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CASE REPORT

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Kagami-Ogata syndrome: an important differential diagnosis to Beckwith-Wiedemann syndrome

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Abstract

We report the case of a fetus with sonographic characteristics of Beckwith-Wiedemann syndrome (BWS). A 30-year-old gravida 2 para 1 was referred to our fetal medicine unit with an omphalocele. Fetal macrosomia, organomegaly, and polyhydramnios but no macroglossia were detected and BWS was suspected. Genetic testing for BWS did not confirm the suspected diagnosis as the karyotype was normal. Symptomatic polyhydramnios led to repeated amnioreductions. At 35 + 5 weeks of gestation, a female neonate of 3660 g was delivered with APGAR scores of 6/7/8, after 1/5/10 min, respectively. The abnormal shape of the thorax, facial dysmorphism, need for ventilation, and generalized muscular hypotonia led to the suspicion of Kagami-Ogata syndrome (KOS), which was confirmed by genetic testing. KOS in our patient was caused by a large deletion in the MEG3-region on chromosome 14q32 affecting the maternal allele. In this report, we highlight the notion that when sonographic signs suggestive of BWS such as macrosomia, polyhydramnios, and omphalocele are present and genetic testing does not confirm the suspected diagnosis, KOS should be tested for.

KEYWORDS

Beckwith-Wiedemann syndrome, bell-shaped thorax, *coat-hanger ribs*, Kagami-Ogata syndrome, overgrowth syndromes, ultrasonography

1 | INTRODUCTION

Kagami-Ogata syndrome (KOS) is characterized by macrosomia, a bell-shaped thorax with coat-hanger ribs and abdominal wall defects. The *coat-hanger sign* was introduced by Offiah et al, who detected these short, abnormally shaped ribs on postnatal chest X-ray.[1] Since many skeletal dysplasias may present with a small thorax, *coat-hanger ribs* serve as a distinct feature of KOS facilitating the differentiation between KOS and other skeletal dysplasias.[2] We report the case of a fetus with KOS whose ultrasound (US) characteristics were initially diagnosed as Beckwith-Wiedemann syndrome (BWS).

2 | CASE REPORT

A 30-year-old gravida 2, para 1 was referred to our fetal medicine unit after the detection of an omphalocele on the 20-week US examination. No first-trimester screening for aneuploidies had been

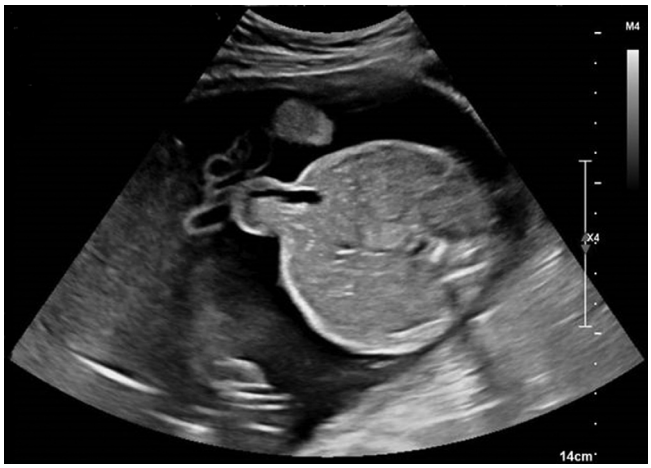

FIGURE 1 Kagami-Ogata syndrome. Sonogram shows fetal omphalocele and polyhydramnios

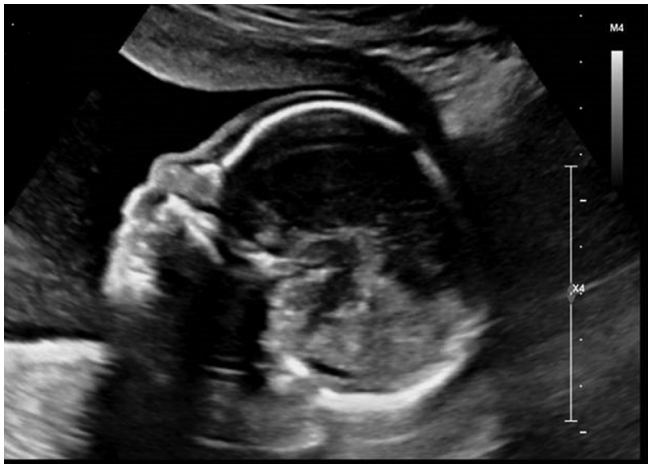

FIGURE 2 Abnormal facial features. Two-dimensional US shows prefrontal edema, a fronto-nasal ratio of 1, and a flat facial profile

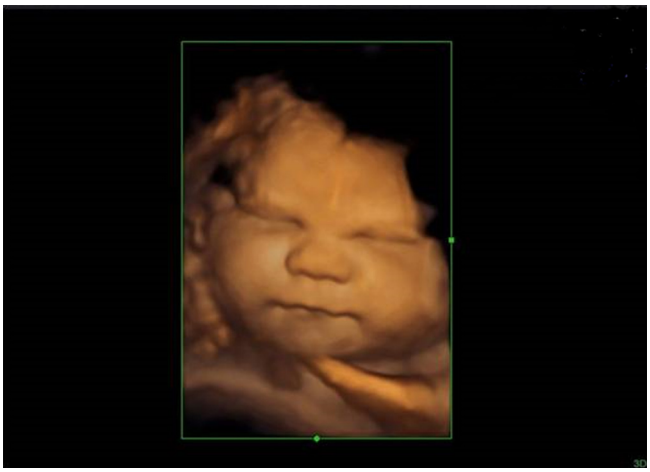

FIGURE 3 3D sonogram of the face

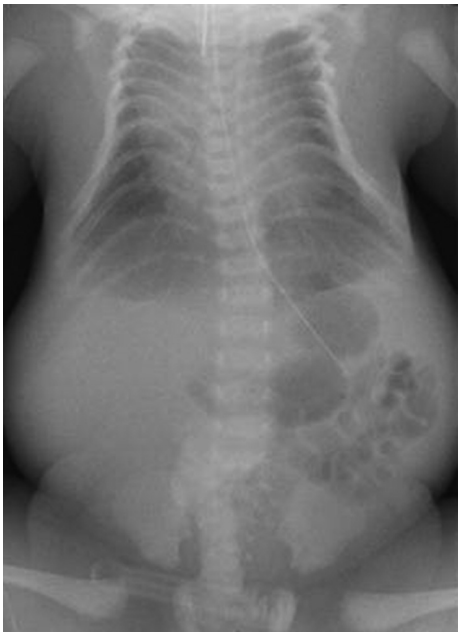

FIGURE 4 Postnatal chest X-ray shows the typical bell-shaped thorax and coat-hanger ribs

performed. In our department, US examinations were performed using a *Philips Epiq7* scanner and a C5-1 convex transducer.

We first scanned the patient at 22 + 0 weeks of gestation. In addition to the small omphalocele (Figure 1), we detected macrosomia with an estimated fetal weight above the 97th percentile and polyhydramnios in the absence of a filled stomach. Abnormal facial features consisting of a prefrontal edema and a flat facial profile were present, while no macroglossia was detected (Figures 2 and 3). No further fetal anomalies were seen. Genetic testing was offered but declined by the patient at this point of the pregnancy. At 23 + 6 weeks, the US features of fetal macrosomia and omphalocele were persistent, the stomach appeared empty. At 25 + 1 weeks of gestation, the amniotic fluid index reached 31 cm and the patient exhibited dyspnoea. We performed an amnioreduction and acquired samples for genetic testing after informed consent was obtained. Karyotyping showed no numerical chromosomal aberrations. The suspected diagnosis of BWS was not confirmed in molecular testing. The amnioreduction was repeated at 30 + 1 and 32 + 2 weeks of gestation without complications.

At 35 + 5 weeks of gestation, the mother presented with premature contractions. Due to the suspected fetal abnormalities and pronounced polyhydramnios, the mother opted for a cesarean section, which was performed without complications. A baby girl of 3660 g (> 97th percentile) was delivered with APGAR scores of 6/7/8 at 1/5/10 min, respectively. Immediately after birth, the neonate showed a low oxygen saturation and was admitted to the neonatal intensive care unit due to respiratory insufficiency. On the second day of life, the neonate was extubated. Until the 16th day of life, she received a high-flow nasal cannula to support ventilation. In addition to macrosomia and diastasis recti with a small omphalocele, congenital

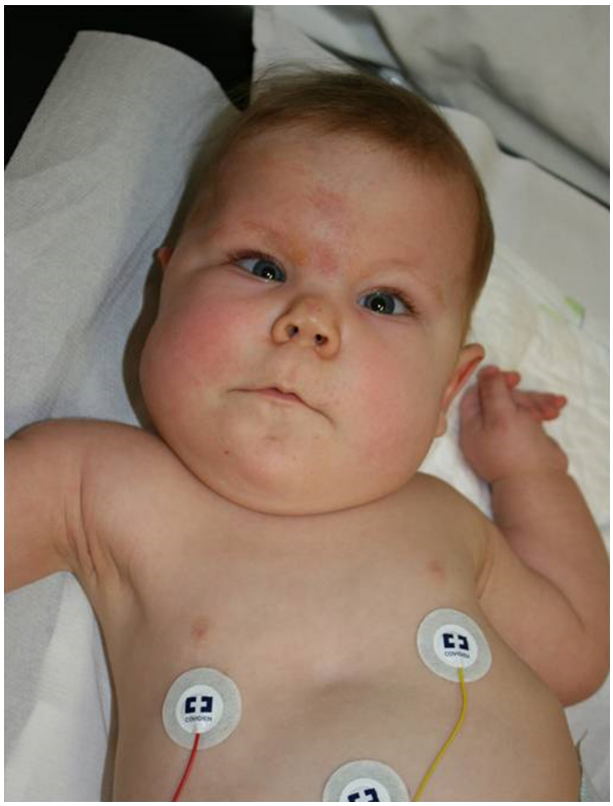

FIGURE 5 Photograph of the neonate after birth shows the dysmorphic facial features and bell-shaped thorax

hip dysplasia and plagiocephaly were present. Additionally, global muscular hypotonia without feeding problems were present. Chest X-ray confirmed the clinical finding of hypoplasia of the thorax with short, abnormally shaped ribs (Figure 4). Apart from a defect of the atrial septum (type ASD II) of 3.5 mm, the echocardiography was normal. A sonography of the brain revealed no abnormalities. Facial anomalies included full checks, prominent and long philtrum, and thin lips (Figure 5).

As a result of the morphological facial anomalies and abnormally shaped ribs and thorax of the child, KOS was then suspected and tested for. Genetical analysis confirmed a deletion of 336 kb of the MEG3-region on chromosome 14q32 affecting the maternal allele: arr [hg19]14q32.2q32.31(100812941-101448860)x1. Deletions of this region affecting the maternal allele are associated with KOS.[1] On the 23th day of life, the neonate was discharged in a stable condition. Because of short, self-limiting periods of apnea, a home monitor was provided for surveillance. At the age of 3 months, mild development delay of motor skills was noted, which was treated with physiotherapy. The family obtained in-depth social-medical counseling and guidance. On the grounds of a high risk of KOS patients to develop malignant abdominal tumors—especially hepatoblastoma—a US examination of the abdomen was performed every 3 months and revealed no signs of abdominal tumors. Last examination at 15 months revealed muscular hypotonia, delayed motor development, small thorax, and mild facial dysmorphism (Figure 5).

3 | DISCUSSION

This is a case of a KOS whose prenatal US features resembled those of BWS. Postnatally, the presence of abnormal shape of the thorax, facial anomalies, and muscular hypotonia of the neonate led to the suspected diagnosis of KOS, which was confirmed by genetic testing.

To date, only a few cases of prenatal diagnoses of KOS have been reported.[3-5] Kagami et al discovered that polyhydramnios was present in all observed patients from about 25 weeks of gestation. Notably, in many cases, several amnioreductions were required.[6,7] A small or empty stomach pouch has also been described before.[8] In our case, an empty stomach on several US examinations was noticed, which retrospectively can be interpreted as an early sign of impaired swallowing due to neuromuscular deficiency.

In our case, the presence of macrosomia, organomegaly, and omphalocele led prenatally to the suspected diagnosis of BWS. With an incidence of 3.8 per 100 000 births, BWS is the most common fetal overgrowth syndrome. The other typical US feature, macroglossia, may be absent in up to 18%.[9] Minor features are visceromegaly, namely nephromegaly and/or hepatomegaly, hydramnios and for male patients genital anomalies (cryptorchidism and/or hypospadias).[10] Genetic diagnosis of BWS is complex: BWS is caused in most cases by sporadic (epi)mutations of 11p15.5 affecting the imprinting control regions 1 and 2.[11]

Other overgrowth syndromes include Sotos, Simpson-Golabi-Behmel (SGBS), Perlmann, Weaver, and Pallister-Killian syndrome (PKS). It is a genetically heterogeneous group whose common denominators are macrosomia and organomegaly in the second trimester leading to a disproportionally larger abdominal circumference in comparison with head circumference and femur length. However, specific prenatal US findings vary from diaphragmatic hernia in SGBS to polydactyly and micromelia in PKS or macrodolichocephaly in Sotos syndrome.[12] KOS needs to be included in the differential diagnosis of fetal overgrowth in the second/third trimester.

The other rare finding in our case is the genotype. Our patient did not show the frequent genetic finding of upd(14)pat, which accounts for 2/3 of KOS patients.[13] Instead, a deletion of 336 kb of the MEG3-region on chromosome 14q32 affecting the maternal allele caused KOS. The classical KOS is caused by a full or segmental upd(14)pat or epimutations (hypermethylations) and microdeletions affecting the intergenic differentially methylated region (IG-DMR) and/or the MEG3-DMR of maternal origin.[13,14] Chromosome 14q32 harbors several imprinting genes: the paternally expressed genes DLK1 and RTL1 and the maternally expressed genes MEG3 and RTL1, along with the germline-derived DLK1-MEG3 IG-DMR and the postfertilization-derived MEG3-DMR.[13] Both sporadic and familial forms are known.[13,15] It is important to take into account that microdeletions can be transmitted recurrently from mothers carrying structural rearrangements predisposing to the formation of microdeletions in their offspring.[16] Maternal uniparental disomy of chromosome 14 or Temple syndrome leads to a different, less severe phenotype. It is characterized by prenatal and postnatal growth retardation, a relative degree of macrocephaly, neonatal hypotonia, small hands and feet, feeding difficulty, and precocious puberty.[17-19]

Prenatal diagnosis is especially important in the case of KOS, because the postnatal course is more severe than in BWS. The thoracic deformities often lead to feeding difficulties due to impaired swallowing and often lethal, respiratory insufficiency during infancy.[7] Almost all patients require mechanical ventilation, sometimes with tracheostomy. In the majority of cases, mechanical ventilation is needed for up to a month.[7] In contrast to the excessive weight at birth, one-third of children with KOS develop growth failure postnatally, especially in height. Other postnatal features of KOS include dysmorphic facial features such as a hairy forehead, blepharophimosis, full cheeks, a broad nasal bridge, a protruding philtrum as well as micrognathia. Plagiocephaly has also been described in these children. Reduced bone hardness has been suggested as a potential underlying cause.[20] Small ears and a short and/or webbed neck are often noticed. Atrial septal defect, ventricular septal defect, or pulmonary stenosis have been described in children with KOS. Some studies report kyphoscoliosis, inguinal hernia, laryngomalacia, and joint contractures. Children with KOS suffer from motoric development delay and/or intellectual disability. Particular attention needs to be paid to the development of abdominal tumors, primarily hepatoblastoma.[7] Therefore, regular screenings including alpha-fetoprotein measurement and abdominal US should be offered. This is also the case in BWS.[21]

In conclusion, we have reported a case of a KOS that resembled BWS on prenatal US. Furthermore, the genetic testing of KOS showed a deletion of 336 kb of the MEG3-region on chromosome 14q32 affecting the maternal allele and not upd(14)pat which is more frequent in KOS. KOS is an important differential diagnosis if clinical signs for overgrowth syndromes and especially BWS, such as macrosomia, polyhydramnios, and abdominal wall defects, are present and genetic diagnosis cannot be established. Therefore, since the most striking prenatal finding of KOS is overgrowth and organomegaly, it must be included in the differential diagnostic workup of fetal overgrowth. In the future, the detection of coat-hanger ribs might be used to differentiate KOS from BWS and other skeletal dysplasias. 3D-imaging and coronal images should help diagnose coat-hanger ribs accurately. Correct prenatal diagnosis is important as the postpartum course is more severe in KOS than in BWS and children with KOS need specific treatment.

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