

**Case report****A female infant with Silver Russell Syndrome, mesocardia and enlargement of the clitoris**

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**ABSTRACT**

**Silver Russell Syndrome (SRS) is a rare condition (1/3000 – 1/100,000 newborns). We present a female infant with SRS, cardiac malposition and asymmetric enlargement of the clitoris. She is the first child of Greek nonconsanguineous parents, born at 38 weeks gestation, following *in vitro* fertilisation (IVF). The patient had intrauterine growth retardation, body asymmetry, enlarged clitoris, hemihypertrophy of external genitalia and features characteristic of SRS. Electrocardiography and chest X-rays revealed a median position of the heart. The infant fulfilled the criteria proposed by Price et al for SRS. Genetic analysis did not reveal mUPD of chromosome 7. This is the first report of a patient with SRS presenting “mesocardia” and asymmetric enlargement of the clitoris. Our case constitutes another paradigm of SRS following IVF, which possibly supports the hypothesis that IVF may be associated with higher prevalence of SRS than natural fertilisation.**

**Key words:** Body asymmetry, Clitoromegaly, Dextrocardia “ambiguous” genitalia, *In vitro* fertilisation, Mesocardia, Silver Russell Syndrome

**INTRODUCTION**

Silver Russell Syndrome (SRS) (OMIM 180860) represents a clinically and genetically heterogeneous congenital disorder whose primary features are growth

retardation, short stature, facial dysmorphism and limb asymmetry. It was first described by Silver in 1953 and then by Russell in 1954.<sup>1,2</sup> Recently, Price et al defined the diagnostic criteria for the classical phenotype. For the diagnosis of SRS at least four of the following criteria should be present: 1) Intrauterine Growth Retardation (IUGR) (birth weight  $\geq 2$  SD below the mean), 2) postnatal growth retardation (body length  $\geq 2$  SD below the mean), 3) preservation of occipitofrontal head circumference, 4) classic facial phenotype (broad prominent forehead with small triangular face, small narrow chin and low set ears)

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and 5) asymmetry (especially of the limbs).<sup>3</sup> The characteristic clinical features are more easily identified in infants and younger children than in adults.

We here report a female infant with SRS, malposition of the heart and asymmetric enlargement of the clitoris. To our knowledge, this is the first case of SRS associated with “mesocardia” and asymmetric enlargement of the clitoris.

## CASE REPORT

The infant was first referred to our Pediatric Endocrinology Department soon after birth due to “ambiguous” genitalia consisting of a large clitoris (length = 2.5 cm) and large labia majora, especially on the right side (Figure 1). This was the first child of Greek nonconsanguineous parents (mother 32 and father 35 years old) born by caesarean section at 38 weeks of gestation following *in vitro* fertilisation. The newborn had a birth weight of 1610 g (<-3SD), birth length of 39 cm (<-3SD), skull circumference of 31.5 cm (-2SD) and also body asymmetry (right side larger). She had the typical triangular face of SRS. The pregnancy was not complicated by maternal infections or preeclampsia. The maternal medical history did not include diseases, smoking, medication and alcohol or drug abuse. The newborn was admit-



**Figure 1.** External genitalia of the girl in the neonatal period: large clitoris and large labia majora, especially on the right side.

ted to the Neonatal Intensive Care Unit for further surveillance. The laboratory findings were normal including hormonal evaluation for “ambiguous genitalia”. Echocardiography and chest X-rays revealed a slightly right position of the heart without any structural anomalies of the large vessels and without any signs of cyanosis or heart murmur (Figure 2). Ultrasonograms of the brain and the abdomen were normal. The patient was discharged and re-admitted at 40 days of life for further evaluation. The physical examination showed a small infant (body weight: 2200 g, <-3SD) with right-sided hemihypertrophy (length measurement: right leg: 48.5 cm <-2SD, left leg: 46 cm <-3SD), normal head circumference (37 cm, 50<sup>th</sup> percentile) and triangular face with prominent forehead and small, pointed chin. Both ears were set low and the mouth was downturned at the edges. The infant had clinodactyly of the fifth finger and the fifth toe bilaterally, as well as congenital dislocation of the left hip. The anterior and the posterior fontanelles were open. The ophthalmologic and neurologic examinations were normal without any signs of delay in cognitive development. The usual laboratory findings were in the normal range. Chromosomal analysis revealed a 46, XX karyotype and a brain Magnetic Resonance Image was normal.

On the basis of the features described, the diagnosis of SRS was made.

When the infant was six months old, blood was taken from baby and parents to investigate and eventually exclude maternal UPD. At that time, the mother was asked about and confirmed excessive sweating and feeding difficulties. The infant’s body measurements



**Figure 2.** The chest X-ray of the child: a) as a newborn, b) at the age of two years.

were: body weight: 3980g <-3SD, length measurement (right leg: 60cm <-2SD, left leg: 57cm <-3SD) and head circumference 41.5cm (25<sup>th</sup> percentile). The motor development was delayed because of decreased muscle tone, but there were no signs of any delay in cognitive development.

At the age of two years the girl was re-evaluated at our department. Her body measurements were: body weight; 8900gr <-3SD, length (right leg: 81 cm <-2SD, left leg: 78 cm <-3SD) and head circumference 47 cm (10<sup>th</sup>-25<sup>th</sup> percentile). The characteristics facial features were again noted (Figure 3). The clitoris continued to be large (2cm) (Figure 1). Her psychomotor development was normal. The X-ray revealed a median position of the cardiac silhouette (Figure 2). The echocardiography showed a cardiac malposition with the heart in the middle of the thorax, the atria in concordance with the ventricles, the great vessels in the normal position, a slight right rotation of the cardiac chambers in the vertical axis while the aortic arch was left-sided. No other intracardiac or extracardiac congenital malformations were identified. The electrocardiogram showed a left axis shift (QRS axis: -15°), positive P waves in lead I of low voltage, ventricular complexes of the QR type in lead I, II and aVL, RS complexes in V1 and morphologies of the QR type in V5 and V6.



**Figure 3.** The girl at the age of two years.

## DISCUSSION

Silver Russell Syndrome constitutes a rare entity. More than 400 cases have been reported internationally, with phenotypes ranging from mild to classic. The incidence ranges from 1 in 3000 to 1 in 100,000 newborns.<sup>4</sup> All races and sexes are equally affected.

The cause of SRS is unknown, most cases being sporadic. The features associated with the syndrome have been described in association with many genetic abnormalities such as chromosome rearrangements and uniparental disomy (maternal UPD7). Some families with apparent autosomal dominant inheritance have been reported, while autosomal recessive and X-linked inheritance has also been suggested.<sup>5</sup> It is most likely that one or more imprinted genes are implicated.<sup>3,6,7</sup> Gicquel et al and Bliet et al have found hypomethylation of the H19 gene in patients with SRS. The implications of this finding cannot be foreseen.

Our infant fulfilled the criteria proposed by Price et al.<sup>3</sup> In an attempt to verify the diagnosis, the characteristics of our patient are compared to 143 patients described by Wollmann in Table 1.<sup>8</sup>

During infancy and early childhood, feeding difficulties, tendency for fasting hypoglycaemia and increased sweating particularly on the head and upper trunk are frequent. Patients usually remain thin with decreased subcutaneous fat.<sup>4</sup> Skeletal anomalies include late closure of the anterior fontanelle, campodactyly, syndactyly, dislocated hip and arm span less than height.<sup>3,7</sup> Individuals have microdontia and dental crowding because of relative micrognathia and small mouth.<sup>8</sup> Common genitourinary tract anomalies are hypospadias and cryptorchidism and less commonly renal anomalies.<sup>3</sup> Gastrointestinal disorders such as gastroesophageal reflux, esophagitis and food aversion may be present.<sup>9</sup> Some of these issues may not be intrinsic but related to the parent attempts to feed the child.

Besides growth issues, neurodevelopment is of greatest concern to parents. Despite reassurances about “normal intelligence” in earlier reports, growing evidence supports significant risk of developmental delay and learning disabilities.<sup>3</sup> A recent report by Blissett et al<sup>10</sup> supports the hypothesis that Oral Mo-

**Table 1.** Frequency (%) of clinical characteristics in 143 children with Silver Russell Syndrome reported by Wollmann et al<sup>7</sup> and those of our patient.

Clinical characteristics	Frequency	Clinical characteristics of our patient
Birth weight <3rd percentile	94%	+
Short stature	99%	+
Asymmetry	51%	+
Relative macrocephaly	64%	+
Triangular face	79%	+
Down-slanting corners of mouth	46%	+
Irregular teeth	28%	n.a.
Ear anomalies	53%	+
Clinodactyly V	68%	+
Brachydactyly V	48%	+
Syndactyly V	19%	-
Simian crease	25%	-
Café-au-lait spots	19%	-
Psychomotor retardation	37%	n.a.
Muscular hypotrophy/-tonia	45%	+
Squeaky voice	22%	+
Early puberty	8%	n.a.
Precocious puberty	5%	n.a.

(+ present, - not present, n.a. not assessable)

tor Dysfunction (OMD) is the primary cause of both feeding problems and speech difficulties in some children with SRS.

The role of Growth Hormone (GH) secretion in the pathogenesis of growth retardation in SRS is not fully understood. Most individuals have normal serum concentration of GH; however, rare instances of SRS with GH deficiency have been described. Abnormalities of pulsatile GH secretion have been reported and GH treatment has some positive effect on the growth pattern.<sup>11</sup>

The management of SRS requires the cooperation of a team of specialists with the parents. A pediatric endocrinologist should consider the use of GH therapy. A pediatric gastroenterologist is needed to deal with gastrointestinal problems. Pediatric dentists, orthodontists and orthognathic surgeons can manage the craniofacial anomalies. The orthopaedics are responsible for the correction of asymmetry

and related dislocated hip and consequent scoliosis. Those with developmental delay should be referred for physical therapy and/or for speech and language therapy. Finally, psychologic counselling is needed for children and parents.

Three features of this case merit attention: the cardiac malposition, the asymmetric enlargement of the clitoris and the occurrence of SRS after *in vitro* fertilisation. As to the cardiac malposition, our case corresponds to the definition of mesocardia in situs solitus as described by Van Praagh et al,<sup>12</sup> while according to the electrocardiographic and echocardiographic findings, it can also be attributed to a variant of dextroversion in situs solitus.<sup>12</sup> Although structural anomalies of the heart have been reported with some frequency in SRS, to our knowledge mesocardia has not been previously described. In males with SRS, hypospadias and cryptorchidism have been reported in several instances.<sup>3</sup> We found only one report of a girl with SRS features and a large clitoris. This was a girl who also had absence of ovaries and a hypoplastic uterus.<sup>7</sup> However, to our knowledge, this is the first time that asymmetric external genitalia and a large clitoris are reported. *In vitro* fertilization has been described as being associated with an increased risk for the birth of small for gestational age babies. Recent reports suggest that the possibility of imprinting diseases, such as Angelman's, Prader-Willi's and Beckwith-Wiedemann's syndrome, is increased in cases with assisted reproductive technology. Recent reports also suggest that *in vitro* fertilization is associated with a higher prevalence of SRS than it is observed with natural fertilisation.<sup>14</sup> Our case constitutes another paradigm of SRS which could be related to *in vitro* fertilization.

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