

SHORT COMMUNICATION

EXPECT THE WORSE OR HOPE FOR THE BEST? PRENATAL DIAGNOSIS OF GELEOPHYSIC DYSPLASIA

A. C. RENNIE^{1*}, G. STEWART², M. WHITEFORD³, T. JOHNSTON⁴ AND J. L. TOLMIE³

¹*Royal Hospital for Sick Children, Yorkhill, Glasgow, U.K.*

²*Royal Alexandra Hospital, Paisley, U.K.*

³*Duncan Guthrie Institute for Medical Genetics, Royal Hospital for Sick Children, Glasgow, U.K.*

⁴*Queen Mother's Hospital, Yorkhill, Glasgow, U.K.*

Received 20 January 1997

Revised 17 April 1997

Accepted 21 April 1997

SUMMARY

Geleophysic dysplasia is a rare, autosomal recessive disorder which causes disproportionate short stature associated with severe physical handicaps, but is compatible with survival into adulthood. We present a case, a first-born child, where genetic counselling difficulties arose following ultrasound recognition of short-limbed dwarfism in association with polyhydramnios and an initial incorrect prenatal diagnosis of lethal chondrodysplasia. After birth of the surviving affected infant, the parents had great difficulty accepting that there had been a prenatal misdiagnosis and they were greatly disappointed by our inability to predict the postnatal survival of an infant to whom no hope of life had previously been given. The correct diagnosis was not made until the proband was nearly 1 year old, and the true prognosis then became clearer. This experience underlines the relative ease of prenatal recognition of skeletal growth abnormalities compared with the considerable difficulties experienced in reaching a precise diagnosis. Thus, following prenatal diagnosis of unspecified chondrodysplasia when parents seek definite information about the prognosis, the temptation to be either overpessimistic or overoptimistic should be avoided.

© 1997 by John Wiley & Sons, Ltd.

Prenat. Diagn. 17: 1067–1070, 1997

No. of Figures: 2. No. of Tables: 0. No. of References: 12.

KEY WORDS: geleophysic dysplasia; chondrodysplasia; misdiagnosis

INTRODUCTION

Geleophysic dysplasia (MIM Catalogue Number 231050) is a rare, autosomal recessive inherited condition which causes short-limbed short stature in association with minor facial dysmorphism (sometimes giving an impression of happiness, *gelios*—happy; *physis*—nature) and accumulation of abnormal lysosomal storage

material. Only 22 cases have been reported world-wide. Unfortunately, the abnormal storage material sometimes infiltrates vital tissues including the heart valves and trachea, leading to heart failure and progressive respiratory distress, which can cause death in early childhood or teenage years (Vanace *et al.*, 1960).

In the absence of precise knowledge of the metabolic defect, prenatal biochemical diagnosis of geleophysic dysplasia is not possible but following the diagnosis of a first-born affected child, ultrasound prenatal diagnosis has been accomplished after 28 weeks of gestation, at which stage

*Correspondence to: Dr Alison C. Rennie, Paediatric Senior Registrar, Royal Hospital for Sick Children, Yorkhill NHS Trust, Glasgow G3 8SJ, U.K.

fetal limb shortening first becomes apparent (Rosser *et al.*, 1995). However, although prenatal recognition of chondrodysplasia is increasingly accomplished in cases *without* a family history, there often remains great difficulty in making a precise diagnosis (Rasmussen *et al.*, 1996). Most skeletal dysplasias that are diagnosed in pregnancies at low prior genetic risk are lethal in the new-born; thanatophoric dysplasia, lethal osteogenesis imperfecta, and campomelic dysplasia are lethal disorders which occur most commonly and are frequently associated with polyhydramnios (Rasmussen *et al.*, 1996). However, not all prenatal-presenting chondrodysplasias associated with polyhydramnios cause death in infancy, and the case of geleophysic dysplasia which we report highlights the genetic counselling difficulties which can arise when prognostication is attempted in the absence of a precise diagnosis.

CASE REPORT

Our patient, a male, was born at 33 weeks gestation by spontaneous vertex delivery to a 24-year-old para 0+0 mother. The parents were unrelated. Birth weight was 1.74 kg (tenth centile) and Apgar scores were 9 at 1 min and 10 at 5 min. His occipito frontal circumference was on the tenth centile and his length at 38 cm was below the third centile. At 29 weeks gestation the mother was thought to be clinically large for dates and a detailed ultrasound scan showed polyhydramnios and short long bones. She was referred to the Regional Fetal Medicine Unit, where the findings of gross polyhydramnios were confirmed. All long bones were less than the fifth centile but were normally shaped. Ossification appeared normal and no fractures were evident. The chest was of normal appearance and the thoracic circumference was within the normal range. The head shape was noted to be slightly unusual, but no other abnormality was seen. A prenatal X-ray was performed and was reported as normal, apart from slight shortening of the long bones only. The diagnosis of skeletal dysplasia was made and although a more accurate diagnosis was not possible, the presence of polyhydramnios was judged a very poor prognostic sign indicating a high likelihood of neonatal lethal chondrodysplasia being present.

Nevertheless, at delivery the baby was born in good condition with no active resuscitation required. He was noted to have a mildly dysmor-



Fig. 1—Typical facial appearance, short limbs, and spade-like hands and feet in geleophysic dysplasia

phic triangular face with wide eyes and a large posterior fontanelle. The limbs were short with small spade-like hands and feet (Fig. 1). Peripheral oedema was present. There was a reduced range of movements in some joints, with flexion of the fingers and toes. Systemic examination showed no other abnormalities with no hepatosplenomegaly.

Chromosome analysis of the patient and both parents showed a normal karyotype. Routine cardiological assessment showed mild branch pulmonary artery stenosis only. Long bone X-rays showed symmetrical shortening only, with no other dysplastic features.

The patient had an uneventful neonatal progress and was assessed by several specialists in genetics, endocrine and metabolic medicine; however, no definitive diagnosis could be reached. The parents found this uncertainty very difficult to come to terms with. The diagnosis of geleophysic dysplasia was finally made when the pictures of the 10-month-old affected infant were reviewed at a



Fig. 2—The patient at age 2. (Consent for the publication of photographs of our patient was obtained from his mother, who is his legal guardian)

meeting of the United Kingdom Dysmorphology Club.

The patient is now 2 years old and is making good developmental progress. Typical dysmorphic features persist (Fig. 2). He walks unaided and has good manual dexterity. Speech is slightly delayed and he attends a speech and language therapist. He has bronchospasm and is prone to recurrent chest infections, but remains well otherwise. His growth parameters remain below the third centiles with disproportionate length.

DISCUSSION

To date, there have been 22 reported cases of geleophysic dysplasia with only one other case report from the United Kingdom. In the original case report, geleophysic dysplasia was described as a focal mucopolysaccharidosis because mesenchymal changes in the skeleton and joints were

associated with focal accumulation of acid-mucopolysaccharides in hepatic and cardiac tissues (Spranger *et al.*, 1971). Follow-up of one of the original patients and description of autopsy findings in his sister indicated that progressive joint contractures and valvular heart disease were associated with intracellular lysosomal inclusions with the staining properties of neutral glycoprotein (Spranger *et al.*, 1984). Subsequent reports of cases lend evidence to support the notion that geleophysic dysplasia is a lysosomal storage disorder (Lipson *et al.*, 1987; Shohat *et al.*, 1990; Wraith *et al.*, 1990) and demonstration of storage vacuoles in chondrocytes and cultured skin fibroblasts implies a generalized defect (Pontz *et al.*, 1996).

The prognosis for patients with geleophysic dysplasia, as judged from the small number of reported cases, is not absolutely clear. Delays in early development are sometimes present (Spranger *et al.*, 1984), but intelligence is usually normal (Shohat *et al.*, 1990; Pontz *et al.*, 1996). Growth failure, which may have prenatal onset, becomes more obvious with age and post-pubertal heights of 140 and 150 cm are recorded (Shohat *et al.*, 1990). Affected siblings show phenotypic variation; for example, Koiffmann *et al.* (1984) reported the disorder in an 11-year-old Brazilian girl whose 'tiny' sister was probably affected, dying of heart failure at age 3 years. The younger sister of Spranger's index case, who was then age 12 years old, died at age 4 years of valvular heart disease and tracheal narrowing when anaesthesia was induced prior to cardiac surgery. Other children survive into adulthood with minimal cardiac involvement (Shohat *et al.*, 1990).

Given the prognostic difficulties in childhood which arise from variations in the phenotype of geleophysic dysplasia (and many other skeletal dysplasias), it is not surprising that there may be difficulties when judging the prognosis from non-specific prenatal ultrasound findings. However, experience with this case emphasizes that prenatal diagnosis of polyhydramnios with chondrodysplasia does not always herald a poor prospect for survival after birth. In their review of fetal imaging in skeletal dysplasia, Lachman and Rappaport (1990) suggest that thoracic cage measurement is important and that the finding of a tiny thoracic diameter strongly suggests a lethal disorder. In this case, the diameter was within normal limits and perhaps the prenatal advice should have been adjusted accordingly. Most interestingly, in an extensive review of errors in the prenatal diagnosis

of achondroplasia, Modaff *et al.* (1996) reported a similar experience in that for 37 infants with achondroplasia who had had prenatal ultrasound scanning, a confident and correct diagnosis could only be made in the presence of a positive family history. In 25 per cent of cases, an incorrect diagnosis of a lethal or very severe disorder was made and Modaff *et al.* (1996) commented that, in the face of uncertainty, physicians often elect to emphasize the most severe of alternative diagnoses.

In these circumstances, advice to parents following an unexpected prenatal diagnosis of chondroplasia should avoid causing unjustified distress through painting the blackest of pictures, whilst optimism should be tempered by emphasizing the range of prognoses applicable to what are essentially non-specific ultrasound findings. Parents should also be informed that even after birth and full investigation, a substantial proportion of skeletal dysplasias remain undiagnosed (Rasmussen *et al.*, 1996).

REFERENCES

- Koiffmann, C.P., Wajntal, A., Ursich, M.S., Plipo, A.A. (1984). Familial recurrence of geleophysic dysplasia, *Am. J. Med. Genet.*, **19**, 483–486.
- Lachman, R.S., Rappaport, V. (1990). Fetal imaging in skeletal dysplasias, *Clin. Perinat.*, **17**, 703–722.
- Lipson, A.H., Kan, A.E., Kozlowski, K. (1987). Geleophysic dysplasia—acromicric dysplasia with evidence of glycoprotein storage, *Am. J. Med. Genet. Suppl.*, **3**, 181–190.
- Modaff, P., Horton, V.K., Pauli, R.M. (1996). Errors in the prenatal diagnosis of children with achondroplasia, *Prenat. Diagn.*, **16**, 525–530.
- Pontz, B.F., Stöß, H., Henschke, F., Friesinger, P., Karbowski, A., Spranger, J. (1996). Clinical and ultrastructural findings in three patients with geleophysic dysplasia, *Am. J. Med. Genet.*, **63**, 50–54.
- Rasmussen, S.A., Bieber, F.R., Benacerraf, B.R., Lachman, R.S., Rimoin, D.L., Holmes, L.B. (1996). Epidemiology of osteochondrodysplasias: changing trends due to advances in prenatal diagnosis, *Am. J. Med. Genet.*, **61**, 49–58.
- Rosser, E.M., Wilkinson, A.R., Hurst, J.A., McGaughan, J.M., Donnai, D. (1995). Geleophysic dysplasia: a report of three affected boys—prenatal ultrasound does not detect recurrence, *Am. J. Med. Genet.*, **58**, 217–221.
- Shohat, M., Gruber, H.E., Pagon, R.A., Witcoff, L.J., Lachman, R., Ferry, D., Flaum, E., Rimoin, D.L. (1990). Geleophysic dysplasia: a storage disorder affecting the skin, bone, liver, heart and trachea, *J. Pediatr.*, **117**, 227–232.
- Spranger, J.W., Gilbert, E.F., Tuffli, G.A., Rossiter, F.P., Opitz, J.M. (1971). Geleophysic dwarfism—a 'focal' mucopolysaccharidosis?, *Lancet*, **2**, 97–98.
- Spranger, J., Gilbert, E.F., Arya, S., Hoganson, G.M.I., Opitz, J.M. (1984). Geleophysic dysplasia, *Am. J. Med. Genet.*, **19**, 487–499.
- Vanace, P.W., Friedman, S., Wagner, B.M. (1960). Mitral stenosis in an atypical case of gargoyism: a case with pathological and histochemical studies of the cardiac tissues, *Circulation*, **21**, 80–89.
- Wraith, J.E., Bankier, A., Chow, C.W., Danks, D.M., Sardharwalla, I.B. (1990). Geleophysic dysplasia, *Am. J. Med. Genet.*, **35**, 153–156.