PERSONAL PRACTICE

Skeletal dysplasias

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Making a diagnosis of a skeletal dysplasia on clinical grounds may be extremely easy but it may be so difficult that it is easy to miss. Table 1 shows the features that should alert the clinician to request a radiographic skeletal survey—the sine qua non of diagnosis. Failure to diagnose mild cases of the more common skeletal dysplasias leads clinicians to reassure patients incorrectly about their future growth prospects because usual prediction methods are not valid. Figure 1 shows the growth chart of such a patient.

Table 1 Indications for performing a radiographic skeletal survey

Disproportionate body segments for age and stage of puberty
Child with height prediction inappropriately short for the family, especially if growing at a normal rate
Unexpectedly poor response to usual doses of growth promoting agents (that is, resistance to a standard dose of growth hormone)
Absent puberty growth spurt
Short child with one (or more) very short parent, especially one with body disproportion
Otherwise unexplained short stature

Case report

A male patient was seen in hospital for advice about short stature at the age of 5.7 years. An adopted child, previous measurements suggested that he had grown at a normal rate since the end of the first year of life and his short stature with delayed bone age was attributed to a failure of the infantile curve of growth. Follow up showed evidence of a mid-childhood growth spurt and the start of pubertal growth around 11 years. He was discharged just before his 13th birthday as all appeared to be well but he was referred again at 14.5 years because he had not grown as predicted. Measurement revealed an inadequate puberty growth spurt in the legs, and skeletal radiography showed features characteristic of hypochondroplasia.

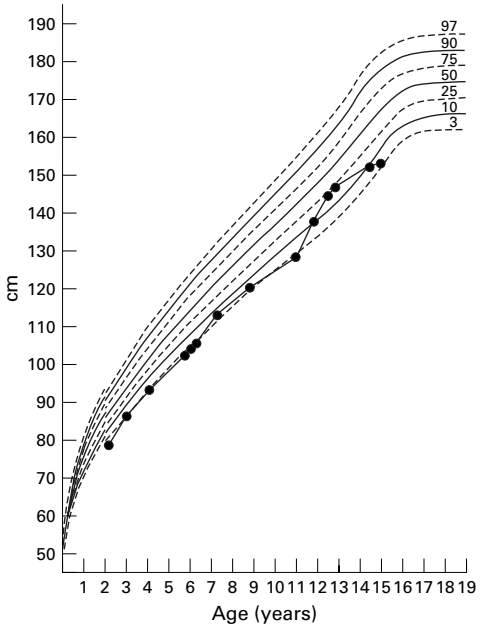

Figure 1 Growth chart of patient with missed diagnosis of hypochondroplasia.

Clinical suspicion

Some skeletal dysplasias are so severe that they are detected by ultrasound before birth. Most severe skeletal dysplasias, especially achondroplasia and conditions resembling achondroplasia, are easily seen in neonates. There may well be disproportion between crown–rump and overall lengths, and associated features, such as a large head and characteristic facies, will reinforce the clinical impression. The interpretation of skeletal radiographs at this age is not easy and, because the categorisation of skeletal dysplasias is important to determine outcome, caution should be exercised in offering a firm diagnosis and prognosis in the first year of life. A problem should be acknowledged but a firm diagnosis postponed until skeletal radiographic appearances in the early childhood years are available. Advances in the understanding of the molecular genetics of skeletal dysplasia may assist in early, possibly prenatal, diagnosis.

During infancy and early childhood, growth disorders associated with the more severe forms of skeletal dysplasia, such as achondroplasia and some forms of spondyloepiphyseal dysplasia, become more obvious. To make a diagnosis, a radiological skeletal survey including the films shown in table 2 is required. The measurement of body proportions may assist

Table 2 Radiographs essential for making a diagnosis of skeletal dysplasia

Postero-anterior and lateral chest
Antero-posterior abdomen to include pelvis
Antero-posterior femora to include knees
Postero-anterior hands
Lateral skull
Lateral lumbar spine

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Table 3 Clinical and molecular characteristics of bone dysplasias

Gene/protein family	*Presenting at*	*Major features*	*Inherited*	*Gene*
Fibroblast growth factor receptor 3 (FGFR3)				
Achondroplasia	Birth	Short limbs low nasal bridge prominent forehead	AD	FGFR3
Hypochondroplasia	Infancy/puberty	Short limbs near normal face	AD	FGFR3
Thanatophoric dysplasia	Birth (lethal)	Very short limbs low nasal bridge prominent forehead narrow chest short/trident hands craniosynostosis	AD	FGFR3
Collagen				
Achondrogenesis II/ hypochondrogenesis	Stillbirth/ neonatal death	Severe micromelia short trunk/neck protuberant abdomen	AD	COL2A1
Spondyloepiphyseal dysplasia congenita	Birth/infancy	Short trunk/lordosis myopia	AD	COL2A1
Kniest syndrome	Birth	Thick/stiff joints flat facies prominent eyes, myopia deafness, cleft palate	AD	COL2A1
Stickler dysplasia	Childhood/adult	Flat face severe myopia Pierre-Robin association	AD	COL2A1 COL11A2
Strudwick dysplasia	Birth	Short limbs severe scoliosis pectus carinatum	AD	COL2A1
Multiple epiphyseal dysplasia	Childhood/ adolescence	Short stature painful/stiff joints waddling gait	AD	COL9A2 COMP
Schmid metaphyseal dysplasia	Childhood	Short bowed limbs lumbar lordosis waddling gait	AD	COL10A1
Cartilage oligomeric matrix protein (COMP)				
Multiple epiphyseal dysplasia (see under collagen)				
Pseudoachondroplasia	Birth/childhood	Short limbs waddling gait lax joints normal face	AD/AR	COMP
Diastrophic dysplasia sulphate transporter (DTDST)				
Achondrogenesis IB	Stillbirth/ neonatal death	Severe micromelia low nasal bridge short neck/thorax protuberant abdomen	AR	DTDST
Atelosteogenesis II	Neonatal death	Severe micromelia short thorax bowed limbs/spine	AR	DTDST
Diastrophic dysplasia	Birth	Rhizomelic shortening swelling of ear hitchhiker thumbs narrow thorax	AR	DTDST
Parathyroid hormone, parathyroid hormone related peptide receptor (PTHrPR)				
Jansen metaphyseal dysplasia	Birth/infancy	Bowing long bones narrow thorax flexion joint deformity prominent eyes/micrognathia	AD	PTH-PTHrP

AD, autosomal dominant; AR, autosomal recessive.

but not necessarily—for example, it is only during the (failure of the) puberty growth spurt that short legs, characteristic of adults with lesser degrees of hypochondroplasia, become easily detectable.

Reporting skeletal radiographs is not easy, and few radiologists see sufficient numbers of such radiographs to give a reliable opinion. For some disorders it is possible to use molecular genetic methods to confirm a suspected diagnosis (table 3), but how best to investigate this aspect without screening the genome depends on clinical acumen. Thus, recognition of clinical and radiological features is the best that can be offered, but as the patient shown in fig 1 indicates, this is not easy.

Diagnosis

There are hundreds of skeletal dysplasias,[1] many of them very rare. Achondroplasia is reported to be the most common with an estimated frequency of 1/15 000–77 000 births,[2] but skeletal dysplasias with less severe phenotypes (for example, the milder end of the spectrum of hypochondroplasia) may go undiagnosed and be much more common. As diagnosis has prognostic and genetic implications, it is important that the clinician, geneticist, and radiologist work closely together.

Before speaking to parents about their child's problem, it is sensible to insist on the radiologist, with whom team work has been established, reporting on the *x* rays. In the case of achondroplasia, most clinicians and radiologists can probably agree a diagnosis and be reasonably sure of the prognosis, but in the less common skeletal dysplasias not every radiologist will classify the appearances identically and there is scope for considerable confusion, especially if the radiologist qualifies opinion—"the

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changes in the radiographs resemble disease X"—and the clinician then addresses the parents as if the patient definitely has disease X.

When my radiologist puts a name to a condition, regardless of whether his peers would put the same name to it, it is known from our experience together what is likely to happen. In practical terms this means that, as in every field of medicine, team work pays off and the referral of a child with their radiographs to a specialist centre for diagnosis, if not for management, is probably wise.

As the phenotypic appearances of the same bone dysplasias can be extremely variable, dysmorphic features, in addition to radiological findings, may be very helpful in reaching a diagnosis. For example, in Stickler syndrome (hereditary arthro-opthalmopathy) the only presenting features at birth may the Pierre-Robin association (micrognathia, glossoptosis, and cleft palate). Mild spondyloepiphyseal dysplasia may develop during childhood as will progressive myopia. If untreated, the latter may give rise to retinal detachment and blindness. A careful family history might also give a clue if—for example, other family members had short stature, flat facies, painful joints, and severe myopia with or without retinal detachment. Mutation analysis of the COL2A1 gene might also confirm the diagnosis, although this is still a research exercise.

Molecular genetics

As a result of developments in molecular genetics, several genes and their products involved in bone dysplasias have been characterised. This allows the confirmation of clinical diagnoses, it broadens knowledge about pathogenesis, and begins to present an opportunity to develop a rational classification of skeletal dysplasias on the basis of the mutated gene(s) (table 3).

Most skeletal dysplasias are dominantly inherited so parental appearance may assist, but the majority arise by de novo mutations and parents are phenotypically normal. Some dysplasias are recessively inherited and there are major implications for further offspring of the parents. In such cases, reliable prenatal diagnosis by ultrasound and/or molecular and biochemical analyses of chorionic villi or amniocytes would be very useful.

Mutations in the fibroblast growth factor receptor 3 (FGFR3) gene are involved in achondroplasia, thanatophoric dysplasia, and hypochondroplasia. The FGFR3 gene, which is expressed in articular chondrocytes, is involved in local regulation of cartilage growth. More than 98% of achondroplasia patients have a glycine→arginine substitution at codon 380 of the FGFR3 gene.[3 4] In thanatophoric dysplasia several mutations in the FGFR3 gene, either substitutions or missense mutations, have been reported.[5 6] The differences in severity between achondroplasia and thanatophoric dysplasia can be explained by the effect of the mutations on the functioning of the fibroblast growth factor receptor. These mutations are thought constitutively to activate the receptor but this effect is relatively weak in achondroplasia mutations, whereas the mutations in thanatophoric dysplasia result in more powerful activation.[7]

The situation in hypochondroplasia, a more common disorder, is complicated. Severe cases with considerably short stature and obvious disproportion have an asparagine→lysine substitution at codon 540[8] but the cases that are easier to miss, such as the patient in fig 1, do not have this mutation, even though the skeletal radiographic findings are identical. We do not yet understand the molecular genetic basis of this disorder, and the spectrum of genotype and phenotype needs to be clarified urgently to know whom to treat and when.

Collagen II is primarily expressed in cartilage and the vitreous of the eye. Various mutations in the COL2A1 gene have been found in chondrodysplasias with ocular abnormalities (mainly severe myopia), such as spondyloepiphyseal dysplasia congenita, Kniest syndrome, and Stickler syndrome.[9–12] Stickler syndrome is genetically heterogeneous as families with mutations in the COL11A2 gene have been reported.[13] These families do not show eye abnormalities because the α2 chain of type XI collagen is replaced by the COL5A2 product in mammalian vitreous. These are early days for genotype–phenotype correlations.

Other mutated collagen genes have also been associated with skeletal dysplasias, such as the COL10A1 gene in Schmid metaphyseal dysplasia and the COL9A2 gene in multiple epiphyseal dysplasia.[14 15] In other families with multiple epiphyseal dysplasia, mutations in the cartilage oligomeric matrix protein (COMP) gene have been reported,[16] which reflects the genetic heterogeneity of this disorder. Mutations of the COMP gene (deletions or duplications) also cause 40% of the cases of pseudoachondroplasia.[16]

For three dysplasias—achondrogenesis IB, atelosteogenesis II, and diastrophic dysplasia[17]—which are all characterised by micromelia and a short, narrow thorax in various degrees of severity, mutations in the diastrophic dysplasia sulphate transporter (DTDST) gene have been reported.[17] All three disorders are recessively inherited and therefore mutation analysis may be very helpful for accurate prenatal diagnosis.

Management

Once a diagnosis has been made, the prognosis becomes (reasonably) obvious as do the genetic implications, but there are still many gaps in our knowledge. For example, there are no data relating parental heights to childhood outcomes. We are not good at predicting which short children with the radiological spinal features of hypochondroplasia, a failure of the interpedicular width to increase from L1 to L5—which we regard as the sine qua non of the diagnosis—will miss out on the puberty growth spurt.[18] We hope that correlating genotype to phenotype (a project in progress) may assist in offering a firm prognosis in this most common of skeletal dysplasias. The genotype of the

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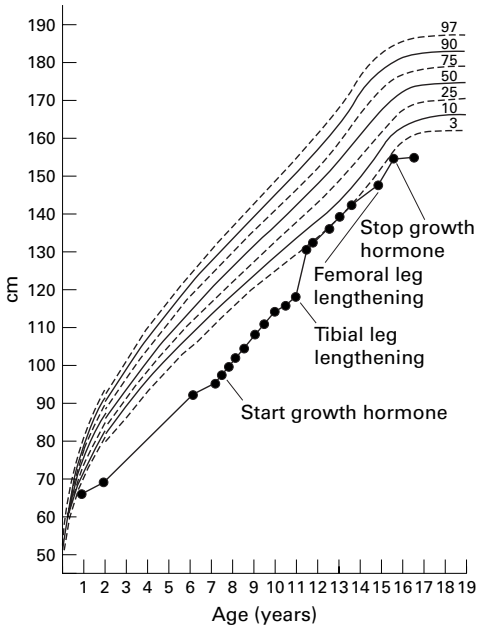

Figure 2 Growth chart of achondroplastic patient treated with growth hormone and surgical procedures.

proband may allow for antenatal diagnosis in future offspring.

Treatment has thus far been confined to limb lengthening. This is a formidable undertaking as it requires one day of stretching for every millimetre of length gained in the limb. Although surgical techniques are improving rapidly, problems with soft tissues during lengthening are common and non-union does sometimes occur. Nevertheless, this is a tried and tested procedure, which can add up to 15 cm in leg length if lengthening is applied to both tibiae and femora. There are no data, but plenty of opinions, available to determine when is the optimal time (medically or psychologically) to operate, whether it is better to operate more than once on a patient, how much lengthening should be attempted, and so on.

Medical treatments are in their infancy. When pituitary derived human growth hormone was withdrawn in 1985 and recombinant human growth hormone (r-hGH) became available, clinicians were presented for the first time with a supply of growth hormone limited only by cost. Many indications for the proper use of r-hGH have been explored but data on final heights achieved are only just becoming available and are frankly rather disappointing in Turner syndrome, precocious puberty, and normal short children.[19]

There are no data available for final heights achievable in skeletal dysplasias. We have been able to restore a missing pubertal growth spurt in patients with hypochondroplasia by administering r-hGH at the appropriate time but its use earlier in childhood does not look promising for significantly improving final height.[20]

The growth of untreated achondroplastic children is well characterised[21]; we have been greatly encouraged to find that we have been able to keep such patients growing at a 50th centile velocity for normal children by using r-hGH at a dosage of 30–40 units/m^2/week (about double that used for replacement treatment in children). The implication of this must be to start r-hGH treatment early before too much height has been lost (as growth velocity in the first year of life is normal[21]), and preliminary analysis of our data in 31 cases suggests that treatment is indeed most effective when started before the age of 2 years (Ramaswami, personnal communication, 1998).

There is no prospect that growth hormone alone will achieve anything resembling a normal final height in these patients. It may at most achieve a gain of about 10–15 cm if treatment is started early, so it will certainly have to be coupled with one or more leg lengthening procedures to obtain a further 10–15 cm. Figure 2 shows the growth chart of our longest treated achondroplastic boy. He received growth hormone from age 7.5 years (late by our standards) and underwent two leg lengthening operations at 11.9 and 14.9 years, resulting in a final height of 154.6 cm (the mean (SD) for untreated achondroplastic boys is 131 (6) cm).[21]

Results of using r-hGH in older achondroplastic children have been rather disappointing in our hands, and compliance with the therapeutic regimen has been a major problem. It is not known whether r-hGH has a place in the management of puberty growth in achondroplasia nor how puberty hormones will impact on an achondroplastic child already on r-hGH treatment.

We have very little experience of medical treatment in the other skeletal dysplasias and no long term results. We have been encouraged by our experience in multiple epiphyseal dysplasia and Jeune syndrome but discouraged by experience in spondyloepiphyseal dysplasias and pseudachondroplasia. Mean results conceal individual successes and we have seen some unexpected ones; therefore, as we have seen no serious side effects from medical treatment, we are inclined to advise an empirical approach to individual cases. In assessing results of such trials of n = 1, the problem of compliance is one that needs serious discussion and consideration. Our recommendation is that such trials of treatment should be carried out only in the context of planned research in an appropriate setting, so that definitive results can be acquired.

Conclusions

Skeletal dysplasias are a common cause of unexplained short stature in children and adults; they present particularly with a failure of pubertal growth. Diagnosis requires a high degree of clinical suspicion. Collaboration between an experienced clinician, an informed radiologist, and a molecular genetic laboratory offers the possibility of a better outcome for some patientss.

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FETAL AND NEONATAL EDITION

September Issue

The following articles—being published in the September issue of the *Fetal and Neonatal* edition of *Archives of Disease in Childhood*—may be of particular general interest as they relate to community, social, and neurodevelopmental paediatrics.

Outcome of very preterm birth: children reviewed with ease at 2 years differ from those followed up with difficulty
Win Tin, Susan Fritz, Unni Wariyar, Edmund Hey

Maternal hypertension and neurodevelopmental outcome in very preterm infants
Peter H Gray, Michael J O'Callaghan, Heather A Mohay, Yvonne R Burns, James F King

Neurobehaviour of school age children born to diabetic mothers
A Ornoy, N Ratzon, C Greenbaum, E Peretz, D Soriano, M Dulitzky

Association of blood pressure in adolescence with birthweight
P O D Pharoah, C J Stevenson, C R West

Birthweight and blood pressure among children in Harare, Zimbabwe
Godfrey Woelk, Irvin Emanuel, Noel S Weiss, Bruce M Psaty

Causes of preterm delivery and intrauterine growth retardation in a malaria endemic region of Papua New Guinea
S J Allen, A Raiko, A O'Donnell, N D E Alexander, J B Clegg

Histochemical, clinical, and in vitro β cell responses in a neonate with persistent hyperinsulinaemic hypoglycaemia of infancy
N S Panesar, C W Poon, C T Liew, G W K Wong, N M Hjelm

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