MOSAIC TRISOMY 22 IN A MALFORMED NEWBORN FEMALE: A NEW CASE

N. Bouayed Abdelmoula [1], N. Ayadi [2], A. Amouri [3], M. Meddeb [4], H.Elguezal [5], A. Saad [5], A. Karray [2], M. Chaabouni [2], T. Rebaï [1]

1 : Laboratoire d'Histologie Faculté de Médecine, Sfax
2 : Service de Pédiatrie Hôpital Hédi Chaker, Sfax
3 : Laboratoire de Cytogénétique Institut Pasteur, Tunis
4 : Laboratoire d'analyses médicales spécialisées en Génétique, Tunis
5 :Laboratoire de Cytogénétique Hôpital Farhat Hached, Sousse

Summury:

We describe a new case of mosaic trisomy 22 in a malformed newborn female who died three month after birth. Our patient was the third child of a healthy non-cosanguineous couple. The father and the mother were respectively 36 and 35 years old. Two previous pregnancies ended in miscarriages. The girl was born at term by spontaneous vaginal delivery. Her birth weight was 1520 g (<3rd centile), her length was 39cm (<3rd centile), and her FOC measured 29cm (<3rd centile). She was noted at birth to have growth retardation and dysmorphic features. Craniofacial features included microcephaly, large anterior fontanelles and widely patent cranial sutures, abnormal posteriorily rotated ears with bilateral preauricular pits and sinus, hypertelorism and downward slanting palpebral fissures, bilateral blepharoptosis and scarce eyebrows. The nose was short and beaked with a flattened nasal bridge, anteverted nares and irregular ear canal. Further findings were a long philtrum, thin lips, cleft velo-palate, micro/retrognathia and short webbed neck. The fingers were longs with hypoplastic nails and syndactyly of the second and third toes.
Organ involvement included a combined heart defect (large atrial septal defect, pulmonary stenosis and patent ductus arteriosus), ectopic left kidney and sacral dimple.
Cytogenetic analysis using RHG and GTG banding revealed a de novo 46,XX/47,XX,+22 karyotype with respective proportion of 40% and 60%. Diagnosis of trisomy 22 mosaicism was confirmed and an eventual supernumerary der(22) syndrome secondary to a parental reciprocal translocation t(11;22)(q23.3;q11.2) was ruled out.

Key words:
Birth defects – Mosaicism -Trisomy 22

1-Introduction

Trisomy 22 is the second most common autosomal trisomy, after trisomy 16, present in miscarriages, accounting for 3 to 5% of all spontaneous abortions [1]. However, the children born with trisomy 22 are relatively rare and have usually unbalanced translocations t (11; 22) or mosaicisms.
In this study, we describe a new case of mosaic trisomy 22 in a female malformed newborn who died three month after birth.

2-Case report

Our patient was the third child of a healthy non-consanguineous couple. The father was 36-years old. The mother was 35-years old, gravida five and para three. Two previous pregnancies ended in miscarriages.
The girl was born at term (37 weeks of a normal gestation) by spontaneous vaginal delivery.
Her birth weight was 1520 g (<3rd centile), her length was 39cm (<3rd centile), and her FOC measured 29cm (<3rd centile). She was noted at birth to have growth retardation and dysmorphic features.
Re-evaluation at the age of 1 month showed other clinical features, including hypotonia, psychomotor retardation, heart defects, and urogenital anomalies.
At dysmorphological examination, craniofacial features included microcephaly, large anterior fontanelles and widely patent cranial sutures, abnormal posteriorily rotated ears with bilateral preauricular pits and sinus, hypertelorism and downward slanting palpebral fissures, bilateral blepharoptosis and scarce eyebrows. The nose was short and beaked with a flattened nasal bridge, anteverted nares and irregular ear canal. Further findings were a long philtrum, thin lips,

Cleft velo-palate, micro/retrognathia and short webbed neck. The fingers were longs with hypoplastic nails and syndactyly of the second and third toes (figures 1, 2 and 3).

Organ involvement included a combined heart defect (large atrial septal defect, pulmonary stenosis and patent ductus arteriosus), ectopic left kidney and sacral dimple, without anal atresia or urogenital anomalies.

At three month, she developed pneumonia/chest infection with severe respiratory distress and died.

3-Cytogenetic analysis

Peripheral blood cytogenetic analysis according to routine procedures was performed for the proposita and her parents. Chromosomal analysis was carried out using RHG and GTG banding.

Examination of 50 metaphases of the PHA stimulated lymphocytes culture of the newborn baby showed trisomy 22 in about 60% of metaphases (figures 4).

Chromosome studies of the parents showed 46, XX and 46, XY karyotypes for respectively the mother and the father (figure 5).

Diagnosis of de novo trisomy 22 mosaicism: 46, XX/47, XX, +22, was confirmed and an eventual supernumerary der (22) syndrome secondary to a parental reciprocal translocation : t(11; 22) (q23.3; q11.2) was ruled out.

We were enable to perform further investigations including fluorescent in situ hybridization (FISH) analysis and molecular microsatellite analysis to search uniparental disomy because of early death.

4-Discussion

Although trisomy 22 is common among spontaneous abortions, it is so rare in liveborn infants [1-16]. The female malformed new born presented in this report had a mosaic trisomy 22 and her mother had two previous miscarriages.

Mosaic trisomy 22 is characterized by an additional chromosome 22 in one of an individual's cell lines, with at least one unaffected cell line also present. The presence of the supplementary chromosome is thought to be responsible for the symptoms and physical findings that characterize the disorder [1-4-16].

In mosaic trisomy 22, the affected individuals appear to be females more frequently than males. In some cases, advanced parental age was reported. The disorder appears to result from errors (e.g., nondisjunction) during cellular division after fertilization (fetal mitosis) [4-15]. A somatic duplication of chromosome 22 in the germline of the mother or the father could not be formally excluded. In fact, there have been reports in which the disorder has occurred in association with uniparental disomy, an abnormality in which affected individuals have inherited both copies of a chromosomal pair from one parent, rather than one copy from each parent. Uniparental disomy 22 (UPD 22) is a rare condition [6]. Normal phenotypes in previous reports have suggested that maternal UPD 22 has no impact on the phenotype. However, when maternal isodisomy 22 arise in mosaic with a trisomy 22, the phenotype overlaps that of non-mosaic trisomy 22-chromosome mosaicism in general and to some extent the Ullrich-Turner syndrome phenotype [6].

Mosaic trisomy 22 syndrome is characterized by multiple and variable congenital abnormalities. The range and severity of associated symptoms and findings may vary, depending upon the percentage of cells in which the extra chromosome 22 is present. Individuals with a low percentage of affected cells may have fewer, less severe symptoms than those with a high percentage of affected cells.

Characteristic features typically described in mosaic trisomy 22 include growth delays, mental retardation, unequal development of the two sides of the body (hemidystrophy), and webbing of the neck. Affected individuals have also cranio-facial malformations and physical abnormalities, particularly of the heart and the uro-genital areas [2-3-8-10-11-13-17].

Partial trisomy 22q11.2 is associated with the major symptoms of Cat Eye Syndrome including coloboma, preauricular anomalies, heart defect, kidney malformation, and anal atresia, which is caused by interstitial duplication of the CES critical region on 22q11.2 [12].

Our patient had a relatively high percentage of trisomic cells (60%) and had most of the congenital malformations typically described in mosaic trisomy 22 syndromes except hemidystrophy.

A part from mosaic trisomy 22, full trisomy 22 is thought to be lethal in early stages. However, some cases with survival beyond the third trimester of gestation have been reported. They may correspond to undetectable mosaicism. The most affected individuals die before or shortly after birth due to severe birth defects and malformations. The clinical features in full trisomy 22 are mental retardation, microcephaly, downward slanting palpebral fissures, cleft palate, micrognathia, low set ears, preauricular tags and/or sinuses, congenital heart disease, urogenital tract anomalies and skeletal abnormalities. Early reports of trisomy 22 (over than 30 cases) are thought to represent

Undetected unbalanced translocation (11; 22) or mosaicisms [1-7-13-14-16].

Partial trisomy 11; 22 known as trisomy 22, supernumerary der (22) syndrome, or unbalanced 11; 22 translocation is usually inherited from a t (11; 22) carrier parent. It is also characterized by microcephaly, moderate to severe mental deficiency, cleft palate (includes Pierre Robins Sequence findings), ear anomalies (includes preauricular pits/tags, hearing loss), long philtrums, broad nose, genital anomalies in males, muscular hypotonia, heart defects, kidney abnormalities, and imperforate anus [5-9-15-18].

Cytogenetic analysis, in the present case, have permitted to confirm diagnosis of de novo trisomy 22 mosaicism and to rule out an eventual supernumerary der(22) syndrome secondary to a parental reciprocal translocation t(11;22) (q23.3;q11.2).

Unfortunately, we were enable to investigate our case at the molecular level, but molecular and FISH studies are needed to appreciate cases of trisomy 22 by detection of low-level mosaicism and/or uniparental disomy [4].

References:

1- Bacino CA, Graham JM (1995) Clinical and molecular studies in full trisomy 22: further delineation of the phenotype and review of the literature. Am J Med Genet. 56: 359-365. Comment in: Am J Med Genet. 1996; 62: 98-99, 100-101.

2- Basaran N, Berkil H, Ay N, Durak B, Ataman C, Ozdemir M, Ozon YH, Kaya I (2001) A rare case: mosaic trisomy 22. Ann Genet. 44: 183-186.

3- Berghella V, Wapner RJ, Yang-Feng T, Mahoney MJ (1998) Prenatal confirmation of true fetal trisomy 22 mosaicism by fetal skin biopsy following normal fetal blood sampling. Prenat Diagn. 18: 384-389.

4- Crowe CA, Schwartz S, Black CJ, Jaswaney V (1997) Mosaic trisomy 22: a case presentation and literature review of trisomy 22 phenotypes. Am J Med Genet. 71: 406-413. Comment in: Am J Med Genet. 1998; 76: 447.

5- Dawson AJ, Mears AJ, Chudley AE, Bech-Hansen T, McDermid H (1996) Der(22)t(11;22) resulting from a paternal de novo translocation, adjacent 1 segregation, and maternal heterodisomy of chromosome 22. J Med Genet. 33: 952-956.

6- De Pater JM, Schuring-Blom GH, van den Bogaard R, van der Sijs-Bos CJ, Christiaens GC, Stoutenbeek P, Leschot NJ (1997) Maternal uniparental disomy for chromosome 22 in a child with generalized mosaicism for trisomy 22. Prenat Diagn. 17: 81-86.

7- Feret MA, Aguilar MS, Serrano JL, Cidras M, Garcia R (1991) Full trisomy 22 in a malformed newborn female. Ann Genet. 34: 44-46.

8- Hirschhorn K (1997) Mosaic trisomy 22: a case presentation and literature review of trisomy 22 phenotypes [letter]. Am J Med Genet. 1998; 76: 447. Comment on: Am J Med Genet.71: 406-413.

9- Kadir RA, Hastings R, Economides DL (1997) Prenatal diagnosis of supernumerary chromosome derivative (22) due to maternal balanced translocation in association with diaphragmatic hernia: a case report. Prenat Diagn. 17: 761-764.

10- Lessick ML, Szego K, Wong PW (1988) Trisomy 22 mosaicism with normal blood chromosomes. Case report with literature review. Clin Pediatr. 27: 451-454.

11- Lund HT, Tranebjaerg L (1990) Trisomy 22 mosaicism limited to skin fibroblasts in a mentally retarded, dysmorphic girl. Acta Paediatr Scand. 79: 714-718.

12- Meins M, Burfeind P, Motsch S, Trappe R, Bartmus D, Langer S, Speicher M R, Mühlendyck H, Bartels I, Zoll B (2003) Partial trisomy of chromosome 22 resulting from an interstitial duplication of 22q11.2 in a child with typical cat eye syndrome. J Med. Genet 40: e62.

13- Schinzel A (1981) incomplete trisomy 22. III. Mosaic trisomy 22 and the problem of full trisomy 22. Hum Genet. 56: 269-273.

14- Shokeir MH (1978) complete trisomy 22. Clin Genet. 14: 139-146.

15- Stoll C, Medeiros P, Pecheur H, Schnebelen A (1997) De novo trisomy 22 due to an extra 22Q-chromosome. Ann Genet. 40: 217-221.

16- Tinkle BT, Walker ME, Blough-Pfau RI, Saal HM, Hopkin RJ (2003) Unexpected survival in a case of prenatally diagnosed non-mosaic trisomy 22: Clinical report and review of the natural history. Am J Med Genet. 118A: 90-95.

17- Van Buggenhout GJCM, Verbuggen J, Fryns JP (1995) renal agenesis and trisomy 22: case report and review. Ann Genet 38: 44-48.

18- Werding N, Holland H, Hueckel D, Froster UG, Hausler HJ, Kiess W (2003) Partial trisomy 22 resulting from rearrangements between chromosomes 11/22 and 16/22: a report of two cases. Acta Paediatr. 92: 865-868.

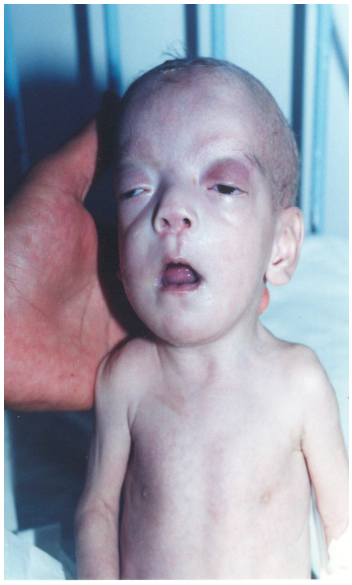


Fig.1: Front view of the Face of the proposita

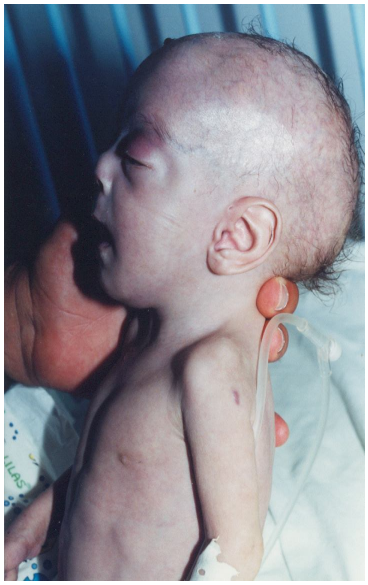


Fig.2: Profile view of the Face of the proposita

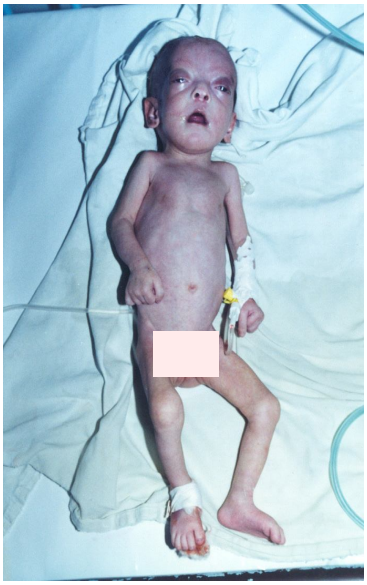
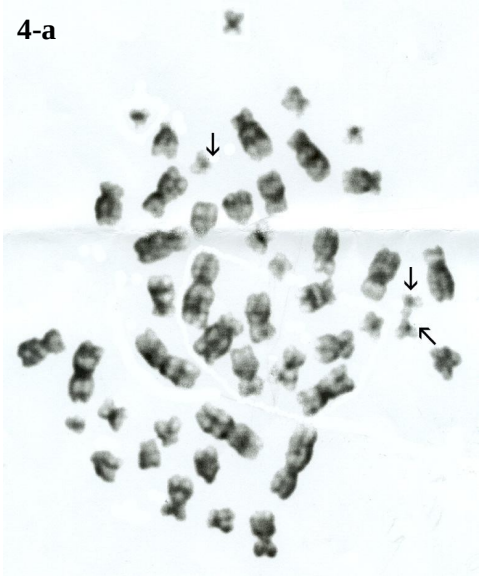


Fig.3: frontal view of the body of proposita

4-a



4-b

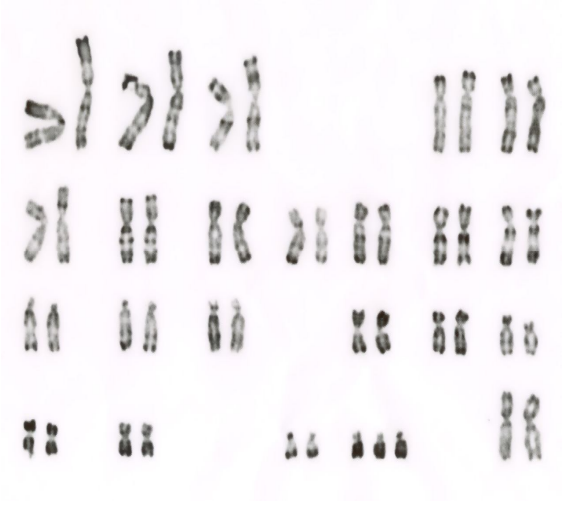


Fig. 4: (a) GTG-banded metaphase spread and (b) RHG-banded karyotype showing the 47,XX,+22 cell population of the proposita

5-a **5-b**

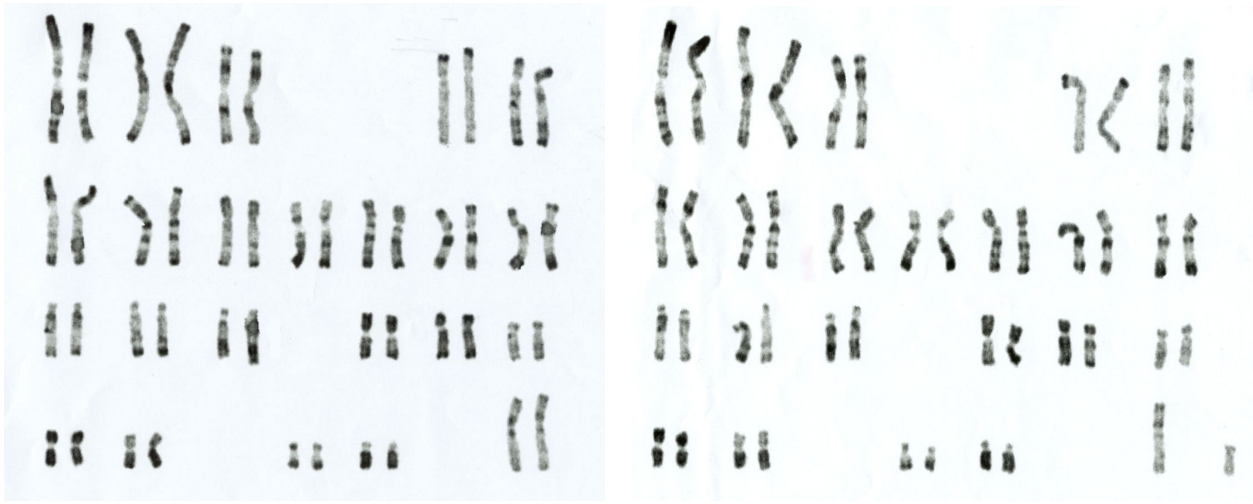


Fig. 5: Parental RHG-banded karyotypes of the mother in (a) and the father in (b)