Electronic letter

A new case of exomphalos, short limbs, and macrogonadism syndrome

EDITOR—A novel lethal syndrome of exomphalos, short limbs, macrogonadism, enlarged and irregular metaphyses, and dysmorphic features has been recently described in fetuses.¹ Interestingly, in all cases, histological examination showed diffuse endocrine hyperplasia, suggesting overlap with Beckwith-Wiedemann syndrome. Here we report a new case of this lethal syndrome in a male fetus diagnosed at 17 weeks of gestation.

The mother, gravida 1, para 0, was first referred at 12 weeks of gestation after ultrasound detection of a large exomphalos. The family history was unremarkable apart from paternal sterility and the pregnancy was achieved with ICSI. A new ultrasound survey performed at 17 weeks showed fetal macrosomy with short limbs, an enlarged hyperechogenic pancreas, and dysplastic kidneys in addition to exomphalos. Amniotic cell karyotype was normal (46,XY). Because Beckwith-Wiedemann syndrome was suspected, *in situ* hybridisation was performed and ruled out a rearrangement of chromosome 11p15 using the telomeric probe (D11S2071, Cytocell). At 22 weeks 5 days, ultrasound survey detected hydramnios, short limbs (below the 3rd centile), and macrogonadism. The pregnancy was terminated at 23 weeks 5 days.

At necropsy, the male fetus had normal weight (695 g), height (vertex-heel length 30 cm), and head circumference (30 cm) for gestational age. Macroscopic examination showed exomphalos (length 5 cm, width 3.7 cm), thoracic and nuchal effusion, and short limbs (fig 1A). Dysmorphic features were noted, namely depressed nasal bridge with anteverted nostrils, infraorbital folds, midface protrusion, long philtrum, large mouth, low set and dysplastic ears, and micrognathia (fig 1B, C). The hands and feet appeared small with a simple palmar crease on the left palm. Organomegaly was noted with enlarged pancreas, kidneys, adrenals, and testes while the lungs were significantly hypoplastic (fig 1D). *X* rays showed short long bones with enlarged and irregular metaphyses and iliac bone spicules (fig 1E). Histological examination showed adrenal cytomegaly, Leydig cell hyperplasia, renal microcysts with medullary fibrosis, and pancreatic fibrosis with Langerhans islet cell enlargement. Finally, cerebral examination showed mild vermis hypoplasia and irregular ossification of the endochondral junction was also noted.

A new case of exomphalos, short limbs, and macrogonadism syndrome is reported. As in the seven previously described cases,¹ the fetus presented with endocrine hyperplasia and enlarged and irregular metaphyses with spicules. Dysmorphic features were similar, including a depressed nasal bridge with anteverted nostrils, long philtrum, large mouth, and low set ears. As in both fetuses of family 3 in the first report, mild cerebellar hypoplasia was noted, suggesting that this anomaly could be regarded as a part of the syndrome. Conversely, as opposed to the seven previous cases, nuchal web was not observed and only mild thoracic and nuchal effusions were reported at necropsy.

According to the originally reported pedigrees, this syndrome is thought to follow an autosomal recessive mode of

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Figure 1 The male fetus at 23 weeks 5 days. Note (A) exomphalos and short limbs, (B, C) facial dysmorphism consisting of midface protrusion, depressed nasal bridge, long philtrum, large mouth, micrognathia, and low set and dysplastic ears, (D) enlarged testes (arrow), (E) iliac bone spicules and irregular metaphyses.

inheritance as the family history of the seven cases was unremarkable and both female and male fetuses were affected. However, a strikingly unbalanced sex ratio in favour of males was clearly observed (seven males and one female including this report). Several different hypotheses could explain such a skewed sex ratio. First, macrogonadism can easily be misdiagnosed in female fetuses since the ovaries are difficult to study by prenatal ultrasound. Second, the penetrance of this syndrome could be different between males and females, mimicking X linked recessive

inheritance. In such a situation, the skewed sex ratio might be suggestive of X linkage because the females would be very mildly affected and misdiagnosed while the males would have severe morbidity and high mortality. Indeed, the high frequency of spontaneous abortions reported in the first article (3/6 pregnancies in family 1 and 2/5 pregnancies in family 2) could be the result of male lethality in early pregnancy. In addition, the female fetus reported to be as severely affected as both her two brothers and the other male fetuses in the series could be accounted for by skewed X inactivation. Unfortunately, the methylation status of each X chromosome was not analysed in this case and asymmetrical skewing responsible for the full blown syndrome in a female fetus could not be excluded.

At present, even though exomphalos, short limbs, and macrogonadism syndrome could still be regarded as an autosomal recessive disorder, genetic counselling should be cautious because X linked recessive inheritance could not be formally excluded. Therefore, it is important that more cases with features suggestive of this syndrome are reported to elucidate the mode of inheritance of this syndrome.

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