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Diagnosis of femoral hypoplasia–unusual facies syndrome in the fetus

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ABSTRACT

Femoral hypoplasia–unusual facies syndrome (FHUFS) is a rare condition characterized by a variable degree of unilateral or bilateral femoral hypoplasia associated with facial clefting and other minor malformations. The prenatal diagnosis of this condition is possible, but so far has been reported prospectively in only two cases. We review all cases of FHUFS reported in the literature and also describe three cases detected prenatally in the mid-trimester, underlining the variable expression of the syndrome. The reported association with maternal diabetes mellitus and differential diagnosis with other syndromes characterized by femoral hypoplasia are also discussed. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.

CASE REPORTS

Case 1

A 30-year-old primigravida was referred to our unit at 21 weeks' gestation because of a suspicion of severe bilateral femoral hypoplasia in her male fetus. The family history was negative for congenital anomalies. The patient did not have insulin-dependent diabetes mellitus. Ultrasound examination showed fetal biometry consistent with a gestational age of 21 weeks, with the exception of the femora, which appeared severely hypoplastic. The left femur was completely absent whereas the right one measured only a few millimeters (Figure 1a and b). Ultrasound imaging of the fetal face revealed the presence of unilateral right cleft lip and palate (Figure 1d). Unilateral right renal agenesis was also observed. In the counseling session, the couple was informed of the putative diagnosis and outcome of femoral hypoplasia–unusual facies syndrome (FHUFS), and the possible management options. After counseling, the couple opted for termination of the pregnancy. The diagnosis of FHUFS was confirmed at autopsy. In particular, severe bilateral and asymmetric femoral hypoplasia (Figure 1c), unilateral cleft lip/palate (Figure 1e) and unilateral renal agenesis were found. In addition, the face showed the typical features of FHUFS: a long philtrum, thin upper lip, moderate micrognathia and low-set ears (Figure 1e). Other features consistent with the diagnosis of FHUFS found at autopsy included a short neck and a pelvis with vertically orientated iliac blades.

Case 2

A 28-year-old obese woman (gravida 2, para 1) with insulin-dependent diabetes mellitus was referred to our unit at 21 weeks' gestation because of an abnormal second-trimester anomaly scan. The family history was unremarkable, with no consanguinity reported. On ultrasound examination, severe hypoplasia of the left femur was observed (Figure 2a), whereas the contralateral femoral shaft appeared unremarkable, with length in the normal range[1]. Examination of the fetal face revealed severe micrognathia (Figure 2c) and the ears appeared low set. No other abnormalities were observed. A diagnosis of FHUFS was made. After counseling, the couple opted for termination of the pregnancy. At autopsy, severe unilateral hypoplasia of the left femur, severe micrognathia and low-set ears were confirmed (Figure 2b and d). Also noted were a short nose with a broad tip, a thin upper lip and a cleft palate (Figure 2d, inset), confirming the diagnosis of FHUFS.

Case 3

A 24-year-old primigravida was referred to our unit at 13 weeks' gestation after the detection of abnormal lower limbs at the nuchal translucency scan. There was no

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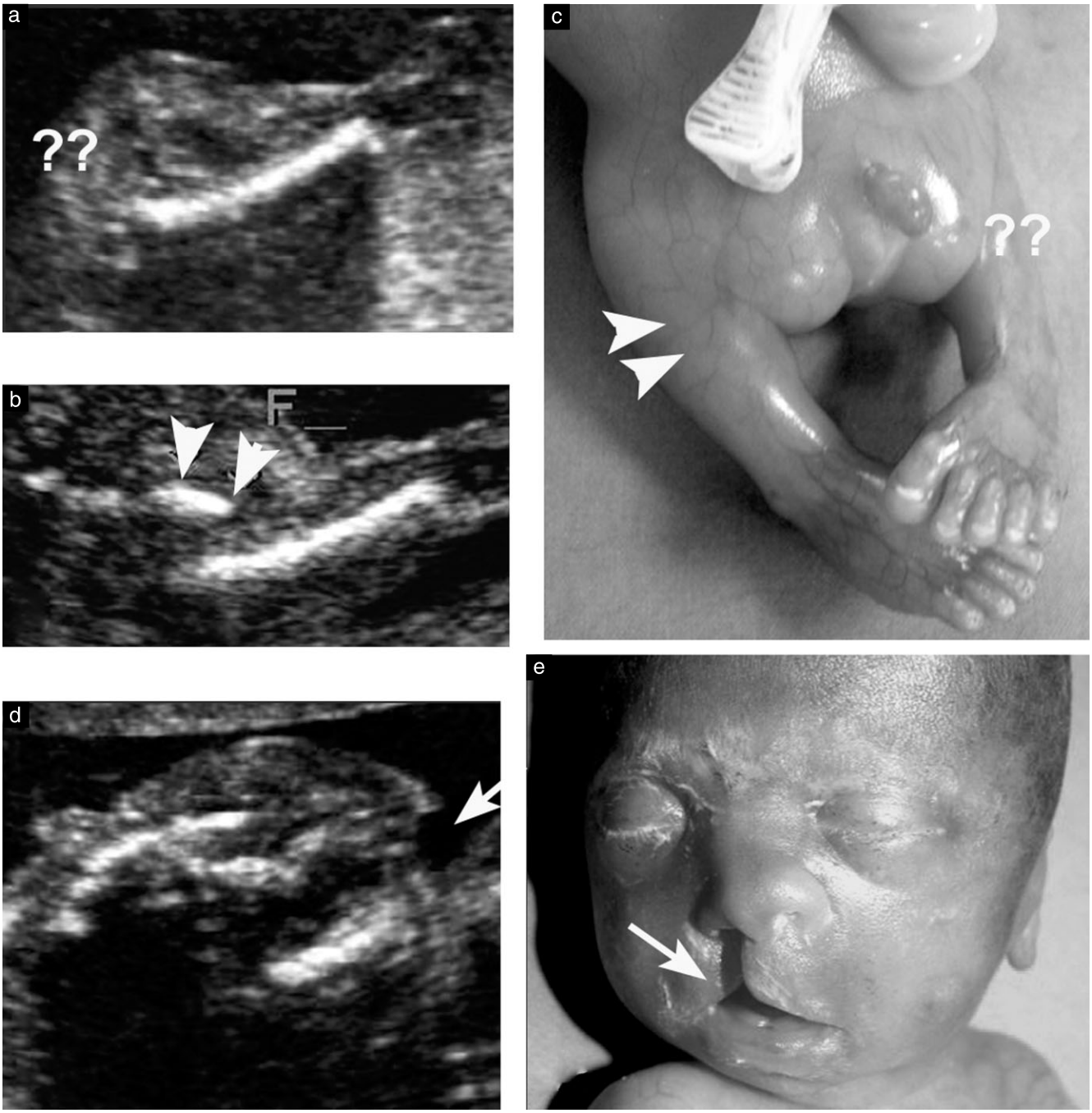

Figure 1 Case 1 at 21 weeks' gestation. (a, b) Ultrasound images showing symmetrical femoral hypoplasia; the femur is completely absent on the left side (a; ??) and severely hypoplastic on the right (b; arrowheads and F). (c) Confirmation of the diagnosis at necropsy; note also the talipes. (d) Axial view of the fetal head showing the wide cleft of lip and palate (arrow). (e) Confirmation of the diagnosis at necropsy; note also the additional subtle facial features, including upslanting palpebral fissures, long philtrum and thin upper lip.

history of either insulin-dependent diabetes mellitus or congenital anomalies. Ultrasound examination revealed a nuchal translucency thickness consistent with gestational age and confirmed the presence of symmetrically hypoplastic femora with normal tibiae and an abnormal left foot (Figure 3a and b). Transvaginal ultrasound examination further confirmed these findings and, in addition, suggested the presence of moderate micrognathia (Figure 3b). Termination was carried out in such a way that an intact specimen was obtained for postmortem examination. The pathologist confirmed the diagnosis of FHUFS and described severely hypoplastic femora, an abnormal left foot and moderate micrognathia (Figure 3c). No additional facial dysmorphisms or other associated anomalies were detected at necropsy at such an early gestational age, but the pathologist felt confident with the diagnosis of FHUFS.

DISCUSSION

Femoral–facial syndrome, or FHUFS, is a rare syndrome, described for the first time in 1975[2]. The pathogenesis of

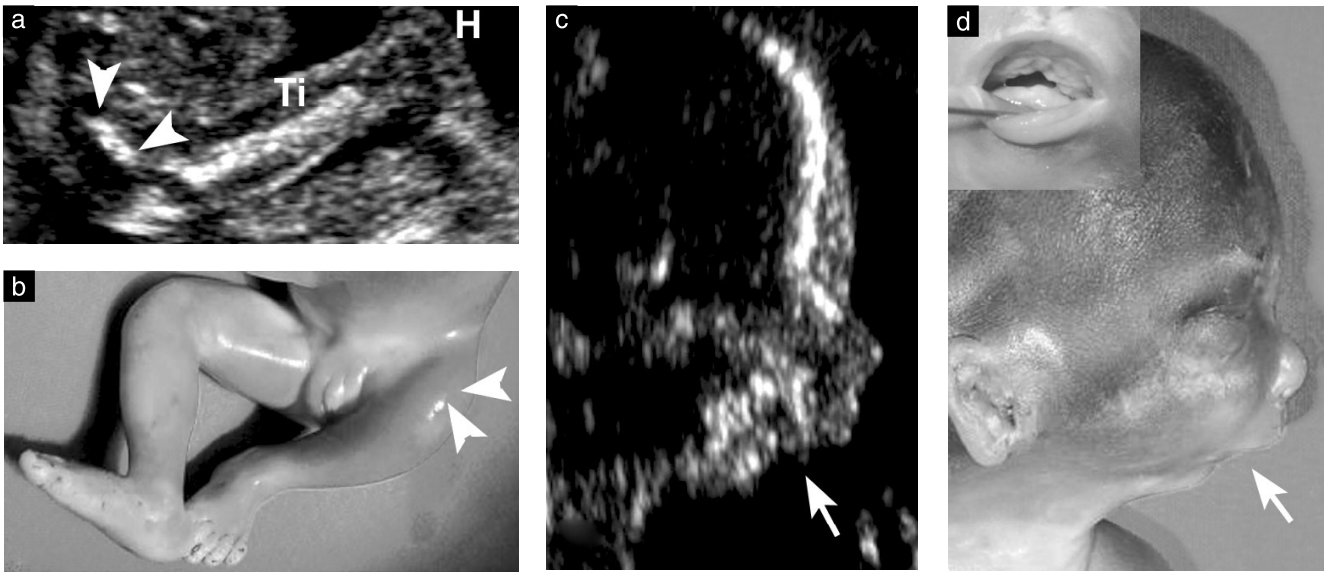

Figure 2 Case 2 at 21 weeks' gestation. (a) Ultrasound image showing severe asymmetrical femoral hypoplasia; note the severely shortened femoral shaft (arrowheads) and the normal tibia (Ti) and foot (H, heel). (b) Confirmation of the diagnosis at necropsy. (c) Sagittal view of the facial profile, showing severe micrognathia (arrow). (d) Confirmation of the diagnosis at necropsy (arrow). Note also the low-set ears, long philtrum and thin upper lip. The associated cleft palate is shown in the inset.

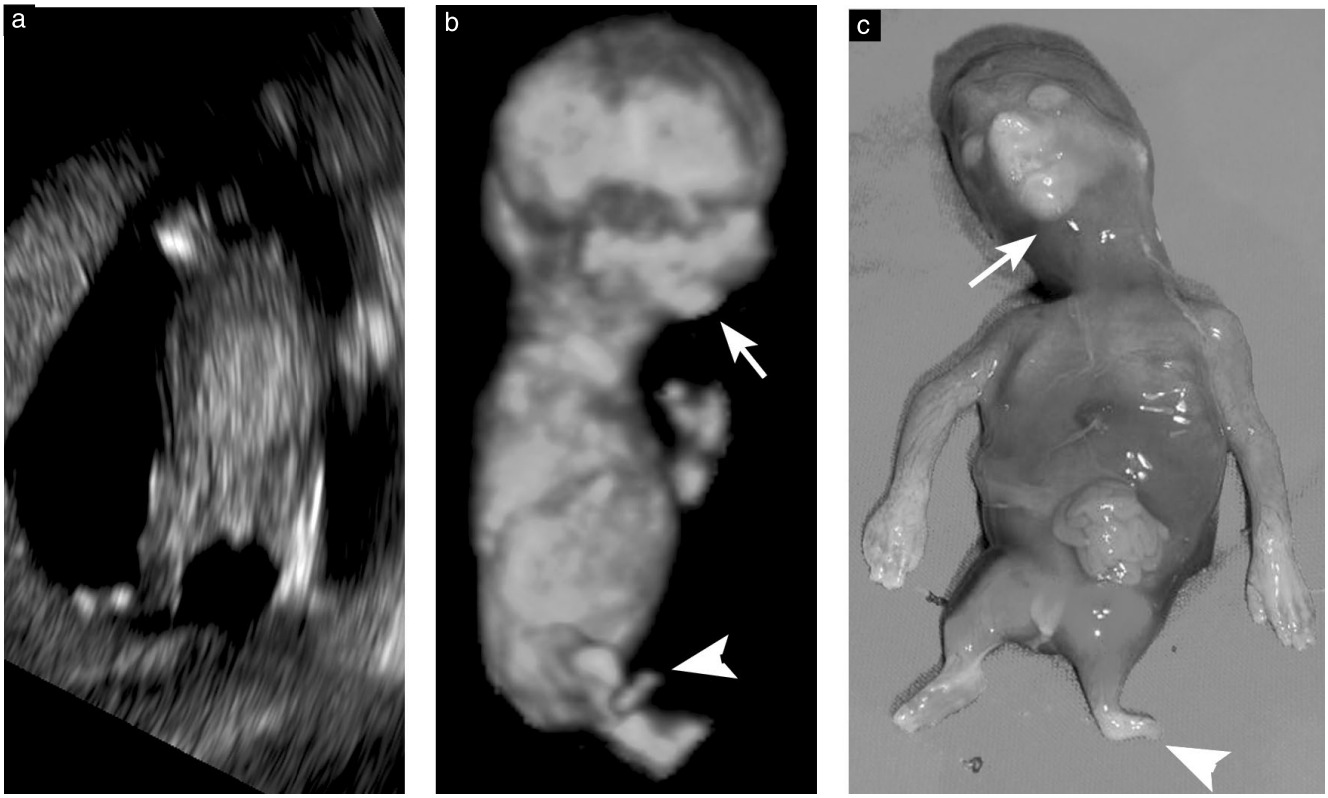

Figure 3 Case 3 at 13 weeks' gestation. (a) Two-dimensional ultrasound image of the severely hypoplastic femora. (b) Three-dimensional surface-rendered image of the whole fetus demonstrating the severe bilateral femoral defect and the abnormal left foot (arrowhead); moderate micrognathia (arrow) was also suspected. (c) Confirmation of the diagnosis at necropsy; the arrow indicates the moderate micrognathia and the arrowhead points to the abnormal foot. The abdominal wall lesion with bowel herniation was traumatic and occurred during expulsion of the fetus following rupture of the membranes.

the syndrome is unknown, although an association with maternal insulin-dependent diabetes is well documented[2], as are the large number of similarities with caudal regression syndrome, another condition frequently seen in infants of diabetic mothers. Most cases of FHUFS have been sporadic, although a few cases of Mendelian inheritance have been reported.

The key features of this condition are bilateral and often asymmetric focal femoral hypoplasia and facial dysmorphism, the latter ranging from evident

Table 1 Time of diagnosis and ultrasound and pathological findings in fetuses diagnosed with femoral hypoplasia–unusual facies syndrome

		Ultrasound findings					
Reference	*GA (weeks)*	*Femoral hypoplasia or aplasia*	*Hypoplasia or aplasia of other bones*	*Facial signs*	*Other anomalies*	*Additional major findings at necropsy*	*Time of diagnosis*
Tadmor *et al.*[4]	32	+	+	CLP	–	–	Prospective
Robinow *et al.*[5]	25	+	–	Micrognathia	–	–	Prospective
Campbell and Vujanic[6]	19	+	–	–	–	Micrognathia, cleft palate, unilateral pelvic kidney	Necropsy
Urban *et al.*[7]	21	+	+	–	–	Micrognathia, cleft palate, abnormal spine segmentation, unilateral renal agenesis	Necropsy
Gillerot *et al.*[3]	25	+	–	–	–	Micrognathia, cleft palate, distal arthrogryposis, hemivertebra, brain heterotopia, partial ACC	Necropsy
Filly *et al.*[8]	20	+	–	–	Clubfeet	Micrognathia, depressed nasal bridge	Necropsy
This study							
Case 1	21	+	–	CLP, micrognathia	Unilateral renal agenesis	Long philtrum, thin upper lip, upslanting palpebral fissures	Prospective
Case 2	21	+	–	Micrognathia	–	Cleft palate, mandibular asymmetry, long philtrum, thin upper lip, low-set ears	Prospective
Case 3	13	+	–	Micrognathia?	–	Micrognathia	Prospective

ACC, agenesis of the corpus callosum; CLP, cleft lip/palate; GA, gestational age.

micrognathia/cleft lip and palate to more subtle features such as upslanting palpebral fissures, short nose with broad tip, long philtrum, thin upper lip, maxillary asymmetry and isolated cleft palate (Figures 1e and 2d). A number of additional malformations have been described occasionally in neonates with FHUFS, including lumbar spine and pelvic abnormalities, absence or hypoplasia of the fibulae, talipes and genitourinary anomalies[2]. Furthermore, severe central nervous system (CNS) malformations have been reported in neonates with fatal FHUFS, including brain heterotopia, agenesis of the corpus callosum and ventriculomegaly[3]. It can therefore be said that there is moderate variation in the phenotypic expression of FHUFS, with occasional reporting of associated CNS and spinal anomalies.

Prenatal ultrasound diagnosis of FHUFS is feasible given that its most consistently reported findings, namely femoral hypoplasia and major facial anomalies, can be recognized *in utero*. However, a prospective diagnosis of FHUFS, based upon the concurrent detection of femoral and facial anomalies, has been reported in very few cases[4,5]; in most published reports the diagnosis was made at autopsy following prenatal diagnosis of the focal femoral defect only (Table 1)[3,6–8]. This is probably because prenatal recognition of the femoral defect, unlike facial anomalies, is relatively straightforward on ultrasound examination. In addition, it should be noted that it is the facial dysmorphisms, although subtle in some cases, that need be recognized to support a prospective diagnosis of FHUFS in the fetus. In fact, the focal femoral defect can occur as an isolated anomaly or represent one of multiple abnormalities characteristic of a number of rare disorders, such as caudal regression sequence, camptomelic dysplasia, Antley–Bixler syndrome and kyphomelic dysplasia[9]. The differential diagnosis of these pathologic entities may present some difficulties. However, in focal femoral hypoplasia the skeletal anomaly is not associated with any malformation of the craniofacial area, whereas in FHUFS micrognathia and/or cleftings are frequently present and recognizable *in utero* (Figures 1d and 2c). As for caudal regression sequence, which is also associated with maternal insulin-dependent diabetes and fetal urogenital abnormalities, a major lower spinal defect is usually present at the same time, which is extremely rare in FHUFS[10]. Camptomelic dysplasia is characterized by bowed and moderately short (rather than severely hypoplastic) femora and tibiae, scapular hypoplasia, micrognathia and sex reversal in males[10]. Antley–Bixler syndrome features multiple synostoses, in addition to bowed long bones[9,10]. Finally, the autosomal recessive disorder kyphomelic dysplasia is characterized by symmetrically hypoplastic and bowed femora and micrognathia[9]; we consider this to be the only condition that may be difficult to distinguish from FHUFS prenatally.

In view of the differential diagnosis described above, we believe that, for a prospective prenatal diagnosis of

FHUFS, at least one other major anomaly of the skeletal or craniofacial region should be detected in addition to focal femoral hypoplasia. If a third malformation is also found, such as unilateral renal agenesis or a spinal or CNS anomaly, then the diagnosis is virtually certain. Despite this relatively simple diagnostic algorithm, only two prospective diagnoses of FHUFS in the fetus have been described to date (Table 1)[4,5]. Here we report another three cases detected at 21, 21 and 13 weeks' gestation, in which the facial features were carefully sought following the detection of the femoral defect. This report demonstrates that prenatal diagnosis of FHUFS is feasible with a high degree of accuracy if expert ultrasound examination is performed. To the best of our knowledge, the case detected at 13 weeks' gestation represents the earliest prenatal diagnosis of FHUFS and the first with three-dimensional imaging.

Regarding three-dimensional ultrasound examination, this approach is of no additional value in the diagnosis of femoral hypoplasia, which is easily detected on two-dimensional ultrasonography (Figures 1a and b, 2a and 3a). However, it can be speculated that its use might enhance the diagnostic capability of ultrasound in relation to minor facial dysmorphisms, such as upslanting palpebral fissures and, especially, nasal dysmorphisms including short nose with broad tip, long philtrum and thin upper lip. We were not able to provide evidence to support this hypothesis because the index fetus examined with three-dimensional ultrasonography was at a very early gestational age (13 weeks); at this early age, the fine facial features are not fully developed and thus the capacity of ultrasound to detect these subtle features is less than that at 20 weeks' gestation. However, despite these limitations, moderate micrognathia was apparent on the three-dimensional surface-rendered image (Figure 3b).

Another important consideration is that the development of femoral hypoplasia may also occur relatively late, although this bizarre finding was reported in only one case. In this case, described by Tadmor *et al.*[4], long bone biometry was unremarkable at scans performed at 19 and 24 weeks' gestation, with facial clefting and shortness of the humeri and femora identified at 32 weeks. At this gestational age, the femur length was described to be at the 50th centile for 24 weeks' gestation. Follow-up examinations at 34 and 37 weeks' gestation showed resumption of normal femoral growth, suggesting that an *in-utero* insult leading to a transient arrest of femoral growth had occurred after the 24th gestational week[4].

Finally, as far as terminology is concerned, we agree with Tadmor *et al.*[4] and Urban *et al.*[7], who suggested that FHUFS should be considered as an association of malformations rather than a syndrome because of the wide range of anomalies observed (Table 1). Generally, the definition of an association is the idiopathic occurrence of multiple congenital anomalies during blastogenesis[11], whereas a syndrome is characterized by a cluster of malformations that are known or causally related[12].

In conclusion, we believe that the diagnosis of FHUFS can be reliably established prenatally if at least one major skeletal or craniofacial anomaly is found in addition to asymmetric femoral hypoplasia. Other associated anomalies amenable to ultrasound diagnosis include major CNS (agenesis of the corpus callosum, hydrocephaly), spinal (hemivertebra) and renal (unilateral agenesis) malformations.

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