Neonatal Silver-Russell Syndrome With Maternal Uniparental Heterodisomy, Trisomy 7 Mosaicism, and Dysplasia of the Cerebellum

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Key Words: Cerebellar dysplasia; Maternal heterodisomy 7; Prenatal trisomy 7; Silver-Russell syndrome

ABSTRACT

Objectives: We report here the unusual association of Silver-Russell syndrome (SRS) and cerebellar dysplasia with trisomy 7 mosaicism and maternal uniparental disomy of chromosome 7 [UPD(7)m].

Methods: Low-level trisomy 7 mosaicism was diagnosed prenatally on amniocytes, and UPD(7)m was confirmed after birth.

Results: Medical examination at birth showed dysmorphic facial features of SRS. Cytogenetic analysis on several tissues and cells confirmed mosaic trisomy 7. Unusual severe psychomotor retardation, hypotonia, and choreoathetoid movement were noted at 6 months. Brain magnetic resonance imaging showed both cerebellar hypoplasia and dysplasia.

Conclusions: This unusual association of SRS and dysplasia of the cerebellum might be related to the presence of the trisomy 7 mosaicism on the cerebellum. Our observation strengthens the hypothesis that the phenotype observed in patients with SRS with UPD(7)m might also result from an undetected low level of trisomy 7 mosaicism that could best be revealed by performing cytogenetic investigations.

Prenatal diagnosis of trisomy 7 in chorionic villi is most often secondary to confined placental mosaicism (CPM) without consequence on fetal intrauterine growth, as observed in other CPMs,1,2 except when trisomy rescue leads to maternal uniparental disomy of chromosome 7 [UPD(7)m] to detect low level of trisomy 7, if present.

Upon completion of this activity you will be able to:
• define and compare uniparental disomy, uniparental heterodisomy, and uniparental isodisomy.
• suggest a workup for patients with both the phenotype observed in Silver-Russell syndrome (SRS) patients and maternal uniparental disomy of chromosome 7 [UPD(7)m] to detect low level of trisomy 7, if present.
• propose a conventional and molecular cytogenetic analysis in different tissues in order to look for trisomy 7 mosaicism when UPD(7)m is displayed in SRS patients.

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(SRS).11-14 After birth, mosaic trisomy 7 was confirmed on cultured fibroblasts but was absent in lymphocytes.7,9,10

The etiology of SRS is heterogeneous. Most cases are associated with hypomethylation of the paternally derived differentially methylated region on chromosome 11p15 (about 50% of cases), while 5% to 10% of patients with SRS are associated with UPD(7)m.15,16

SRS is a congenital imprinting disorder characterized by severe intrauterine growth restriction (IUGR) and a preserved head circumference in association with a spectrum of additional dysmorphic features first described by Silver et al17 and Russell.18 Postnatal examination of patients with SRS has shown postnatal growth retardation, retarded bone age, body asymmetry, relative macrocephaly, typical triangular face, downturned mouth corners, brachydactyly, fifth-finger clinodactyly, and other less constant abnormalities such as genital abnormalities in males, psychomotor retardation, and café au lait spots. Patients with UPD(7)m have shared most of the same features.15,19,20

These relatively nonspecific features of SRS present a challenge to elaborate diagnostic criteria and genotype/phenotype correlation for this syndrome, especially when UPD(7)m is associated with mosaic trisomy 7, and reflect the complexity of chromosomal mechanisms leading to the SRS phenotype.21 To our knowledge, no SRS has been reported in association with cerebellar abnormalities. We report on a prenatal SRS case with mosaic trisomy 7, UPD(7)m, and cerebellar dysplasia and discuss their possible relationships.

Case Report

A 43-year-old woman, gravida 6, para 4, aborta 2, underwent amniocentesis at 19 weeks’ gestation (WG) because of advanced maternal age and an increased risk for Down syndrome after maternal serum screening (1/180). The parents were healthy and consanguineous. Family history had noted mild psychomotor retardation and hypospadias in their 14-year-old son. Cytogenetic analysis on cultured and uncultured amniocytes revealed the same features.

After birth, karyotype on chorionic villus tissue showed mosaic trisomy 7 in about 40% of the 54 analyzed cells, while all cord blood samples had a normal karyotype. Interphase FISH analysis using the chromosome 7 centromeric probe (D7Z1; Vysis, Downers Grove, IL) showed that 21 (14%) of 160 cells analyzed had three chromosome 7.

Cytogenetic Investigations

Prenatal Studies

Cytogenetic analysis on cultured amniocytes revealed the presence of a cell line with an extra chromosome 7 in eight (32%) of 25 colonies: 47,XY+7. Interphase fluorescence in situ hybridization (FISH) analysis on uncultured amniocytes using a chromosome 7 centromeric probe (D7Z1; Vysis, Downers Grove, IL) showed that 21 (14%) of 160 cells analyzed had three chromosome 7.

Postnatal Studies

At 36 WG, a caesarian section was performed because of prematurity rupture of membranes leading to maternal-fetal streptococcus B infection and perturbed fetal heart rate. A male infant was delivered with a birth weight of 1,960 g (below the 10th percentile), length of 43 cm (below the 10th percentile), and head circumference of 32 cm (25th percentile). Apgar score was 4 at 1 minute and 10 at 5 minutes after brief ventilation. Physical examination showed a hypotonic baby with some minor dysmorphic features, including small triangular face, prominent forehead, narrow palpebral fissures, antverted nostrils, downturned corners of mouth, posterior-rotated low-set ears, small and pointed chin, clinodactyly of the left fifth finger, single crease on the left hand, hypospadias, and angled penis. No body asymmetry was noted.

After birth, cytogenetic analysis on various cells confirmed the true fetal mosaicism, with trisomic cells in the urinary pellet but not in lymphocytes or in jugal cells. The infant had a complicated neonatal period, with severe feeding difficulties requiring nutrition by a nasogastric tube and neonatal jaundice with unconjugated hyperbilirubinemia (at 206 mol/L). Transfontanel ultrasound, echocardiography, and ophthalmologic examination were normal. Examination at 3 months showed depigmented skin areas in limbs. A skin biopsy was not performed. Asymmetry in inferior limb length was noted clinically but not confirmed by x-ray examination. Unusual severe psychomotor delay, hypotonia, and choreoathetoid movement were noted at 6 months. Brain magnetic resonance imaging (MRI) showed both hypoplasia and dysplasia of the cerebellum.

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Polymerase chain reaction–based analysis for microsatellite markers on chromosome 7 was performed using fluorescent primers. Repeat alleles were resolved on an ABI PRISM 3130 capillary automate (Applied Biosystems, Foster City, CA) and analyzed by standard semiautomatic methods according to the manufacturer’s protocols (GeneMapper; Applied Biosystems). Microsatellite marker analyses revealed maternal heterodisomy on chromosome 7 (Figure 1). Biparental inheritance was ascertained using markers on chromosome 15 (sample controls; data not shown).

Discussion

We report on a patient with prenatally ascertained SRS with trisomy 7 mosaicism and cerebellar hypoplasia. Trisomy 7 was detected in cultured and uncultured amniocytes with fractions of 32% and 14% of trisomic cells, respectively. Despite the discovery of fetal growth retardation on ultrasound examination, the parents declined further analysis for UPD(7)m. Trisomy 7 mosaicism was confirmed after birth in cultured chorionic villi (40%) and in urinary cells (16%) but was absent in peripheral blood.
cells and jugal cells. Maternal heterodisomy was confirmed after birth on diploid peripheral lymphocytes.

Trisomy 7 mosaicism has been diagnosed at least 14 times during the prenatal period by amniocentesis,5-14 with reported fractions of trisomic cells in amniocytes ranging from 5% to 78%. Among the prenatal mosaic trisomy 7 cases, seven were associated with minor phenotypic abnormalities7-13 that can be observed in SRS such as intrauterine and postnatal growth retardation, triangular facies, body asymmetry, and fifth-finger clinodactyly. For these cases associated with phenotypic anomalies, fractions of trisomic cells ranged from 23% to 78%7,8,10-12 in cultured amniocytes. The remaining cases with a normal phenotype at birth had a wide range of trisomic cells (from 5%-48%) in cultured amniocytes.

In our case, the proportion of trisomic cells in cultured and uncultured amniocytes was 32% and 14%, respectively. These results emphasize that a high level of trisomy 7 in cultured amniocytes might be derived from a cell culture effect, as suggested by Chen et al.8

Among the true mosaic trisomy 7 cases diagnosed prenatally and associated with minor phenotypic abnormalities of SRS after birth, UPD(7)m was documented in only three cases.11-14 In all these cases, microsatellite analyses revealed maternal heterodisomy of chromosome 7, as in our case.

Uniparental disomy (UPD) is the inheritance of two homologous chromosomes from one parent in a euploid offspring. Two types of UPDs can be distinguished: uniparental heterodisomy, which occurs when both homologous chromosomes are transmitted from the same parent, and uniparental isodisomy, in which two copies of the same parental chromosome are present.

Heterodisomy associated with mosaic trisomy 7 in our case indicates that the etiology of mosaicism is likely conception of the trisomy 7 zygote following a maternal meiotic nondisjunction event with incomplete trisomy rescue by loss of one chromosome 7 in some cell lineages. In this situation, maternal heterodisomy arises when the paternal homologue is lost. Thus, the most likely mechanism of UPD(7)m in our case should be a trisomic zygote rescue.

Kalousek et al1 reported 14 cases with CPM for trisomy 7. In five of six cases studied for the origin of placental mosaicism, DNA evidence suggests that the trisomic cell line arose by a somatic duplication event within the placental lineage. Their study substantiates the hypothesis that UPD(7)m is most frequently due to somatic duplication; therefore, they conclude that the risk of fetal UPD(7)m is low. However, our observation provides evidence that UPD(7)m should be considered when trisomy 7 mosaicism is detected prenatally, because the association of mosaic trisomy 7 and UPD(7)m may lead to a poorer condition than isolated UPD(7)m, hence modifying genetic counseling. To our knowledge, the association between SRS and trisomy 7 mosaicism has been documented in only three cases.11-14 All those cases were associated with severe developmental delay and typical facial dysmorphism. The first one had facial dysmorphism, severe growth retardation, hypoglycemia, and severe development delay. Font-Montgomery et al14 hypothesize that the patient’s exceedingly poor growth before growth hormone therapy and her subsequent response to hormonal replacement might be due to homozygosity of a mutant growth hormone–releasing hormone receptor, which is located in the short arm of chromosome 7. The authors also suggested that her severe developmental delay might be related to her UPD that was associated with mosaic trisomy 7.

In the second case, Flori et al12 reported the unusual association of SRS with UPD(7)m, trisomy 7 mosaicism, and Hirschprung disease. Trisomy 7 mosaicism was present in nervous plexuses of the intestine as well as in the epithelium or the connective and muscular tissues. Therefore, it was suggested that an increased dosage of a nonimprinted gene due to trisomy 7 mosaicism in the intestine results in Hirschprung disease.

Our case presents the unique association of hypoplasia and dysplasia of the cerebellum, which to our knowledge has never reported in patients with SRS with UPD(7)m. However, cerebellar hypoplasia was reported in a girl with mosaic trisomy 7.22 This girl had psychomotor delay and facial dysmorphism, including high forehead, antimongolian slant, deep-set eyes, esotropia, myopia, depressed nasal bridge, dysplastic low-set ears, short neck, and widely spaced inverted nipples. She had also lesions of depigmentation on the trunk and all four limbs. Brain MRI demonstrated mild hypoplasia of the cerebellum and midbrain.

Therefore, we suggest that cerebellar hypoplasia might be related to the presence of trisomic cells in the cerebellum, leading to an increased dosage of nonimprinted genes or an overexpression of specifically maternally expressed imprinted alleles. In fact, the human growth factor receptor–bound protein 10 (GRB10) mapped on 7p is an imprinted gene that is implicated in the developing central nervous system, including brain and fetal spinal cord.23,24 Moreover, it is known that overexpression of certain GRB10 isoforms has been shown to inhibit tyrosine kinase activity, resulting in growth suppression and fetal CNS development inhibition.23

Thus, our report strengthens the hypothesis that the SRS phenotype observed in patients with UPD(7)m might also result from an undetected low-level trisomy 7 mosaicism. We do not have any information regarding trisomy 7 mosaicism for most patients with postnatally ascertained UPD(7)m SRS. Such information would help refine the genotype/phenotype correlation between patients with and without mosaicism. In fact, the phenotype can be modified by the presence of trisomic cells in some tissues, such as observed in our case. In this regard, the urinary cells represent one biologic sample that can be easily studied by FISH to search for this mosaic trisomy.
### Table 1
Prenatal Patients With Silver-Russell Syndrome With the Combination of Mosaic Trisomy 7 and Maternal Heterodisomy of Chromosome 7

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Present Case</th>
<th>Bilimoria and Rothenberg&lt;sup&gt;11&lt;/sup&gt; and Font-Montgomery et al&lt;sup&gt;14&lt;/sup&gt;</th>
<th>Flori et al&lt;sup&gt;12&lt;/sup&gt;</th>
<th>Petit et al&lt;sup&gt;13&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for amniocentesis</td>
<td>Abnormal triple marker screen</td>
<td>Abnormal triple marker screen</td>
<td>IUGR and moderate oligoanomies</td>
<td>Severe IUGR; abnormal triple marker screen</td>
</tr>
<tr>
<td>Prenatal findings</td>
<td>IUGR</td>
<td>Two-vessel cord at birth; slight cardiomegaly; IUGR</td>
<td>IUGR</td>
<td>IUGR</td>
</tr>
<tr>
<td>Prenatal cytogenetic analysis</td>
<td>47,XY,+7[5]/46,XY[17] (32% of colonies)</td>
<td>47,XX,+7[13]/46,XX[19] (41% of colonies)</td>
<td>47,XY,+7[8]/46,XY[18] (44% of colonies)</td>
<td>46,XY (100% of colonies); 47,XY,+7[20]/46,XY[30] (flask culture)</td>
</tr>
<tr>
<td>Postnatal cytogenetic analysis</td>
<td>47,XY,+7[21]/46,XY[33]; placenta (32% of colonies); 46,XY[50]: cord blood</td>
<td>47,XX,+7[9]/46,XX[20]: skin fibroblasts; 47,XX,+7[19]: chorionic villi; 46,XX[50]: cord blood</td>
<td>47,XX,+7[15]/46,XX[85]: intestine; 46,XX[100]: skin fibroblasts; 46,XX[100]: cord blood</td>
<td>46,XY[100]: blood; 46,XY[12]/47,XY,+7[8]: skin fibroblasts</td>
</tr>
<tr>
<td>Maternal heterodisomy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dysmorphic features</td>
<td>Triangular face, prominent forehead, narrow palpebral fissures, anteverted nostrils, downturned corners of mouth, posterior-rotated low-set ears, small and pointed chin, clinodactyly of left fifth finger, single crease on left hand, hypoplasias, and angled penis</td>
<td>Triangular-shaped face, broad forehead, short nose with prominent nasal bridge, thin lips with downturned corners, broad and low-set ears, micrognathia, fifth-finger clinodactyly</td>
<td>Triangular-shaped face, frontal bosses, narrow palpebral fissures, small mouth with thin lips, pointed chin, low-set posteriorly rotated ears, fifth-finger clinodactyly</td>
<td>Low-set and posteriorly rotated ears</td>
</tr>
<tr>
<td>Pigmentary anomalies</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>Severe developmental delay</td>
<td>Severe developmental delay</td>
<td>Developmental delay</td>
<td>Developmental delay</td>
</tr>
<tr>
<td>Other features</td>
<td>Feeding difficulties, hypotonia, choreoathetoid movement, cerebellar dysplasia, hypoplasia, limb asymmetry, and failure to thrive</td>
<td>Hypoglycemia, failure to thrive, patent ductus arteriosus, diminished subcutaneous fat, mild peripheral hypotonia</td>
<td>Feeding difficulties, postnatal growth retardation, ventricular septal defect, Hirschsprung disease</td>
<td>Patent ductus arteriosus, ventricular septal defect, Dandy-Walker variant, failure to thrive</td>
</tr>
<tr>
<td>Age at last examination</td>
<td>13 mo</td>
<td>25 mo</td>
<td>5 y</td>
<td>4.5 y</td>
</tr>
</tbody>
</table>

IUGR, intrauterine growth retardation; –, negative; +, positive.

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References


