Prenatal diagnosis of Kagami-Ogata Syndrome

Short running title: Prenatal diagnosis of KOS14

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No NGS or methylation array data were generated during this study.

Bulleted statement

What is already known about this topic?

Kagami-Ogata Syndrome (KOS14) is a rare entity with severe prognosis that is associated with different (epi)genetic aberrations resulting in abnormal dosage for genes within the chromosome 14q32 imprinted domain.

What does this study add?

KOS14 has previously been studied *in utero* once before by genetic testing in a known affected family. This may be the first case where ultrasound findings prompted directed family interrogation finally leading to the prenatal diagnosis of KOS14.

ABSTRACT

Kagami-Ogata syndrome (KOS14) is a rare congenital disorder associated with defective genomic imprinting of the chromosome 14q32 domain. Typical features include polyhydramnios, small and bell-shaped thorax, coat-hanger ribs, dysmorphic facial features, abdominal wall defects, placentomegaly, severe postnatal respiratory distress and intellectual disability. To the best of our knowledge, this may be the first case where ultrasound findings such as: severe polyhydramnios, a small bell- shaped thorax, a protuberant abdomen and characteristic dysmorphic face prompted directed family interrogation finally leading to the prenatal diagnosis of KOS14.

Key words: polyhydramnios, protruding philtrum, coat-hanger ribs, bell-shaped thorax, malformations, obstetrics

Introduction

Rare genetic diseases are normally sporadic with severe outcomes. Dysmorphic features can be suspected prenatally by ultrasound investigations, and guide suitable genetic testing for confirmation. Here we report a case in which the ultrasound features triggered the focused questioning of the family history, and ultimately the diagnosis of Kagami-Ogata Syndrome (KOS14). KOS14 is a rare entity with a severe prognosis that is characterized by different (epi) genetic aberrations, all resulting in abnormal dosage for genes within the chromosome 14q32 imprinted domain. There is only one previous report of a prenatal genetic diagnosis in a family harboring a chr14q32 microdeletion [1].

Case Report

A healthy 35-year-old gravida 5, para 2, was referred to our Fetal Medicine Unit at 29+6 weeks of gestation because of severe polyhydramnios in the follow-up ultrasound scans. Upon initial consultation, the couple reported unremarkable medical histories and no familial record of congenital anomalies. There was no consanguinity and the mother had no exposure to drugs, radiation or teratogenic agents. The course of the pregnancy had been uneventful, with normal first and second trimester scans. Ultrasonography using a 2-7 MHz volume probe (RAB6, Voluson E10 system, General Electric Company, 5th Necco St., Boston, MA 02210) in our hospital revealed severe polyhydramnios (amniotic fluid index of 45 cm) with cervical shortening (15 mm), and a fetus with a small bell-shaped thorax [figure 1] and abdominal protrusion [figure 2]. Bi-parietal diameter, head and abdominal circumference, and limb length were within normal ranges for gestational age, and no other structural malformations were detected in the remaining organs. A 3D ultrasound study was performed showing dysmorphic face features such as mild retrognathia, bulky cheeks and protruding philtrum, leading us to the suspicion of KOS14 (OMIM 608149) [figure 3].

An amnioreduction of 4000 ml was performed to avoid premature delivery. Following a second consultation and guided interrogation of the parents, the father explained that a previous child from a former relationship was born with a polymalformative syndrome, whilst the mother had two healthy children from an earlier relationship. Cytogenetic testing of the father was performed, revealing a Robertsonian translocation between chromosomes 13 and 14. Subsequent additional molecular analyses on amniotic fluid were performed. At 31 weeks, karyotyping revealed a Robertsonian translocation between chromosomes 13 and 14: 45, XX, der(13:14) (q10;q10), whilst an array-CGH was normal, ruling out the involvement of a copy-

number variant. Segregation studies of six short tandem repeat (STR) markers distributed along the length of chromosome 14 was performed on DNA derived from amniocytes and parents. Of the six markers, one was not informative, three were partially informative coinciding with those of the father and 2 were exclusively paternal inherited, confirming the diagnosis of UPD(14)pat. Parents were informed and after extensive multidisciplinary counselling they decided to continue the pregnancy.

At 34 weeks gestation a second amnioreduction of 5000 ml was required because of recurrence of severe polyhydramnios (AFI 50 cm) and cervical shortening (10 mm). Finally, labor begun at 36+2 weeks of gestation, and an emergency cesarean section was required due to signs of fetal distress. The female newborn had a birthweight of 2050 g, length was 43 cm and head circumference 32 cm. Apgar score at 5 min was 8.

She showed respiratory distress, was hypotonic and required intubation in the delivery room. Physical examination revealed bell-shaped thorax, diastasis recti [figure 4], a hairy forehead, mild blepharophimosis, full cheeks, protruding philtrum, and mild retrognathia [figure 5]. A chest X-ray confirmed the typical bell-shaped thorax with coat-hanger shaped *ribs.* [*figure 6*]. She was admitted to the neonatal intensive care unit, ventilated for 24 hours after birth, and extubated to non-invasive support (first nasal CPAP and later high-flow nasal cannula). She showed difficulty for managing secretions and for swallowing, so was tube-fed. She remained hypotonic, displayed little motor activity and scarce engagement cues. She died in her sleep at 41 days of life.

Discussion

To the best of our knowledge, this could be the first reported case of prenatal diagnosis of KOS14, where the suspicion arose from ultrasound findings, prompting family re-interrogation and the uncovering of a chr13-14 Robertsonian translocation in the father. KOS14 had been considered in the differential diagnosis of fetal ultrasound images in previous cases [2-4], but none had a prenatal confirmation of diagnosis.

Historically UPD(14)pat was described by Wang and colleagues in 1991 in a child with an unbalanced chr13-14 Robertsonian translocation[5]. A subsequent cohort analysis by Kagami and colleagues described the unique constellation of clinical features with epi(genetic) aberrations affecting the chr14q32 imprinted domain[6]. Although UPD(14)pat is the most prevalent molecular cause accounting for approximately 70% of cases, KOS14 can also be caused by maternally-inherited deletions (around 20%) or imprinting defects (gain of methylation at the IG-DMR; 10%). Their phenotypes are largely indistinguishable but with different recurrence risks[7].

Clinically, KOS14 is characterized by a retrospective diagnosis of polyhydramnios (100% of cases) and placentomegaly (82%), dysmorphic facial features, including protruding philtrum, bulky cheeks, micrognatia and depressed nasal bridge (>95%), a spectrum of abdominal wall defects (100%, such as omphalocele in 30% or rectus diastasis in 70% of cases), bell-shaped thorax (100%), coat-hanger ribs (100%), developmental delay (100%), postnatal growth retardation (30%) and hepatoblastoma (13%)[8]. Many of these defects were readily detectable in our patient. Offspring of parents carrying a balanced Robertsonian translocations or isochromosomes are at higher risk of UPD (0.5-1%)[3]. Consequently, if one of the parents has an alteration involving chr14, prenatal testing is recommended.

Fetal ultrasound findings of polyhydramnios and small thorax must give rise to suspicion of common skeletal dysplasias, but if an abdominal wall defect or protrusion is present, one of the entities to be ruled out is KOS14[3]. Identification of coat-hanger-shaped ribs on routine ultrasound is difficult and, although it had been reported before, we were unable to visualize them clearly in this case. On the other hand, the bell-shaped thorax and the typical facial dysmorphia can be easily diagnosed in coronal and longitudinal views[3,8], and using 3D ultrasound[4], respectively. KOS14 and Beckwith-Wiedemann syndrome (BWS) coincide in many clinical features as placentomegaly, abdominal wall defects and polyhydramnios. If BWS is suspected, KOS14 should be included in the differential diagnosis because postnatal course is much more severe than in BWS.[9]

Prenatal diagnosis of KOS14 is relevant as it may enable better counselling for parents and better management options. Since up to 30%[8] of cases die shortly after birth or during early infancy, and survivors have profound intellectual disability, termination of pregnancy before viability (depending on local regulation) or referral for delivery in a tertiary care center should be considered together with the family.

Our case illustrates the importance of an accurate ultrasound examination after the diagnosis of polyhydramnios in order to detect rare congenital syndromes. It also emphasizes that prenatal diagnosis of rare genetic syndromes, such as KOS14 and others, is feasible using advanced ultrasound in conjunction with a good family anamnesis and directed genetic testing.

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References

1. Sasaki A, Sumie M, Wada S, et al. Prenatal genetic testing for a microdeletion at chromosome 14q32.2 imprinted region leading to UPD(14)pat-like phenotype. Am J Med Genet A. 2014;164A(1):264.
2. Yamanaka M, Ishikawa H, Saito K, et al. Prenatal findings of paternal uniparental disomy 14: report of four patients. Am J Med Genet A. 2010;152A(3):789.
3. Curtis L, Antonelli E, Vial Y, et al. Prenatal diagnostic indicators of paternal uniparental disomy 14. Prenat Diagn. 2006;26(8):662.
4. Suzumori N, Ogata T, Mizutani E, et al. Prenatal findings of paternal uniparental disomy 14: Delineation of further patient. Am J Med Genet A. 2010;152A(12):3189.
5. Wang JC, Passage MB, Yen PH, et al. Uniparental heterodisomy for chromosome 14 in a phenotypically abnormal familial balanced 13/14 Robertsonian translocation carrier. Am J Hum Genet. 1991;48(6):1069.
6. Kagami M, Sekita Y, Nishimura G, et al. Deletions and epimutations affecting the human 14q32.2 imprinted region in individuals with paternal and maternal upd(14)-like phenotypes. Nat Genet. 2008;40(2):237.
7. Kagami M, Kurosawa K, Miyazaki O, et al. Comprehensive clinical studies in 34 patients with molecularly defined UPD(14)pat and related conditions (Kagami-Ogata syndrome). Eur J Hum Genet. 2015;23(11):1488.
8. Ogata T, Kagami M. Kagami-Ogata syndrome: a clinically recognizable upd(14)pat and related disorder affecting the chromosome 14q32.2 imprinted region. J Hum Genet. 2016;61(2):87.
9. Altmann J, Horn D, Korinth D, et al. Kagami-Ogata syndrome: an important differential diagnosis to Beckwith-Wiedemann syndrome. J Clin Ultrasound. 2020 May;48(4):240.

Figure 1. Abnormal thorax. Two-dimensional US coronal view shows a small bell-shaped thorax.

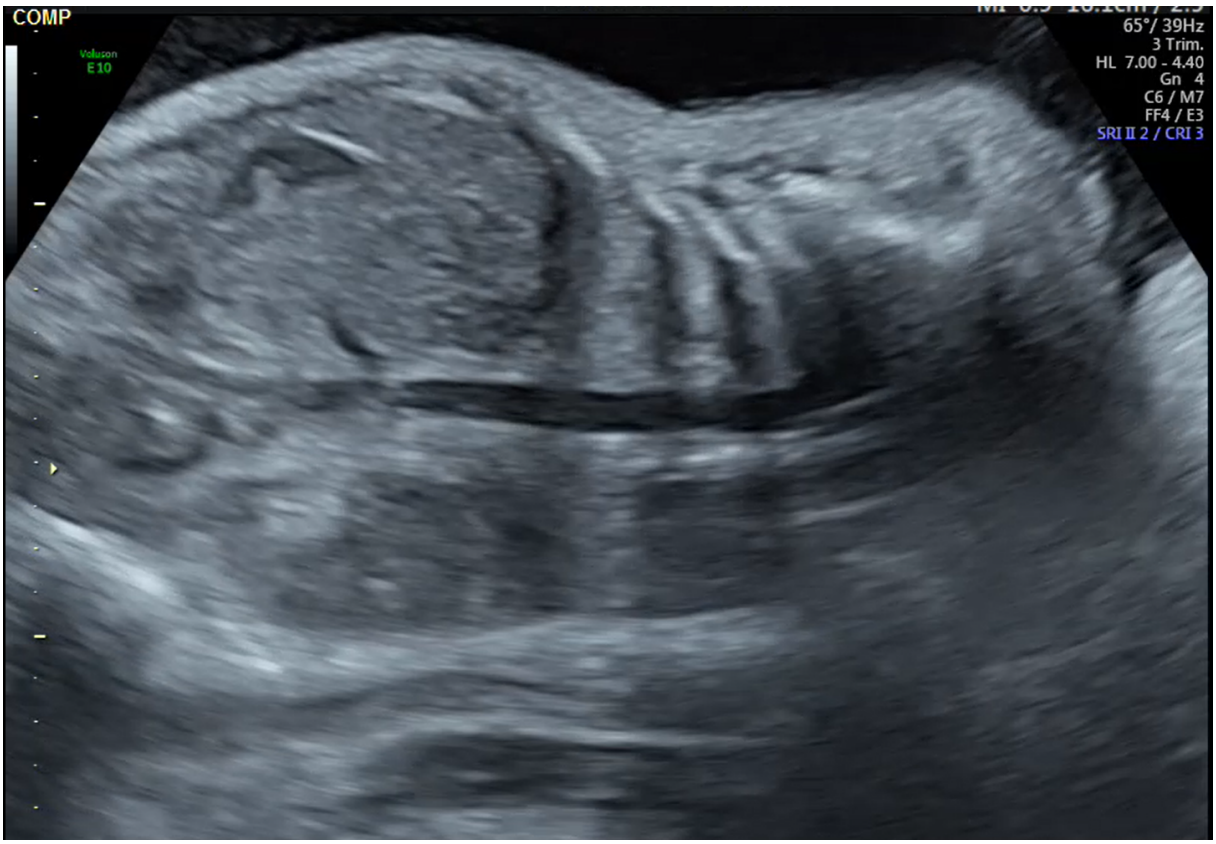

Figure 2. Abnormal abdomen. Two-dimensional US longitudinal view shows an abdominal anterior wall protrusion.

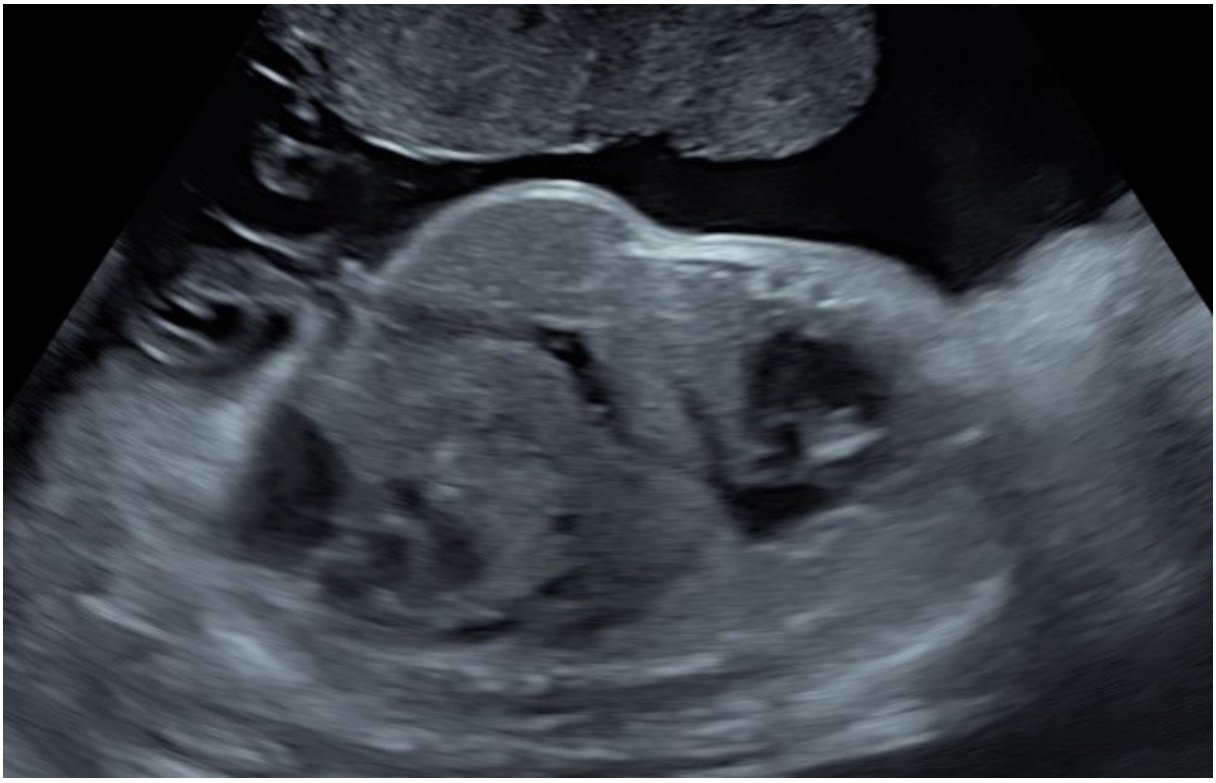

Figure 3. 3D sonogram of the face shows mild retrognathia, bulky cheeks and protruding philtrum.

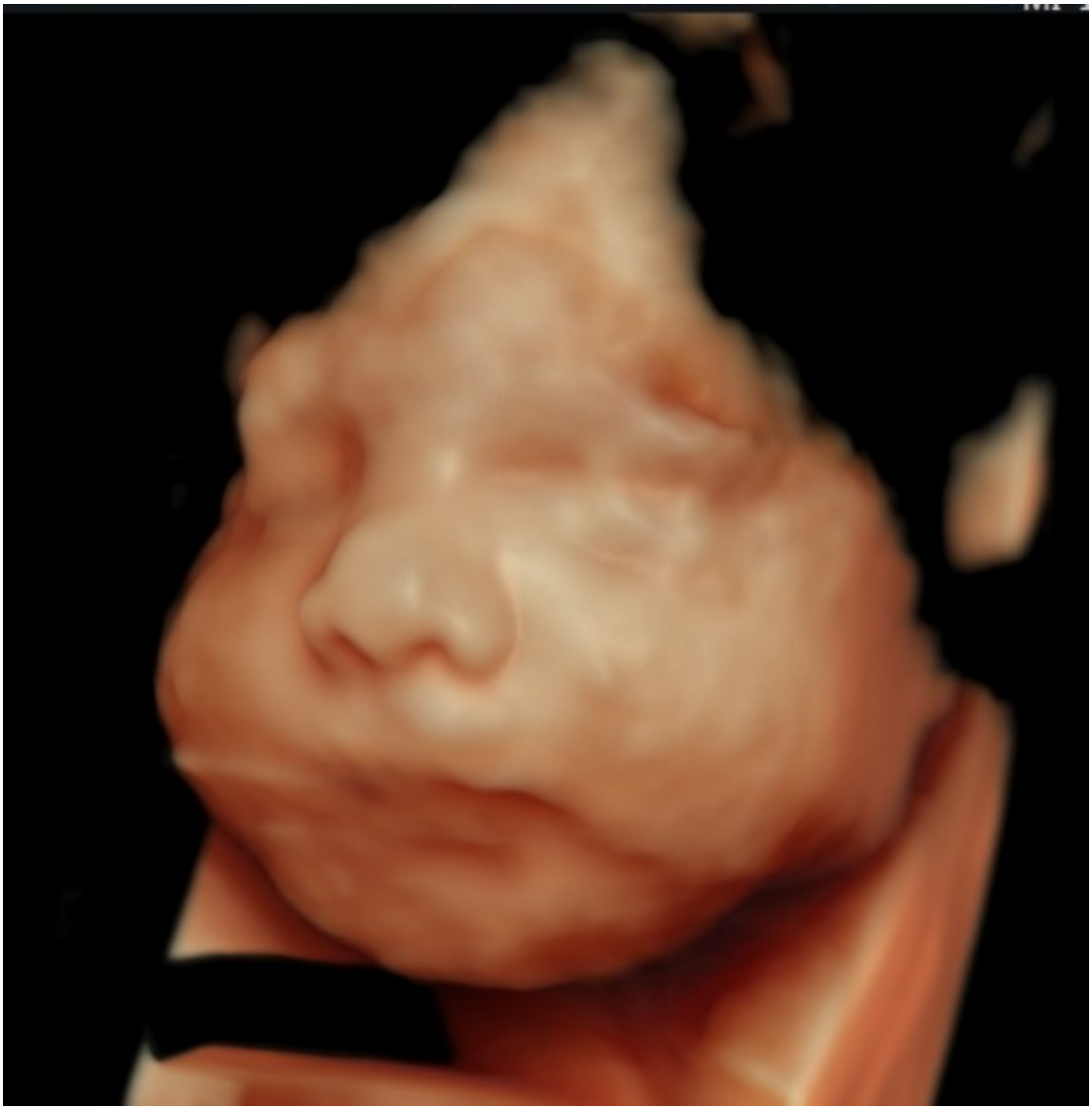

Figure 4. Photographs of the neonate after birth shows the abdominal ventral protrusion.

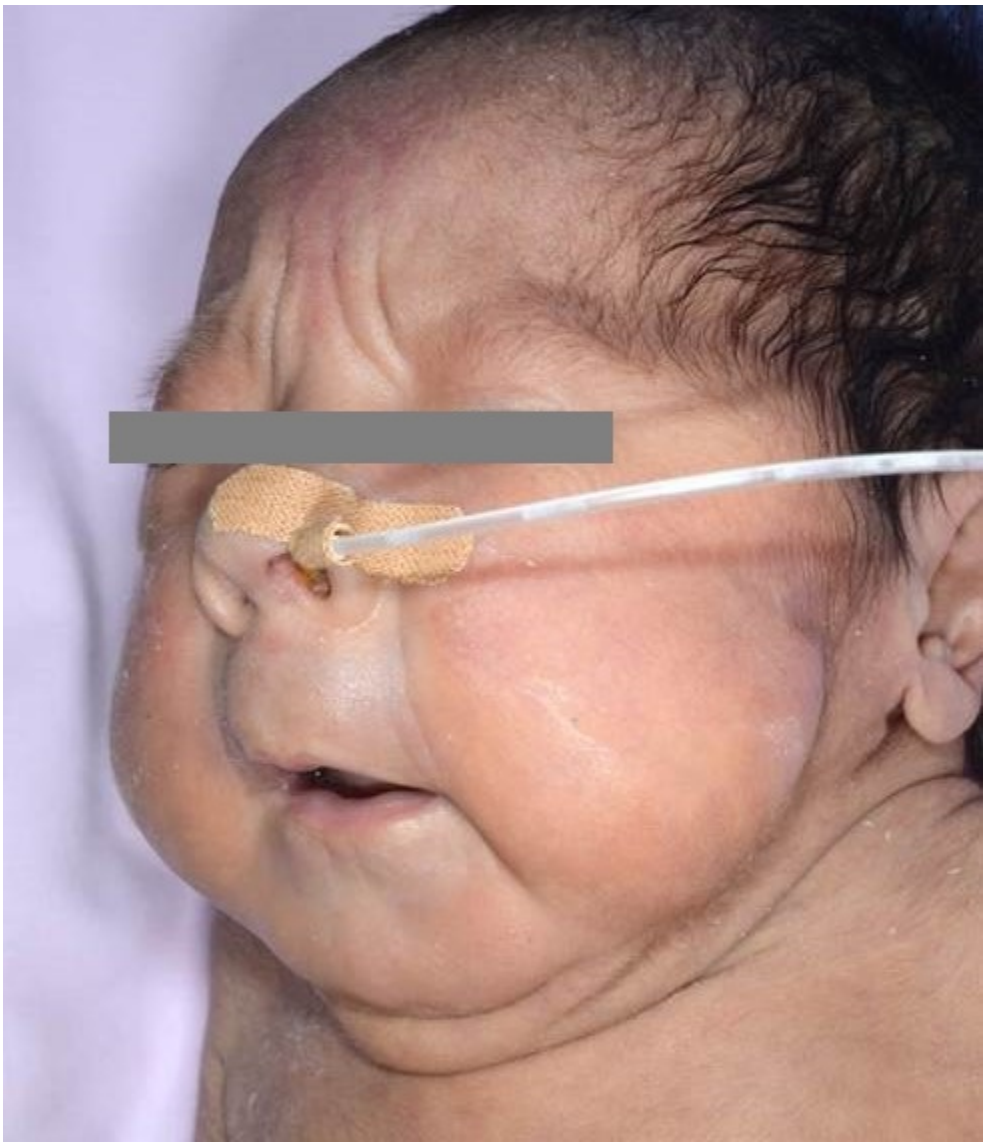

Figure 5. Photographs of the neonate after birth shows the dysmorphic facial features of Kagami-Ogata Syndrome.

Figure 6. Postnatal chest X-ray shows the typical bell-shaped thorax with coat-hanger ribs.