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Prenatal detection of trisomy 8 mosaicism: Pregnancy outcome and follow up of a series of 17 consecutive cases

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ABSTRACT

Objective: To study the outcome of a series of individuals with prenatal detection of trisomy 8 mosaicism by chorionic villus sampling (CVS) and/or amniocentesis.
Study design: The databases of two Italian genetics units were reviewed to identify all consultations requested during pregnancy because of trisomy 8 mosaicism. To evaluate the pregnancy outcome, the regional registry of congenital malformations (including terminations of pregnancies) was consulted; additional follow-up data were collected by a telephone interview. The following outcomes were analysed: delivery, pre- and post-natal growth, psychomotor development, major malformations, other diseases/complications.
Results: A total of 17 consecutive cases of trisomy 8 mosaicism were identified. Fourteen cases were first detected among women undergoing prenatal diagnosis by CVS; the remaining ones were identified among women who underwent amniocentesis. In most cases diagnosed by CVS, the chromosomal anomaly was only detected in long-term cell cultures (10/14) and was not confirmed by amniocentesis (11/13). There were two terminations of pregnancy and 15 live births; no major birth defects were observed among live born infants and only a case with prenatal and postnatal growth retardation was observed (mean age at follow-up interview was 5.9 years).
Conclusion: Our data showed an overall positive prognosis for cases with an apparent confined placental mosaicism and those with low-level mosaicism in amniotic fluid if no congenital anomalies were detected by foetal ultrasound examinations. However, larger studies are warranted to better define the associated risk of neurodevelopmental anomalies.

Introduction

Chromosomal mosaicism is a condition characterized by the presence of two or more chromosomally different cell lines in the same individual. Trisomy 8 mosaicism is usually the consequence of a post zygotic non-disjunction in an initially chromosomally normal conceptus [1]; it is a rare, viable condition, with an estimated prevalence ranging from 1:25000 to 1:50000 newborns [2], 5-fold higher in males [3].

The clinical phenotype associated with trisomy 8 mosaicism is highly variable. The most common features are mental retardation and facial dysmorphisms, including hypertelorism, micrognathia, large and dysplastic ears, deep palmar and plantar creases. Malformations, including corpus callosum agenesis and renal abnormalities, have been described in subjects carrying this anomaly [4]. However, individuals with cognitive development within the normal range have been reported in the literature [5]. The wide clinical variability is not related to the level of mosaicism in the peripheral blood and patients with a small proportion of trisomic cells may show a severe phenotype [6]. Trisomy 8 mosaicism is rare in prenatal diagnosis and the genetic counselling is difficult because it has been well-known for a long time that this chromosomal anomaly can be missed analysing the amniotic fluid [7–10]. In fact, a cryptic, true foetal mosaicism cannot be excluded in those cases classified as having the chromosomal anomaly confined to the placental tissues; in addition, studies evaluating the long-term outcome (growth, psycho-motor development,

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onset of post-natal disorders) of children with prenatal detection of trisomy 8 mosaicism are lacking.

In this paper, we report the pregnancy outcomes and post-natal follow-up data in a series of 17 consecutive cases with prenatal detection of trisomy 8 mosaicism referred to our institutions for genetic counselling.

Materials and methods

Patients

The databases of the Clinical Genetics Unit of the University Hospital of Padova and the Genetics and Molecular Biology Unit of the Vicenza Hospital have been reviewed to identify all consultations requested during pregnancy because of trisomy 8 mosaicism detected by chorionic villus sampling (CVS) or amniocentesis.

To evaluate the outcome of these pregnancies, the regional registry of congenital malformations (including terminations of pregnancies) was consulted; additional follow-up data were collected by a telephone interview, using a specific questionnaire (available upon request), assessing the characteristics of the pregnancy, delivery, psychomotor development, growth, and the presence of birth defects and other diseases/complications. Mothers were asked to check the medical reports written by the paediatrician at the physical examination controls performed at 3, 6, 9, 12 and 24 months of life, according to the regional public health service, reporting in particular the psychomotor milestones. Eventually, they were requested to give their own point of view on the health and auxological data of the child.

All interviews were carried out by medical personnel trained in medical genetics. All the information was recorded in a database. If post-natal genetic tests had not been performed, chromosome analysis or fluorescence in situ hybridization (FISH) were not recommended for subjects with no anomalies and older than 1 year.

Cytogenetic investigation

Transabdominal CVS, amniocentesis and cordocentesis were performed under ultrasound guidance according to standard techniques. Conventional karyotyping (GTG or QFQ banding) and FISH were performed using standard protocols and according to Italian Guidelines.

In most cases, the cytogenetic examination on chorionic villus samples was carried out combining the analysis of the two placental cell lineages: the cytotrophoblast by short-term culture (STC) and the mesenchyme by long-term culture (LTC). Karyotype analysis of amniotic fluid samples was performed on cells cultured in flasks.

Chromosomal anomalies were reported according to the most updated International System for Human Cytogenetic Nomenclature [ISCN] Guidelines.

When both CVS and amniocentesis were performed, prenatal mosaicism was classified as confined placental mosaicism (CPM) or true foetal mosaicism (TFM) according to the distribution of trisomic cell lines in the cytotrophoblast (STC), the mesenchyme (LTC), and the amniotic fluid (Table 1) [11,12]. CPM was defined by the detection of the abnormal cell line only by CVS; conversely, TFM was defined by the presence of the chromosomal abnormality in both the chorionic villus sample and the amniotic fluid. In addition, CPM was classified as mosaicism type I when the chromosomal anomaly was detected only in the cytotrophoblast, type II when detected only in the mesenchyme, type III when detected in both placental tissues. TFM was classified as mosaicism type IV when the chromosomal anomaly was detected by CVS only in the cytotrophoblast, type V when detected only in the mesenchyme, type VI when detected in both placental tissues.

When CVS was not performed, the mosaicism detected by amniocentesis was classified as follows [11]:

- Level I mosaicism: detection of a single abnormal cell (pseudomosaicism);
- Level II mosaicism: two or more abnormal cells in a culture from a single flask or a single abnormal colony derived from an *in situ* culture (in most cases this is a pseudomosaicism)
- Level III mosaicism: two or more abnormal cells in two or more independent cultures (true mosaicism).

Results

A total of 17 pregnancies with a prenatal detection of trisomy 8 mosaicism were included in the present study. The indication for invasive prenatal diagnosis was the advanced maternal age for 15 women and a high risk for aneuploidies by non-invasive screening tests for 2 women. Details regarding the selected pregnancies are summarised in Table 2.

In our series, 14 out of 17 cases were first detected among women undergoing prenatal diagnosis by CVS; the remaining 3 cases were identified among women who underwent amniocentesis.

In the CVS group, trisomy 8 was only detected in cells obtained by LTC in 10 cases (No. 1–10), by both STC and LTC in one case (No. 11) (Fig. 1). In one pregnancy, no details are available regarding the tissue in which the chromosomal anomaly was observed (case 15); in another case, trisomy 8 mosaicism was observed in STC, while

Table 1
Definition of confined placental mosaicism (CPM) or true foetal mosaicism (TFM) according to the distribution of trisomic cell lines in the cytotrophoblast, the mesenchyme, and the amniotic fluid.

Type of mosaicism		Cytotrophoblast (CVS - STC)	Mesenchyme (CVS - LTC)	Amniotic Fluid
CPM	I	Abnormal	Normal	Normal
	II	Normal	Abnormal	Normal
	III	Abnormal	Abnormal	Normal
TFM	IV	Abnormal	Normal	Abnormal
	V	Normal	Abnormal	Abnormal
	VI	Abnormal	Abnormal	Abnormal

CVS: chorionic villus sampling; STC: short-term culture; LTC: long-term culture.