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

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Abstract

We report a new lethal multiple congenital abnormality (MCA) syndrome of exomphalos, short limbs, nuchal web, macrogonadism, and facial dysmorphism in seven fetuses (six males and one female) belonging to three unrelated families. *X* rays showed enlarged and irregular metaphyses with a heterogeneous pattern of mineralisation of the long bones. Pathological examination showed adrenal cytomegaly, hyperplasia of Leydig cells, ovarian stroma cells, and Langherans cells, and renal microcysts. We suggest that this condition is a new autosomal recessive MCA syndrome different from Beckwith-Wiedemann syndrome, especially as no infracytogenetic deletion or uniparental disomy of chromosome 11 was found.
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Keywords: MCA syndrome; exomphalos; short limbs; abnormal metaphyses

Exomphalos is a defect in the ventral abdominal wall with herniation of the abdominal viscera through a widened umbilical ring covered by a sac consisting of amnion and lined by peritoneum. The incidence of exomphalos is about 2.5 per 10 000 live births.[1] It can be found in several multiple congenital abnormality (MCA) syndromes. The best known and documented syndrome including exomphalos associated with other abnormalities is the Beckwith-Wiedemann syndrome. Here we report on seven fetuses with a novel MCA syndrome consisting of exomphalos, short limbs with uncommon metaphyseal abnormalities, and macrogonadism, and we particularly emphasise the clinical differences between this syndrome and the Beckwith-Wiedemann syndrome.

Case reports (table 1, fig 1)

FAMILY 1

Two unrelated white parents aged 26 and 24 years were referred because of a recurrent MCA syndrome during the fifth and sixth pregnancy. The first three pregnancies were spontaneously aborted at 6, 6, and 13 weeks of gestation respectively and a healthy boy was born after the fourth pregnancy (fig 1).

The sixth pregnancy was terminated at 17 weeks shortly after ultrasound showed exomphalos and hyperechogenic kidneys in a male fetus. *X* ray examination showed short long bones, enlarged metaphyses with irregular demineralisation, thin ribs, a cleft vertebra (L4), striped ribs, and bone maturation delay. At necropsy, the weight was normal for age (17 weeks, 240 g) but length (18 cm) and head circumference (13 cm) were consistent with a 15.5 week fetus. General examination showed a 18 mm exomphalos, short limbs, hypoplastic penis with balanic hypospadias, nuchal web, and facial dysmorphism including retrognathia with midface protrusion, low set ears, and a

Table 1 Clinical features of the exomphalos-short limbs-macrogonadism syndrome

	Family 1		*Family 2*			*Family 3*		
	Fetus 1	*Fetus 2*	*Fetus 1*	*Fetus 2*	*Fetus 3*	*Fetus 1*	*Fetus 2*	*Total*
Age at diagnosis (wk)	16.5	16	16	14	16	9	13	9–16.5 wk
Age at examination (wk)	17	17	24	15	17	15.5	14	14–24 wk
Spontaneous death	–	–	+	+	–	–	–	2/7
Sex	M	M	M	F	M	M	M	6M/1F
Exomphalos	+	+	+	+	+	+	+	7/7
Short limbs	+	+	+	+	+	+	+	7/7
Irregular metaphyses	+	+	+	+	+	+	+	7/7
Nuchal web	+	+	+	+	+	Hygroma	Hygroma	7/7
Facial dysmorphism	+	+	+	+	+	+	+	7/7
Macrogonadism	+	+	?	+	+	+	+	6/6
Gonadal cell hyperplasia	+	+	?	+	+	+	+	6/6
Adrenal cytomegaly	+	+	–	+	+	+	+	6/7
Langherans cell hyperplasia	–	–	–	+	+	+	+	4/7
Abnormal kidneys	+	+	–	+	+	–	–	4/7
Associated malformations	Common mesentery Meckel diverticulum Hypoplastic penis Balanic hypospadias	Caudal appendix Cleft palate Vertebral abnormalities	Toe abnormalities	Hemiuterus Ear creases	Lung hypoplasia	Microgyria Cerebellar hypoplasia Large fontanelles	Microgyria Cerebellar hypoplasia Large fontanelles	

wk = weeks of gestation.

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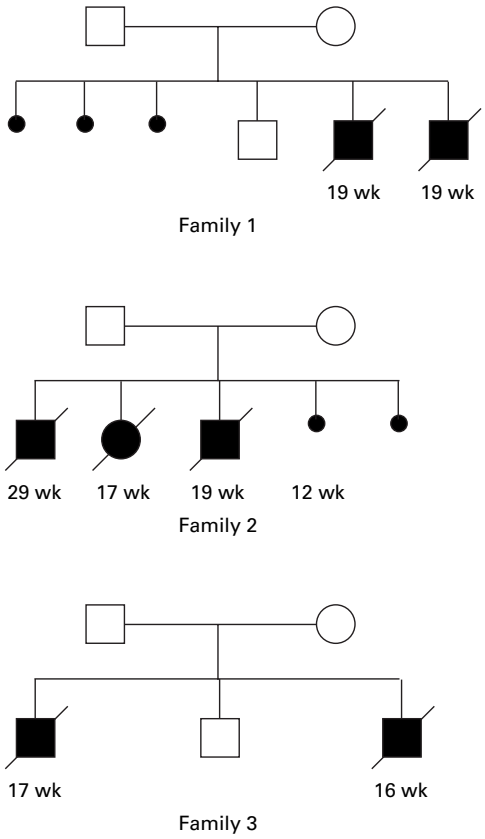

Figure 1 Pedigrees of the three families included in this study.

prominent nasal bridge. The exomphalos contained small intestine, common mesentery with Meckel diverticulum, and a small thymus. The right heart cavity was smaller than the left. Enlarged para-adrenal paraganglia and testes were noted. No cerebral abnormality was observed. Histological examination showed adrenal cytomegaly, Leydig cell hyperplasia, renal microcysts, and pancreatic fibrosis with enlargement of the endocrine glands. The post mortem fetal karyotype was normal. No genetic counselling could be given but a careful ultrasound survey was offered for the next pregnancy.

The pregnancy of fetus 2 was terminated when recurrence of a large exomphalos and short limbs was noted at 17 weeks. At necropsy, the fetus (weight 260 g, vertex-heel length 21.5 cm, head circumference 16.5 cm) was a male with exomphalos, short limbs, caudal appendix, nuchal web, and facial dysmorphism including brachycephaly, ocular hypertelorism, bilateral cleft palate, long philtrum, large upper lip, thick gums, labiogingival frenulum, anteverted nostrils, micrognathia, and low ears with an irregular helix (fig 2, A1, A2, A3). There was no visceromegaly except for enlarged testes (6 mm). Radiological examination showed short limbs (below the 10th centile) with irregular mineralisation, abnormal posterior vertebrae (D12 and L1) and cleft vertebrae (L2 and L4), and striped ribs (fig 3A). Histological examination showed adrenal cytomegaly, Leydig cell hyperplasia, medullary kidney microcysts, mild periductal pancreatic fibrosis, and mild portal fibrosis (fig 4). Post mortem fetal karyotype was normal (table 1).

FAMILY 2

Fetus 1 died in utero at 24 weeks of the first pregnancy of unrelated white parents (aged 28 and 32 years). Ultrasound performed eight weeks earlier had detected an exomphalos with short limbs and hydramnios. *X* rays showed enlarged and irregular metaphyses. At necropsy, the male fetus had a weight at the upper limit (980 g) and normal height for age (vertex-heel length 33 cm). Exomphalos, short limbs, superposition of the fourth and fifth toes, nuchal web, and facial dysmorphism (difficult to describe because of maceration) were noted. No organomegaly was noted, the testes were not measured, and only an incomplete histological examination was performed. Amniotic cell karyotype was normal.

Fetus 2 was spontaneously aborted at 15 weeks. Ultrasound performed one week before showed an exomphalos, short femora, enlarged and hyperechogenic kidneys, nuchal web, and thick placenta. *X* rays showed short proximal long bones with irregular, enlarged metaphyses (fig 3B). At necropsy, the fetus was a female of low weight for age (97 g) but other parameters

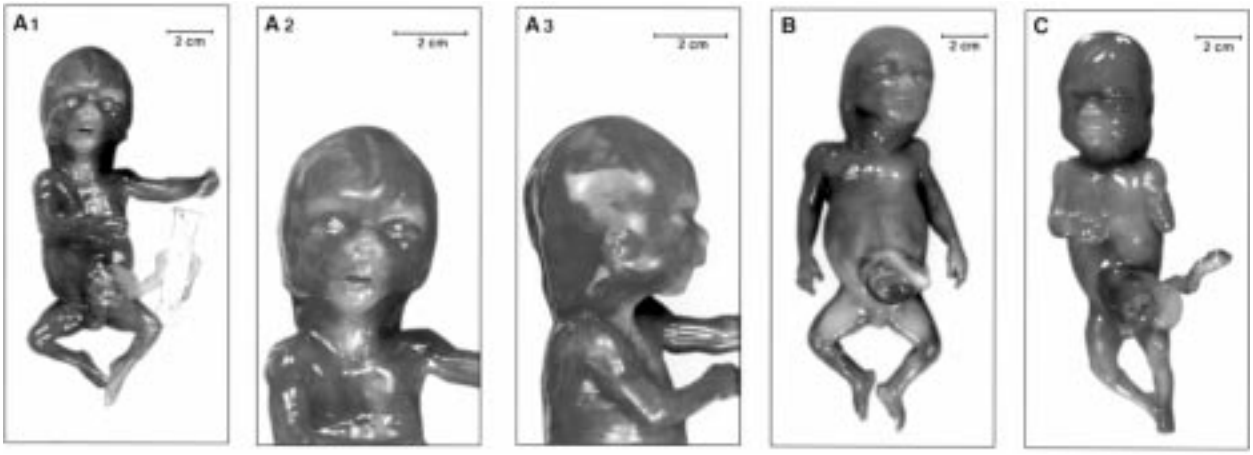

Figure 2 Pictures of the fetuses after termination of pregnancy. (A1-3) Fetus 2, family 1. (B) Fetus 2, family 2. (C) Fetus 1, family 3. Note exomphalos, short limbs, nuchal web, and facial dysmorphism including hypertelorism, depressed nasal bridge, anteverted nostrils, long philtrum, large mouth, micrognathia, and low set ears.

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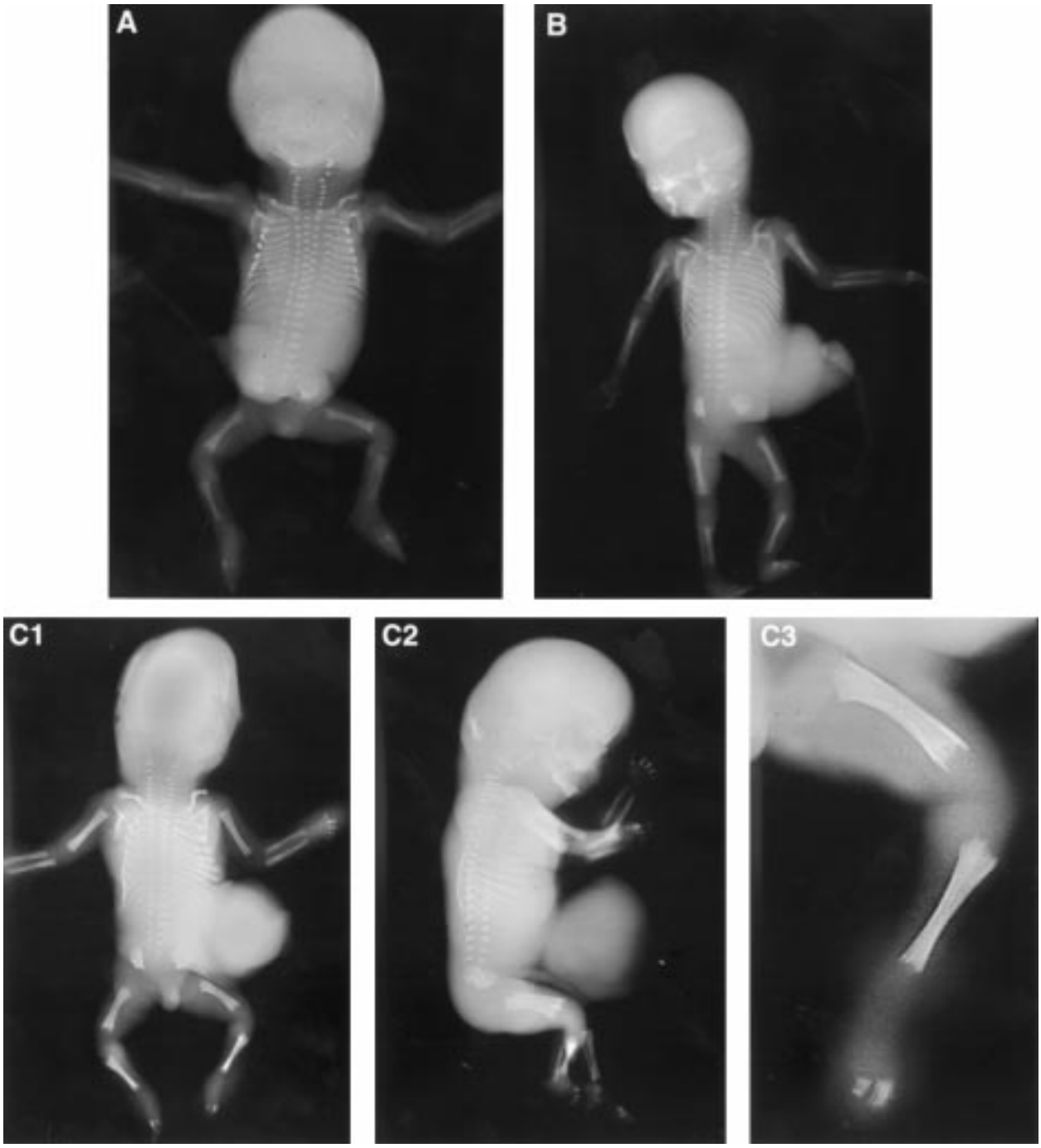

Figure 3 X rays in the three families. (A) Family 1, fetus 2. (B) Family 2, fetus 2. (C1-3) Family 3, fetus 1. The long bones are short with enlarged and irregular metaphyses. Note the cupula deformation with spicules and irregular pattern of mineralisation.

were normal (vertex-heel length 16 cm). General examination showed exomphalos, nuchal web, and facial dysmorphism including protruding eyeballs with an infraorbital fold and a bilateral ear crease (fig 2B). Visceral examination showed a hemiuterus with enlarged ovaries and histological evidence of adrenal cytomegaly, ovarian stroma cell hyperplasia, Langherans islet cell hyperplasia, and tubular kidney dilatation. Amniotic cell karyotype was normal. The diagnosis of Beckwith-Wiedemann syndrome was considered and ultrasound survey was offered for the next pregnancy.

The third pregnancy was terminated at 17 weeks, after ultrasound detection of an exomphalos with short limbs (below the 3rd centile), macrosomia, nuchal web, hyperechogenic kidneys, enlarged adrenals, enlarged hyperechogenic pancreas, and an unusual profile. Amniotic cell karyotype was normal and *x* rays showed irregular metaphyses. At necropsy, the fetus was a male (weight 320 g, vertex-heel length 24.5 cm) with enlarged adrenals, kidneys, and testes, normal pancreas, and small lungs and spleen. Histological examination showed adrenal cytomegaly, Leydig cell hyper-

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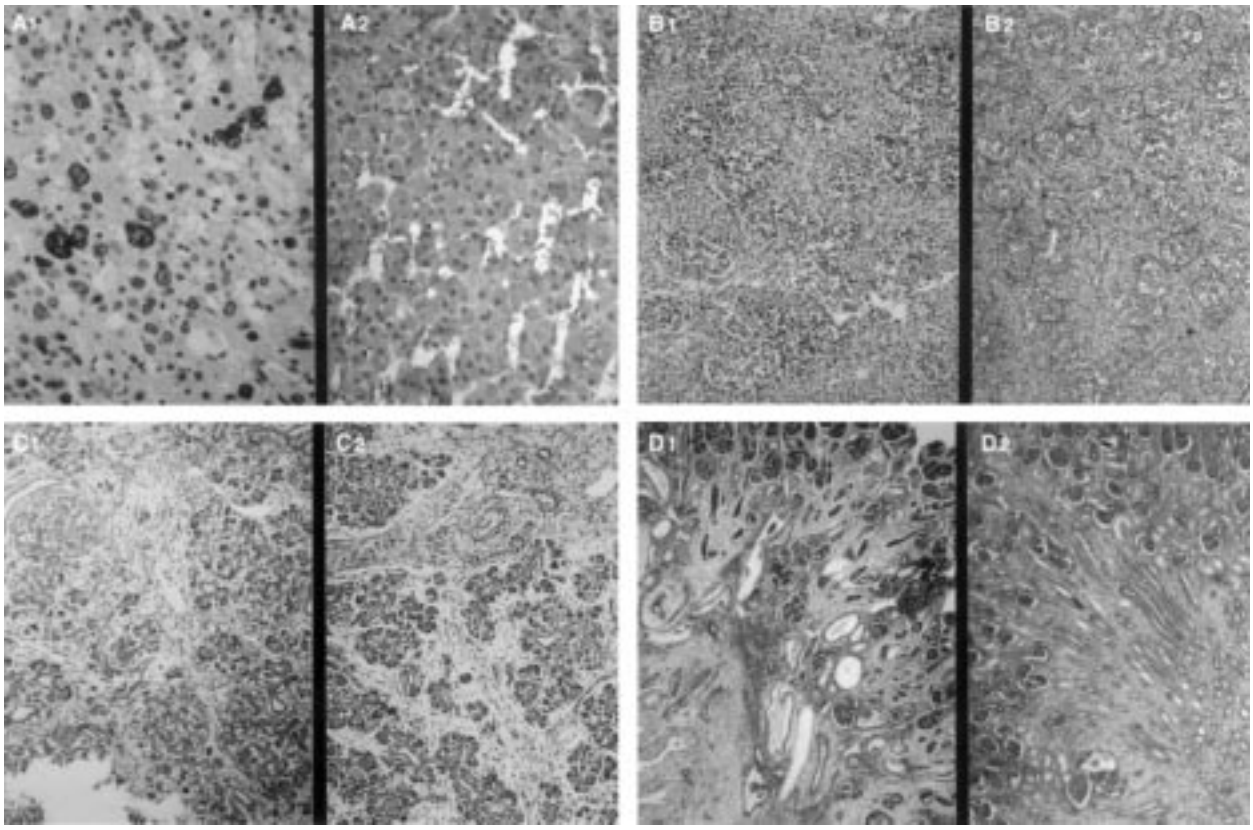

Figure 4 Pathological changes observed in the exomphalos-short limbs-macrogonadism syndrome (fetus 2, family 1). (A) Adrenal cytomegaly (A1) as compared to control (A2). (B) Leydig cell hyperplasia (B1) as compared to control (B2). (C) Langherans islet hyperplasia (C1) as compared to control (C2). (D) Renal microcysts (D1) as compared to control (D2).

plasia, Langherans islet cell hyperplasia, and medullary renal microcysts. Because Beckwith-Wiedemann syndrome was considered, cytogenetic investigations were performed and ruled out a rearrangement or uniparental disomy of chromosome 11.

The fourth pregnancy resulted in a spontaneous abortion at 10.5 weeks shortly after ultrasound detection of hydramnios with cystic hygroma. During the fifth pregnancy, a spontaneous abortion occurred at 6 weeks and histological examination showed oedematous and invaginated chorionic villosities.

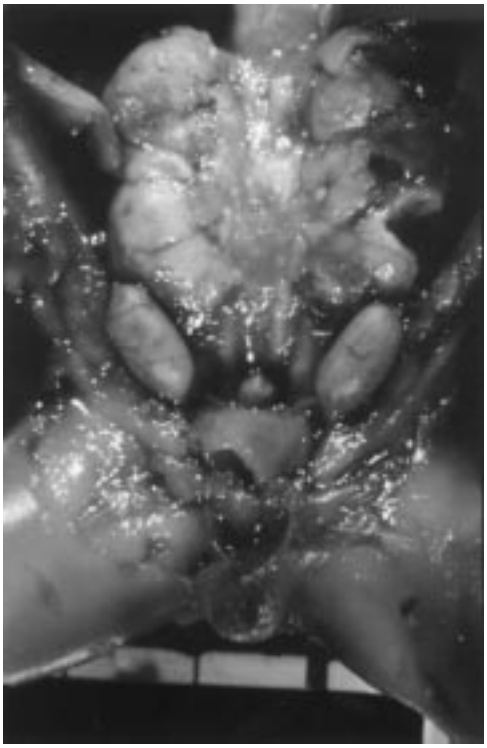

Figure 5 Macrogonadism in family 3 (fetus 1).

FAMILY 3

The first pregnancy of healthy, unrelated parents was terminated at 15.5 weeks following the discovery of a major exomphalos (11 weeks) followed by hydrops fetalis, short limbs, and cerebellar agenesis (15 weeks). Amniotic cell karyotype was normal and *x* rays showed short femora with irregular metaphyses (fig 3C). At necropsy, the male fetus (weight 177 g, vertex-heel length 17.5 cm, head circumference 12.5 cm) had exomphalos, diffuse oedema, nuchal web, large fontanelles, and facial dysmorphism including ocular hypertelorism, depressed nasal bridge with anteverted nostrils, a long philtrum, a large mouth, and low set ears (fig 2C). Pathological examination showed enlarged testes (fig 5), cerebellar agenesis, and microgyria, and histological evidence of adrenal cytomegaly, Leydig cell hyperplasia, Langherans islet cell hyperplasia, and irregular ossification of the endochondral junction.

The third pregnancy was terminated at 14 weeks following detection of exomphalos, short limbs, and cerebellar hypoplasia. *X* rays showed short long bones with irregular meta-

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Table 2 Syndromes with exomphalos as a frequent or occasional symptom

	Syndrome	Clinical features	Causation
Frequent symptom	BWS[3]	Anterior abdominal wall defects, macroglossia, pre- or postnatal overgrowth, ear crease or pits, facial naevus flammeus, hypoglycaemia, nephromegaly, hemihypertrophy	Sporadic, AD, uniparental isodisomy
	OEIS[4]	Omphalocele, exstrophy of the bladder, imperforate anus, spinal defect	Sporadic
	Shprintzen-omphalocele[5]	Omphalocele, pharynx and larynx hypoplasia, learning disability, dysmorphic facies, scoliosis	AD
	Omphalocele-cleft palate[6]	Omphalocele, posterior cleft palate, genital abnormalities	AR
	Simpson-Golabi-Behmel[7]	Omphalocele, pre- and postnatal overgrowth, postaxial polydactyly, hepatosplenomegaly, cystic kidney dysplasia, coarse facies, macroglossia	XLR
	Trisomy 13[8]	Holoprosencephaly, cleft lip and palate, polydactyly, scalp defects, rocker bottom feet	De novo or translocation
	Trisomy 18[8]	Clenched hand, short sternum, low arch dermal ridge patterning on fingertips	De novo
	Triploidy[8]	Lethality, syndactyly, body asymmetry, pigmentation abnormalities, facial dysmorphism	De novo
Occasional symptom	Marshall-Smith[9]	Increased length and bone age at birth, failure to thrive, mental retardation, facial dysmorphism, broad proximal and middle phalanges	Uncertain
	Elejalde[10]	Macrosomia, swollen globular body, short limbs, polydactyly, craniosynostosis, acrocephaly	AR
	Boomerang dysplasia[11]	Dwarfism with bowed limbs, characteristic facies	AR
	Beemer short rib[12]	Narrow thorax, cleft lip, cardiac defects, micropenis, renal cysts	AR
	Melnick-Needles[13]	Prominent eyes, bowing of long bones, ribbon-like ribs	XLR
	CHARGE[14]	Coloboma, heart defect, atresia choanae, growth deficiency, mental deficiency, genital hypoplasia, ears anomalies/deafness	Sporadic

Table 3 Incidence of clinical symptomes in the exomphalos-short limbs-macrogonadism syndrome as compared to Beckwith-Wiedemann syndrome

	Exomphalos-short limbs-macrogonadism syndrome (this study)	Beckwith-Wiedemann syndrome (Elliott et al[3])
Exomphalos	7/7 (100%)	60%
Macrosomia	4/7 (57%)	87%
Macroglossia	0/7 (0%)	99%
Ear abnormalities	1/7 (14%)	75%
Kidney abnormalities	4/7 (57%)	62%
Adrenal cytomegaly	6/7 (85%)	Frequent
Langherans cell hyperplasia	4/7 (57%)	Classical
Macrogonadism	6/6 (100%)	Possible
Short limbs	7/7 (100%)	0%
Nuchal web	7/7 (100%)	0%
Sex ratio	6/1	1.1/1

physes. At necropsy, the male fetus (weight 135 g, length 17.5 cm, head circumference 13 cm) had exomphalos, diffuse oedema, short limbs, facial dysmorphism similar to the previous fetus, and enlarged testes, kidneys, and adrenals. Pathological anomalies were similar to those of the previous fetus.

Discussion

Here we report the association of exomphalos, short limbs, and macrogonadism in seven fetuses belonging to three unrelated families. Other common features included nuchal web, facial dysmorphism (depressed nasal bridge with anteverted nostrils, long philtrum, large mouth, low set ears), enlarged and irregular metaphyses, and a heterogeneous pattern of mineralisation of long bones. Histopathological examination showed adrenal cytomegaly, hyperplasia of ovarian stroma cells, Leydig cells, and Langherans cells, and renal microcysts. The high rate of lethality (2/7 fetuses) and spontaneous abortions in the reported families (6/15 pregnancies) support the view that this new syndrome is a consistently fatal condition.

Exomphalos, the major feature of the syndrome, is frequently associated with other malformations (40-88%),[2] such as heart malformations or neural tube defects, and conversely, a number of malformation syndromes involve exomphalos (table 2). The most common among them, Beckwith-Wiedemann syndrome (BWS), includes exomphalos in 60% of cases and 3% of cases of exomphalos are BWS.[15]

It is interesting to note that in addition to exomphalos, the syndrome reported here shares several features with BWS, namely adrenal cytomegaly, Leydig cell or ovarian stroma cell hyperplasia, Langherans cell hyperplasia, and kidney abnormalities. Absent macroglossia and inconstant macrosomia are not sufficient to exclude BWS as these features are known to occur at the end of the third trimester in BWS.[16–21] Yet we believe that the exomphalos-short limbs-macrogonadism syndrome and BWS are indeed two different entities for several reasons (table 3). First, short limbs with irregular metaphyses and nuchal web are not observed in BWS. Second, macrogonadism is an inconstant feature in BWS and is not an inclusion criteria. Third, familial segregation of the disease is suggestive of autosomal recessive inheritance, which is not the case in BWS. Fourth, prenatal death or spontaneous abortion are not common in BWS. Linkage studies to exclude the BWS locus were considered but were not possible because of the lack of usable material.

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Similarly, we believe that the exomphalos-short limbs-macrogonadism syndrome is distinct from Simpson-Golabi-Behmel and Perlman syndromes.[7 22] While kidney abnormalities and Langherans islet cell hyperplasia are common in the three conditions, no polydactyly, macrocephaly, hepatosplenomegaly, or renal hamartomata were described in our series. Conversely, no patients with Perlman syndrome and Simpson-Golabi-Behmel syndrome have been reported with short limbs, metaphyseal changes, macrogonadism, or nuchal web.

Metaphyseal changes are characteristic features of the disease. Metaphyses are enlarged and irregular, with cupula deformation, spicules, and an irregular pattern of mineralisation. Limbs and long bones are short but not stubby. These features cannot be ascribed to any known chondrodysplasia. The chondrodysplasia Shiraz type and short rib syndrome Le Marec type or Verma-Naumoff type are well known lethal chondrodysplasias[23] that can possibly give rise to similar metaphyseal changes but none of the other features of the syndromes are present, and no short ribs or iliac bone or vertebral body abnormalities were present in the affected fetuses.

The recurrence of the disease in the offspring of healthy, unrelated parents supports the view that exomphalos-short limbs-macrogonadism syndrome is probably an autosomal recessive condition. Alternatively, the excess of affected subjects and the high frequency of spontaneous abortions in each sibship is also suggestive of an unbalanced cytogenetic event resulting from a balanced parental cytogenetic rearrangement. However, careful cytogenetic examination of the affected fetuses and their parents has not confirmed this hypothesis. Furthermore, X linked recessive inheritance is unlikely because the affected female was as severely affected as the male fetuses in family 2.

In conclusion, the lethal syndrome of exomphalos, short limbs, and macrogonadism reported here in seven fetuses appears to represents a novel condition different from Beckwith-Wiedemann syndrome. Future studies will hopefully help to refine the clinical profile and genetic basis of this hitherto unreported lethal condition.

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1 Curry CJ, Aonore L, Boyd E. The ventral wall of the trunk. In: Stevenson RE, Hall JG, Goodman RM, eds. *Human malformation and related anomalies.* Vol II. Oxford: Oxford University Press, 1993:879-82.
2 Kaplan MS, McGregor SN. Perinatal management of congenital diaphragmatic hernia and anterior abdominal wall defect. *Clin Perinatol* 1989;**16**:917.
3 Elliott M, Maher ER. Beckwith-Wiedemann syndrome. *J Med Genet* 1994;**31**:560-4.
4 Carey JC, Greenbaum B, Hall BD. The OEIS complex (omphalocele, exstrophy, imperforate anus, spinal defects). *Birth Defects* 1978;**6B**:253-63.
5 Shprintzen RJ, Goldberg RB. Dysmorphic facies, omphalocele, laryngeal and pharyngeal hypoplasia, spinal anomalies, and learning disabilities in a new dominant malformation syndrome. *Birth Defects* 1979;**5B**:347-53.
6 Czeizel A. New lethal omphalocele-cleft palate syndrome. *Hum Genet* 1983;**64**:99.
7 Verloes A, Massart B, Dehalleux I, Langhendries JP, Koulischer L. Clinical overlap of Beckwith-Wiedeman, Perlman, and Simpson-Golabi-Behmel syndromes: a diagnostic pitfall. *Clin Genet* 1995;**47**:257-62.
8 Benacerraf BR, Saltzman DH, Estroff JA, Frigoletto FD. Abnormal karyotype of fetuses with omphalocele: prediction based upon omphalocele contents. *Obstet Gynecol* 1990;**5**:317-19.
9 Charon A, Gillerot Y, Van Maldergem L, Van Schaftingen PH, de Bont B, Koulischer L. The Marshall-Smith syndrome. *Eur J Pediatr* 1990;**150**:54-5.
10 Thornton CM, Stewart F. Elejalde syndrome: a case report. *Am J Med Genet* 1997;**69**:406-8.
11 Winship I, Cremin B, Beighton P. Boomerang dysplasia. *Am J Med Genet* 1990;**36**:440-3.
12 Cideciyan D, Rodriguez MM, Haun RL, Abdenour GE, Bruce JH. New findings in short rib syndrome. *Am J Med Genet* 1993;**46**:255-9.
13 Von Oeyen P, Holmes LB, Trelstad RL, Griscom NT. Omphalocele and multiple severe congenital anomalies associated with osteodysplasty (Melnick-Needles syndrome). *Am J Med Genet* 1982;**13**:453-63.
14 Harvey AS, Leaper PM, Bankier A. CHARGE association: clinical manifestations and developmental outcome. *Am J Med Genet* 1991;**39**:48-55.
15 Baird PA, MacDonald CE. An epidemiologic study of congenital malformations of the anterior abdominal wall in more than a half million consecutive live births. *Am J Hum Genet* 1981;**33**:470-8.
16 Stratakis CA, Garnica A. Premature infant with Wiedeman-Beckwith syndrome: postnatal changes in facial appearance and somatic phenotype. *Am J Med Genet* 1995;**57**:635-6.
17 Lodeiro JG, Byers JW, Chuipek S, Feinstein SJ. Prenatal diagnosis and perinatal management of Wiedemann-Beckwith syndrome: a case and review. *Am J Perinatol* 1989;**6**:446-9.
18 Fremond B, Poulain P, Odent S, Milon J, Treguier C, Babut JM. Prenatal detection of a congenital pancreatic cyst and Beckwith-Wiedemann syndrome. *Prenat Diagn* 1997;**17**:276-80.
19 Shah YG, Metlay L. Prenatal ultrasound diagnosis of Beckwith-Wiedemann syndrome. *J Clin Ultrasound* 1990;**18**:597-600.
20 Takayama M, Soma H, Yaguchi S, *et al*. Abnormally large placenta associated with Beckwith-Wiedemann syndrome. *Gynecol Obstet Invest* 1986;**22**:165-8.
21 Viljoen DL, Jaquire Z, Woods DL. Prenatal diagnosis in autosomal dominant Beckwith-Wiedemann syndrome. *Prenat Diagn* 1991;**11**:167-75.
22 Neri G, Martini-Neri ME, Katz BE, Opitz BE. The Perlman syndrome: familial renal dysplasia with Wilms tumor, fetal gigantism and multiple congenital anomalies. *Am J Med Genet* 1984;**19**:195-207.
23 Spranger J, Maroteaux P. The lethal osteochondrodysplasias. In: Harris H, Hirschhorn K, eds. *Advances in human genetics*. New York: Plenum Press, 1990:38-52.

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