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CASE REPORT

MOSAIC TRISOMY 7

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Summary

Trisomy 7 mosaicism is a very rare chromosomal disorder where there is an extra copy of chromosome 7 in some of the body's cells. Most cases with this chromosomal abnormality have no clinical symptoms. The presence of abnormalities in some cases is dependent on which body cells contain the chromosomal defect. Here we report a case diagnosed incidentally, in which is raised a suspicion of trisomy 21 in fact, based on a biochemical screening test for the second quarter (triple test). Two contradictions have led us to publish this case: first, the fact that although the triple test raised the suspicion of Down syndrome with a biochemical risk calculated from 1 to 225 with a very low level of free Estriol under 0.45 MoM corrected, it turned out to be about an extremely rare mosaicism. Secondly the fact that pregnancy has stopped evolving a few days after amniocentesis, although subsequently anatomopathological examination found no fetal or placental abnormalities. We searched in the specialty literature and found very few cases described, usually diagnosed after birth at children with various congenital abnormalities, growth retardation and developmental delay. Trisomy 7 has variable expression, most common symptoms are: facial asymmetry, hypomelanosis of Ito, kidney abnormalities. In our case we identified only facial dysmorphism and severe ulnar deviation of both hands without any malformations of internal organs. Because we did not anticipate such a genetic defect and considering the fact that the pregnancy has stopped in evolution we have not performed cultures of fibroblasts and we could not determine at what level and how the fetus was genetically affected so it was impossible to speculate how it would have evolved the pregnancy and how it would have been the baby after birth.

Résumé

La trisomie 7 en mesaïque

La trisomie 7 en mosaïque est une anomalie chromosomique rare dans laquelle il y a une copie supplémentaire du chromosome 7 dans certaines cellules du corps. Dans la plupart des cas avec cette anomalie chromosomique il n'y a aucun symptôme clinique. La présence d'anomalies dans certains cas dépend de cellules du corps qui contiennent l'anomalie chromosomique. Nous rapportons ici un cas diagnostiqué par hasard qui a soulevé une suspicion de trisomie 21 en effet, sur la base d'un test de dépistage biochimique pour le deuxième trimestre (test triple). Deux contradictions nous ont amené à publier ce cas: d'une part le fait que bien que le triple test ait soulevé la suspicion de syndrome de Down à un risque biochimique calculé de 1 à 225 avec un très faibles niveau d'estriol libre, au-dessuns de 0,45 MoM, il s'est avéré être un cas extrêmement rare de mosaïcisme. Deuxièmement le fait que la grossesse a cessé d'évoluer quelques jours après l'amniocentèse bien que l'examen pathologique n'ait trouvé aucune anomalie fœtale ou placentaire. Nous avons cherché dans la littérature de spécialité et nous avons trouvé très peu de cas décrits, généralement diagnostiqués après la naissance à des enfants avec des anomalies congénitales variées, un retard de croissance et un retard du développement. La trisomie 7 a une expression variable, les symptômes les plus courants sont: l'asymétrie faciale, la dépigmentation de Ito et les anomalies rénales. Dans notre cas, nous avons identifié seulement la dysmorphie du visage et la déviation ulnaire sévères des mains sans malformations des organes internes. Parce qu'on n'a pas prévu un tel défaut génétique et considérant que la grossesse a cessé d'évoluer, nous n'avons pas effectué de cultures de fibroblastes

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et n'avons pas pu déterminé à quel niveau et comment le foetus était génétiquement affecté de sorte que c'était impossible d'envisager l'évolution de la grossesse et de l'enfant après la naissance.

Mots Clés: Trisomie 7, mosaïcisme, syndrome de Silver-Russell, asymétrie faciale, l'albinisme, test triple, estriol libre, disomie 7 unipaternelle

INTRODUCTION

Trisomy 7 is extremely rare at birth and is generally considered lethal in embryogenesis, only a few dozens cases have been reported globally [1]. All surviving children are mosaics with variable and nonspecific clinical features [2,3]. Complete trisomy 7 has never been reported in a liveborn child. Chromosomal mosaicism may be suggested by body asymmetry and skin pigmentary dysplasia associated with developmental delay. In those cases, cultured skin fibroblasts cytogenetic analysis confirms mosaicism and identifies its chromosomal origin [2,4]. The presence of abnormalities in some cases is dependent on which body cells contain the chromosomal defect. Trisomy 7 which is confined to the placenta (CPM) appears to be primarily of mitotic origin, resulting from somatic duplication of chromosome 7 [5,6,7,8]. However, there are some cases in which the abnormality is attributable to meiotic error, in some of these cases uniparental disomy (UPD 7) is present. Occult trisomy 7 may also be causal. Trisomy 7 mosaicism at amniocentesis has been reported to be associated with maternal uniparental disomy for chromosome 7 (UPD 7) and Silver-Russell syndrome (SRS) [8,9,10]. Maternal UPD 7 is well established to be associated with severe growth restriction and is found in approximately 10% of cases with Russell-Silver syndrome phenotype [11]. An imprinting effect has been firmly established for maternal UPD7. Molecular evaluation of UPD 7 should be considered in patients with unexplained growth retardation or features similar to Russell-Silver syndrome. DNA studies should be considered when prenatal diagnosis indicates trisomy 7 mosaicism [12,13]. Here we want to report a case of trisomy 7 mosaicism and the discrepancy between the triple test and the analysis of fetal karyotype from amniotic fluid.

CASE REPORT

A 32 years old woman, 21 weeks pregnant, with increased risk of Down syndrome at the triple test (1/225) is admitted to our clinic in order to establish therapeutic specialist conduct. In the patient's personal history we noted that she has a normal birth with a normal child 5 years ago and 4 miscarriages, is nonsmoker, without teratogenic potential disease, exposure to radiation or toxic substances in the first trimester. Also there was no personal family history of congenital malformations. A screening for chromosomal abnormalities in the first trimester or other tests to assess fetal DNA, the duble test and the nuchal translucency were not performed. After completing the clinical and laboratory exams with blood tests within normal limits, a detailed ultrasound examination was performed which seems normal with biometrics appropriate gestational age of 21 weeks. We decided together with the patient, after informed consent to perform diagnostic amniocentesis.

The evolution was favorable without complications, with normal uterine tone, with fetal active movements and normal cardiac activity at 24 hours, without uterine contractions, without blood or amniotic fluid loss. Ultrasound control after a few hours of the amniocentesis and the next morning was in the normal range. The patient returns to our clinic 48 hours later and affirms absent fetal active movements. At the control ultrasound the diagnosis of pregnancy stopped in evolution is established with absent fetal cardiac activity. Under antibiotic prophylaxis and monitoring in the delivery room, patient spontaneously aborting a product of conception with no signs of viability, female gender, weighing 540 g, which is sent along with the placenta at histopathological examination.

Phenotypically fetus has short neck, triangular face, low set ears, small and retruded chin and ulnar clubbing of both hands. (fig. 1, fig. 2)

At autopsy the internal organs appeared normal on gross examination and congested on microscopy, no anomalies were found. The genitalia were feminin with a normal uterus. The kidneys, heart and spine were normal. Placenta was normal.

After analyzing fetal DNA from amniotic fluid we have not detected the presence of aneuploidies of chromosomes 13, 18, 21 and X it is recommended to confirm the result by analyzing fetal karyotype. Karyotype analysis of the amniotic fluid puts the final cytogenetic diagnosis of mosaic trisomy 7.

Cytogenetics formula was (fig. 3): 47, XX, + 7 [15]/46, XX [5] .

Fifteen metaphases had an extra chromosome 7 and the rest had a normal karyotype.

DISCUSSION

Humans normally have 46 chromosomes in each cell, divided into 23 pairs. Two copies of chromosome 7, one copy inherited from each parent, form one of the pairs. Chromosome 7 spans about 159 million DNA building blocks (base pairs) and represents more than 5 percent of the total DNA in cells. Identifying genes on each chromosome is an active area of genetic research. Chromosome 7 likely contains 900 to 1,000 genes that provide instructions for making proteins. These proteins perform a variety of different roles in the body. Changes in chromosome 7 include an extra copy of some genetic material

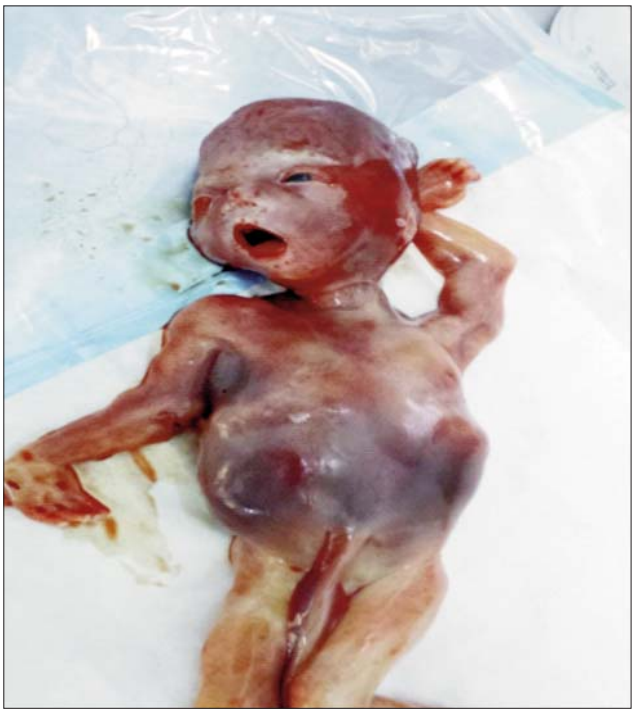

Figure 1 - Fetus phenotype

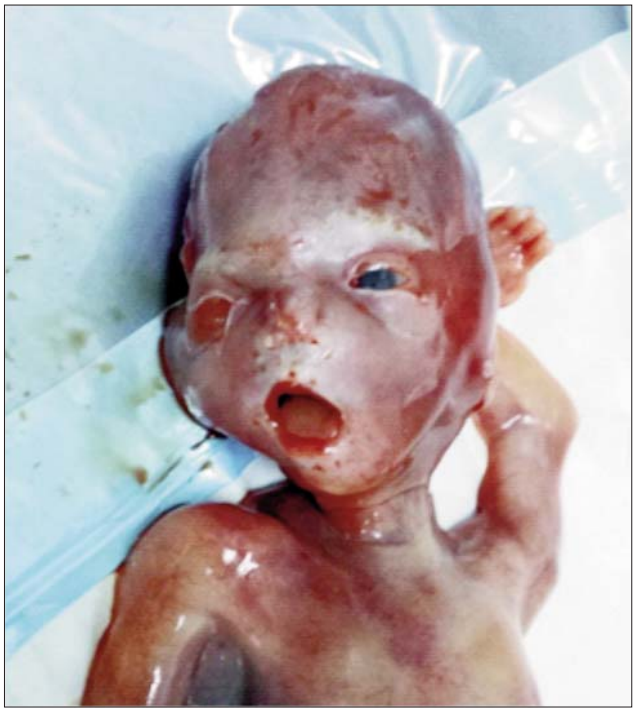

Figure 2 - Fetal face

from this chromosome in each cell (partial trisomy 7) or a missing segment of the chromosome in each cell (partial monosomy 7). In some cases, several DNA building blocks (nucleotides) are abnormally deleted or duplicated in part of chromosome 7. Complete trisomy 7 has never been reported in a liveborn child. In general, prenatal detection of trisomy 7 is associated with a good outcome. UPD 7 (uniparental disomy for chromosome 7) is well established to be associated with severe growth restriction and is found in approximately 10% of cases with Russell-Silver syndrome phenotype (Robinson et al, 1997). Trisomy 7 mosaicism at amniocentesis has been reported to be associated with maternal uniparental disomy for chromosome 7 (UPD 7) and Silver-Russell syndrome (SRS) [9,10]. Silver Russell Syndrome - SRS includes severe IUGR, postnatal short stature, retarded bone age, relative macro-

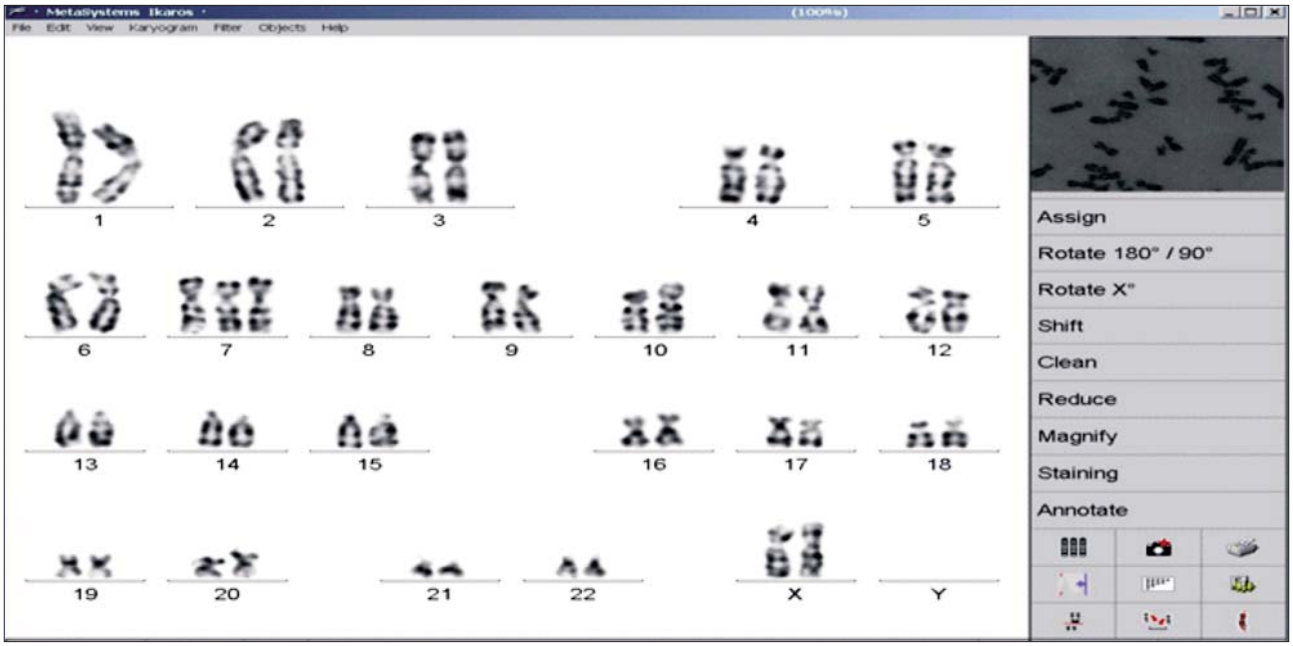

Figure 3 – Karyotype analysis

cephaly, triangular face, prominent and bossed forehead, small chin, micrognathia, craniofacial disproportion, down-turned mouth corners, brachydactyly and clinodactyly of fifth fingers, variable asymmetry of the face, body and limbs and café-au-lait spots [10]. UPD refers to inheritance of homologous chromosomes from only one parent. It results either in heterodisomy when the two homologs are different or isodisomy when they are two copies of the same chromosome. Heterodisomy implies parental meiosis nondisjunction. Isodisomy may result from mitotic duplication in a monosomic zygote or from chromosome loss of a trisomic zygote originating from a postzygotic segregation error. In 7 percent to 10 percent of cases of Russell-Silver syndrome, people inherit both copies of chromosome 7 from their mother instead of one copy from each parent. This phenomenon is called maternal uniparental disomy (UPD). UPD may be either a complete disomy of an entire chromosome or a mixed disomy with combination of iso-and heterodisomy due to meiotic recombination events. For some genes, however, only the copy inherited from father (the paternal copy) is expressed. For other genes, only the copy inherited from mother (the maternal copy) is expressed. These parent-specific differences in gene expression are caused by a phenomenon called genomic imprinting. Confined placental mosaicism (CPM) represents a discrepancy between the chromosomal makeup of the cells in the placenta and the cells in the baby. CPM was first described by Kalousek and Dill in 1983 [6,7]. CPM is diagnosed when some trisomic cells are detected on chorionic villus sampling and only normal cells are found on a subsequent prenatal test, such as amniocentesis or fetal blood sampling. In theory, CPM is when the trisomic cells are found only in the placenta. However, the fetus is involved in about 10% of cases [8]. The pregnancy loss rate in cases with confined placental mosaicism, diagnosed by chorionic villus sampling, is higher than among pregnancies without placental mosaicism. It may be that sometimes the presence of significant numbers of abnormal cells in the placenta interferes with proper placental function.

Duplication of the long arm of chromosome 7 is extremely rare, most of the reported cases are partial trisomies. The first case of complete 7q duplication was reported in 1978 by Wahrman et al who described a child at 3 years of age with a phenotype including a large face with sloping forehead, downward slanting palpebral fissures, bilateral epicanthic folds, low set, malformed ears, short neck, and genitourinary and renal anomalies. The second case of duplication of the whole of 7q have phenotypic characteristics similar to most reported cases of partial trisomy 7q, which include frontal bossing, low set, malformed ears, micrognathia, hypertelorism and skeletal abnormalities. Trisomy 7q produces abnormalities affecting virtually every system in the body including the central nervous system, the face, the musculoskeletal system, the heart, and the genitourinary system. This second case reported by Wahrman et al include hydrocephalus, bilateral clubbing of the hands and feet, micrognathia, increased intermammary distance, and pulmonary hypoplasia. Kidney abnormalities and lung hypoplasia have been reported in trisomy 7 and mosaic trisomy in 7 cases [1,14,15,16]. In 13 cases of trisomy 7 diagnosed, five were associated with abnormal phenotype. Data from both prenatal and postnatal diagnosed cases indicate that trisomy 7 mosaicism is associated with a variably expressed phenotype that can include hypotonia, abnormal face, renal anomalies, sparse hair, and pigmentary anomalies (hypomelanosis) [1,3,17,18].

Hypomelanosis of Ito, frequent associated with trisomy 7, is a rare genetic neurocutaneous disorder characterized by unusual patterns of depigmented skin and associated disorders such as seizures, psychomotor retardation with musculoskeletal symptoms and eye abnormalities. Hsu (1997) summarized the findings of 8 reported cases of trisomy 7 mosaicism found in amniotic fluid. Only one was found with facial asymmetry, mild developmental delay and hypomelanosis at 7 years. The other 7 liveborns were reported to be normal. Mosaicism was confirmed in skin fibroblasts in 2 cases with 4 year follow-up. He reviewed six postnatal diagnoses of trisomy 7 mosaicism. Three of the cases were found to have kidney abnormalities [19]. However, the presence of the trisomy 7 mosaicism in intestine as well as in skin fibroblasts suggests that SRS and Hirschsprung's disease HSCR might possibly be related. Cultured skin fibroblasts cytogenetic analysis confirms mosaicism and identifies its chromosomal origin [2,4]. The great majority of trisomy 7 mosaicism detected at chorionic villous samples (CVS) arises mitotically, does not imply a risk for UPD, is confined to the placenta, does not obviously compromise intrauterine growth, and is associated with the birth of a normal baby [22].

We tried to look in other studies if there was a connection between biochemical parameters that make up the triple test and trisomy 7 and we found nothing conclusive. Estriol (E3) is the predominant hormone estrogen in the blood and urine of pregnant women. The largest part of circulating estriol is a product of the feto-placental unit, resulting from a precursor (16-α-hydroxy-dehydroepiandrosterone) synthesized in the adrenal glands of the fetus and converted into estriol by fetal liver and placenta. The normal production of this hormone is an indicator of the integrity unit placental and fetal well being [23]. Unconjugated estriol low levels (<0.4 MoM) are found in Down syndrome, trisomy 18 and Smith-Lemli-Opitz syndrome. Also low levels of estriol is associated with risk: delayed fetal growth, fetal death, preeclampsia, Rh isoimmunization. Lower levels can be found in anemia, diabetes, malnutrition, liver disease [23]. Estriol levels may be decreased in the presence of an alive anencefalic fetus [24]. AFP is a protein synthesized mainly by the fetal liver. The concentration of AFP during pregnancy increases progressively, at a level of 0.1 ng/mL up to approximately 250 ng/mL in week 32 of pregnancy. Levels (MoM) AFP are higher in the pregnancies associated with neural tube defects (anencephaly, open spina bifida, encephalocele) and on average lower in the

presence of Down syndrome, trisomy 18 and trisomy 13. In our case there were values at the boundary of AFP (0.96 MoM) and a very low value of free Estriol (0.42 MoM). The present case provides evidence for a discrepancy between the results of the triple test with increased risk of Down syndrome (1/225) and the results of amniocentesis in which is analysed fetal karyotype with the final cytogenetic diagnosis of mosaic trisomy 7. A question still arises if there is a connection between low level of free estriol and trisomy 7. Genetic counseling of mosaic trisomy at amniocentesis is difficult because of the phenotypic variability associated with the condition. Some fetuses exhibit the typical phenotype, while others are normal [10,20]. Trisomy 7 mosaicism has variable and non-specific clinical features. Most patients with trisomy 7 mosaicism have a normal karyotype in blood lymphocytes, but mosaic trisomy 7 in fibroblasts derived from the skin show pigment abnormalities [10,21].

Conclusions

Mosaic trisomy 7 is an extremely rare abnormality with variable symptoms. In the literature we found reported very few cases and the clinical manifestations described were highly varied from a normal child without nothing pathological or just some facial dysmorphism up to severe malformations of internal organs, kidney abnormalities, lung hypoplasia, musculoskeletal symptoms, important retardation of growth or intellectual developmental delay, slow motor acquisition in the first years of life observed in children monitored and diagnosed in pediatric services. In the case reported by us there is this discrepancy between the result of the triple test and the result of amniocentesis. It was a coincidence that mosaic trisomy 7 was signaled by the triple test or free estriol levels are lower in these cases? It's a question that requires further detailed studies. If there is any connection it's probably very difficult to prove statistically because of the very low incidence of this trisomy 7. Amniocentesis and fetal karyotype analysis established the final diagnosis. We did not anticipate such a genetic defect and we have not performed cultures of fibroblasts and because of that we could not determine at what level and how the fetus was affected genetically so it was impossible to speculate how it would have evolved the pregnancy and how it would have been the baby after birth, considering the fact that the pregnancy has stopped in evolution. Maternal uniparental disomy (mUPD) for chromosome 7 was not investigated . Molecular evaluation and DNA studies should be considered when prenatal diagnosis indicates trisomy 7 mosaicism. Actually for both parents has been proposed an extensive genetic test in order to obtain a future pregnancy. Prenatal counseling in these cases is extremely difficult if there is no major malformation detectable by ultrasound because is very difficult to predict how it will evolve the child after birth. It is required to confirm mosaicism and after birth are necessary very extensive and expensive tests to determine the supernumerary chromosome 7 from the various tissues. Preimplantation genetic diagnosis is a current option for couples with IFV procedures. When CVS or amniocentesis is combined with DNA studies to reveal the origin of CPM (mitotic or meiotic) and parental origin of the chromosome 7s, a more reliable prediction for pregnancy outcome can be discussed. The difficulty lies in the extreme variability of these cases of mosaic trisomy 7, virtually any tissue may be affected more or less seriously and it is impossible to predict the evolution or any course of treatment without extensive analysis and further continuous monitoring of these children.

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