosomes on the phenotype is an increase in somatic malformations and mental retardation [7]. Severe retardation in language development in 49,XXXXY patients has been described in previous studies especially in expressive language while their receptive language skills and non-verbal skills like spatial tasks were intact as seen in our case also [5,7]. It has been suggested in case of supernumerary X slow rates of prenatal neuronal growth selectively retard the development of left hemisphere hence interfere with language development and also cause intellectual disability [2].

The 48,XXXY syndrome differs from Klinefelter syndrome by the presence of intellectual deficit, more marked genital hypoplasia, congenital skeletal malformations and by more frequently observed facial dysmorphism[10]. Clinodactyly of the fifth finger commonly associated with this syndrome and other manifestations such as arthropathies, obesity, behavioral problems also can appear with age [6]. Renal anomalies were found in Klinefelter's syndrome and 49,XXXXY syndrome and was never associated with 48,XXXY syndrome [5]. Our patient also had no renal anomalies, we believe that it was because of higher percentage (80%) of 48,XXXY cell line proportion.

Since the initial report of 49,XXXXY karyotype nearly 40 years ago, many more cases have been reported and proved that 49,XXXXY is the outcome of nondisjunction of the X chromosome during both meiosis I and meiosis II [8]. The extra X chromosomes result sporadically from either meiotic non disjunction where a chromosome fails to separate during the first or second division of gametogenesis or from mitotic non disjunction in the developing zygote[4]. It is believed that the 49,XXXXY syndrome occurs during maternal non-disjunction, however, the occurrence of this syndrome does not appear to be related to maternal age [8].

Parental origin has been reported in five cases of 48,XXXY. In two of these cases, the origin was successive non-disjunction in formation of the sperm (XpXpYp) fertilizing a normal female oocyte (Xm) and the other three cases showed XmXmXmYp, indicated double nondisjunction events during oogenesis[2,9]. Unfortunately, the parents of the child in our report were not willing to support us to observe the parental origin.

Proband has 80% of 48,XXXY and 20% of 49,XXXXY cell line as determined by gold standard karyotyping chromosomal analysis. FISH analysis also confirmed the same with slight difference. This shows that FISH analysis is a rapid, reliable technique with the accuracy rate of 99% and is extremely helpful in the detection of low level mosaicism. To our knowledge, this is the rare report of mosaicism in the literature with clinical phenotype of 48,XXXY/49,XXXXY syndrome, but with different cell line proportion when compared to previous case reports.

We conclude that 48,XXXY/49,XXXXY syndrome should be considered as a distinct clinical entity and not just a variant of Klinefelter syndrome since the former have distinctive facial features, are more mentally handicapped, have greater speech difficulty and are shorter than those the latter. Males with the above phenotypic description with significant speech impairment are candidates for chromosome analysis to rule out underlying sex chromosomal aneuploidy disorders and also for determining the parental origin. This will enable early intervention and helps in appropriate genetic counseling.

Acknowledgement

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors/editors/publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

Source of Funding: Nil
Conflicts of Interest: Nil

References:

1. Gupte GL, Bharucha A, Kotvaliwale SV, Mahajan PV, Kher AS, Kanade SP. 48 XXXY Variant of Klinefelter Syndrome. Indian Pediatr 1995;32.
2. Tartaglia N, Ayari N, Howell S, D'Epagnier C, Zeitler P. 48,XXYY, 48,XXXY and 49,XXXXY syndromes: not just variants of Klinefelter syndrome. Acta Paediatr 2011;100(6):851–860.
3. Dueñas-Arias JE, Aguilar-Medina M, Arámbula-Meraz E, Valenzuela-Camacho1 JB, Vega-Solano A, Granados J et al. 47,XXY/48,XXXY/49,XXXXY mosaic with hydrocephaly: a case report and review of the literature. J Med Case Rep 2007;1:94.
4. Hadipour F, Shafeghati Y, Bagherizadeh E, Behjati F, and Hadipour Z. Fraccaro Syndrome: Report of Two Iranian Cases: An Infant and an Adult in A Family. Acta Medica Iranica 2013;51(12):907-909.
5. Kojima Y, Hayashi Y, Maruyama T, Sasaki S, Mogami T, Kohri K. 49,XXXXY Syndrome with Hydronephrosis Caused by Intravesical Ureterocele. Urol Int 1999;63:212–214.
6. Visootsak J, Rosner B, Dykens E, Tartaglia N, and John M. Graham Jr. Behavioral Phenotype of Sex Chromosome Aneuploidies: 48,XXYY, 48,XXXY, and 49,XXXXY. AmJ Med Genet Part A 143A:1198–1203.
7. Guzel AI, Demirhan O, Pazarbasi A, Yuksel B. Parental Origin And Cell Stage Errors In X-Chromosome Polysomy 49,XXXXY. BJMG 2009;12(1).
8. Cathy A Lomelino, Allan L Reiss. 49,XXXXY syndrome: behavioural and developmental profiles. J Med Genet 1991;28:609-612.
9. Peet J, Weaver DD, Vance GH. 49,XXXXY: a distinct phenotype. Three new cases and review. MJedGenet 1998;35:420-424.
10. Şimşek PO, Ütine GE, Alikaşifoğlu A, Alanay Y, Boduroğlu K, Kandemir N. Rare sex chromosome aneuploidies: 49,XXXXY and 48,XXXY syndromes. Turk J Pediatr 2009;51: 294-297.

Legends:

Fig 1: A. Side profile showing dysplastic ears with cleft of helix, B: Clinodactyly of bilateral fifth finger, C: Cubitus varus deformity, D: Radiographs of the left wrist showing bone age of one year.

Figure 2: GTG-banded karyogram of the patient with mos48,XXXY/49,XXXXY

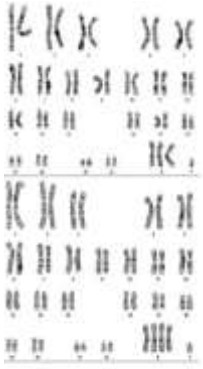

Figure 3: FISH analysis showing 48,XXXY/49,XXXXY mosaicism.