Acromicric dysplasia: long term outcome and evidence of autosomal dominant inheritance

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Abstract

Acromicric dysplasia is a rare bone dysplasia characterised by short stature, short hands and feet, normal intelligence, mild facial dysmorphism, and characteristic *x* ray abnormalities of the hands. Only a very small number of children with this condition have been reported so far. Here we report on a series of 22 patients including 10 boys and 12 girls with acromicric dysplasia. Length was normal at birth and height fell progressively off the centiles postnatally. The mean adult height was 130 cm (133 cm in males, 129 cm in females). The hands, feet, and limbs were short and OFC was normal. Intelligence was normal and mild dysmorphic features were noted. Other occasional features included well developed muscles, a hoarse voice, generalised joint limitation in some patients, frequent ear, tracheal, and respiratory complication, and spine abnormalities. Long term follow up showed that facial dysmorphism was less obvious in adults and that carpal tunnel syndrome was frequent in older patients. Apart from short metacarpals and phalanges, internal notch of the second metacarpal, external notch of the fifth metacarpal, and internal notch of the femoral heads, there were no major *x* ray abnormalities. No major complications, such as cardiac disease or major orthopaedic problems, occurred in the course of the disease. The condition appeared to be sporadic in 16 cases but the observation of vertical transmission in three families was consistent with an autosomal dominant mode of inheritance.
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Keywords: acromicric dysplasia; geleophysic dysplasia; long term outcome; autosomal dominant inheritance

In 1986, Maroteaux *et al*[1] described a novel bone dysplasia in six unrelated children presenting with short stature, short hands and feet, normal intelligence, mild facial dysmorphic features, and characteristic *x* ray abnormalities of the hands. They called this condition "acromicric dysplasia".[1] Only a few cases with features of acromicric dysplasia have been reported since then, but all children presented overlapping features with geleophysic dysplasia or Moore-Federman syndrome.[2–4] In the last 14 years, we have ascertained 18 additional cases of acromicric dysplasia in 15 families from five different countries and followed up four of the previously reported cases. Here we describe the clinical data and *x* ray features of these patients, with particular emphasis on the long term outcome in 10 adult patients, and provide further support for the autosomal dominant inheritance of this condition.

Patients and methods

Twenty-two patients (12 girls, 10 boys) from 15 families and five different countries were included in our study (table 1). Their ages ranged from 4.5 to 53 years with a mean age of 19 years. The diagnosis of acromicric dysplasia was based on the observation of short stature, short hands and feet, short and stubby metacarpals and phalanges with an external notch on the second metacarpal and an internal notch on the fifth metacarpal, and mild deformity of the femoral heads. Sixteen of our 22 patients were seen at least once in the medical genetics clinic of Necker-Enfants Malades Hospital. Questionnaires were sent to the referring physicians and patients were contacted directly for follow up information. Eight patients were identified through medical reports sent to our clinic for advice and questionnaires were sent to the referring physician for additional information.

Results

The mean length at birth was 48.6 cm (48.8 cm in boys, 48.5 cm in girls) and the mean adult height was 130 cm (133 cm in males, 129 cm in females), with a range from 115 to 140 cm. In all cases, the height fell progressively off the centiles (fig 1). The limbs were short and OFC was normal. One case showed significant improvement after a limb lengthening procedure and one patient received growth hormone with no significant effect on final height. Short stature was generally well accepted by the patients and their quality of life was not affected. Adults did well in their professional lives and intelligence was normal.

Facial dysmorphism was very similar in all cases (fig 2). It included a round face (17/22 cases), narrow palpebral fissures (17/22 cases), well defined eyebrows (14/22 cases), long eyelashes (14/22 cases), a bulbous nose with anteverted nostrils (19/22 cases), a long and prominent philtrum (16/22 cases), and thick lips (13/22 cases) with a small mouth (12/22 cases). Facial dysmorphism seemed less obvious in older patients.

Occasional features included joint limitation (13/20 cases), kyphoscoliosis or lordosis (12/20 cases), recurrent ear, tracheal, and respiratory complications (otitis, tracheal infections, and

Table 1 Clinical features in acromicric dysplasia patients

	Familial cases						*Sporadic cases*																
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*Total*
Ethnic origin	Fr	Fr	Fr	Fr	A	A	Fr	Fr	Fr	Fr	Fr	A	Fr	USA	USA	Sp	Sp	Fr	It	Fr	Fr	It	
Sex	F	M	F	M	F	M	F	M	F	F	M	F	F	F	M	F	F	M	M	F	M	M	10M/12F
Familial case	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	6/22
Length at birth (cm)	49	47	49	48	48	46	48	49	47.5	49	48	49	46	48	49.5	NA	NA	49	51	51	50	50	48.6
Follow up																							
Age (years)	48	21	53	22	33	4	8	12	19	20	14	11	9	16	9.5	7	8	15	11	21	33	18	18.8
Height (cm)	132	138	120	128	140	93	98	112	115	135	120	118	116	138	111	97.5	92	114	106	120 +20*	140	125	130 in adults
Abnormal voice	−	−	+	+	+	−	−	−	+	−	−	NA	NA	−	NA	NA	NA	NA	NA	+	−	−	5/15
Well developed muscles	−	+	+	+	−	−	+	−	−	+	−	−	NA	−	NA	NA	+	+	NA	+	+	−	10/18
Joint limitation	−	H,Fi	All	All	−	−	E,Fi	−	S	Fi	−	Fi	−	−	E,Fi	NA	NA	H,E	E,F, H,K	E,Fi, H	H	E,H, Fi	13/20
Facial dysmorphism	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	22/22
Heart malformations	−	−	−	−	−	−	−	−	+	−	+	−	−	−	+	−	−	+	−	-	-	-	4/22
Hepatomegaly	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	-	-	-	0/22
Eye abnormalities	+	+	+	−	+	−	−	−	+	−	+	−	−	+	−	NA	NA	−	−	+	-	-	8/20
Ear abnormalities	+	+	+	−	−	−	+	−	−	−	−	−	−	+	+	NA	NA	−	−	−	-	-	6/20
Tracheal, respiratory	−	+	+	+	−	−	−	−	+	−	−	−	−	+	−	−	−	+	−	+	-	-	7/22
Spine abnormalities	+	−	+	+	+	−	−	+	+	+	+	−	+	−	+	NA	NA	+	−	+	-	-	12/20
Carpal tunnel	+	−	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	-	-	-	3/22

Fr, France; A, Africa; Sp, Spain; It, Italy.
F, female; M, male.
H, hips; Fi, fingers; E, elbows; K, knees; S, shoulders.
NA, not available.
*+20 cm after limb lengthening procedure.

asthma, 10/20 cases), well developed muscles (10/18 cases, fig 3), eye refraction defects (hypermetropia, myopia, and astigmatism, 8/20 cases), abnormally hoarse voice (5/15 cases), heart malformations (atrial septal defect and bicuspid aorta, 4/22 cases), and carpal tunnel syndrome in older patients (3/22 cases, table 1). No pain, thickened skin, or hepatomegaly was observed. Finally, irregular leg length (1/22 cases), osteoarthritis (1/22 cases), clenched fingers (1/22 cases), Brown syndrome (limitation of upward gaze) (1/22 cases), pulmonary hypertension (1/22 cases), autoimmune diabetes (1/22 cases), hepatitis (1/22 cases), delayed puberty (1/22 cases), and precocious puberty (1/22 cases) were occasionally noted.

Besides short metacarpals and phalanges, internal notch of the second metacarpal, and external notch of the fifth metacarpal, other consistent features were shortened fourth and fifth metacarpals and markedly delayed bone age. Mild pointing of the second to fifth metacarpals was observed in 15/22 cases and cone shaped epiphyses in 5/22 cases. *X* rays of the older patients showed that the notches of the hands disappeared in adulthood (fig 4). An internal notch of the femoral heads was consistently observed and persisted in adulthood (fig 5). There was neither osteopenia nor

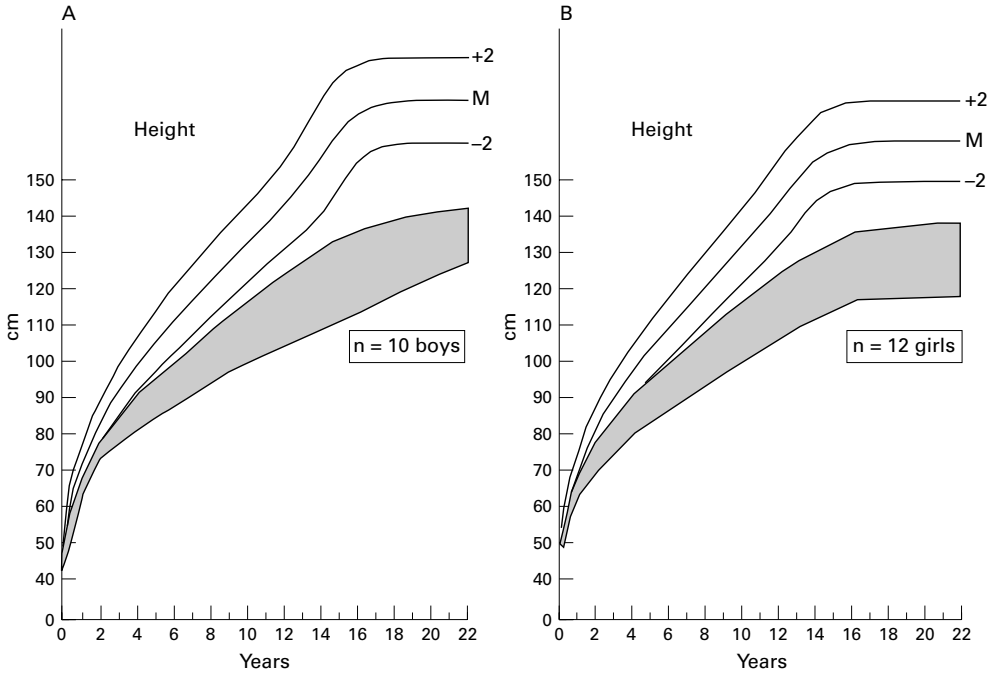

Figure 1 Maximum and minimum growth curve in 22 acromicric dysplasia patients. Birth length ranged from 45 to 51 cm. Adult height ranged from 115 to 140 cm.

Figure 2 Facial dysmorphism in 12 patients with acromicric dysplasia. Note the round face, narrow palpebral fissures, well defined eyebrows and long eyelashes, a bulbous nose with anteverted nostrils, a long and prominent philtrum, and thick lips with a small mouth. The facial dysmorphism seems less obvious in adults.

obvious vertebral, epiphyseal, or metaphyseal anomalies.

Urinary oligo- and mucopolysaccharides showed no evidence of storage disorder. Histology of the skin performed in one case at the age of 53 years was normal as well as liver and tracheal histology in another patient. Similarly, there were no endocrine or cytogenetic abnormalities, except in one patient with partial growth hormone deficiency.

Sixteen out of 22 cases were sporadic with parental age within normal limits (mean father's age at birth 29 years, mean mother's age at birth 27 years). Six of our 22 cases were familial with vertical transmission, suggesting an autosomal dominant mode of inheritance (fig 6).

Discussion

Here we report progressive dwarfism, short hands and feet, normal intelligence, and mild dysmorphic features in 22 patients with acromicric dysplasia. Additional clinical features of the syndrome were identified in this study, namely well developed muscles, hoarse voice, generalised joint limitations, frequent ear, tracheal, and respiratory complications, and spine abnormalities. Long term follow up showed that facial dysmorphism was less obvious in adults and that carpal tunnel syndrome was frequent in older patients. The severity of dwarfism was quite variable, but consistently below 3 SD, and OFC was consistently normal. Life expectancy was normal and no major complications, such as cardiac disease or major orthopaedic problems, occurred in the course of the disease. Only mild *x* ray abnormalities were noted and notches of the hands disappeared in adulthood.

Several acromicric dysplasia patients with features of geleophysic dysplasia and Moore-Federman syndrome, namely stiff joints, thickened skin, and hepatomegaly, have been reported, raising the question of whether geleophysic dysplasia, Moore-Federman syndrome, and acromicric dysplasia could be the same entity.[2–4] Moreover, short stature with short hands and feet, normal birth length with reduced postnatal growth rate, and delayed bone age are common features in all three conditions. Table 2 summarises the differences between the three entities. First, thickened skin

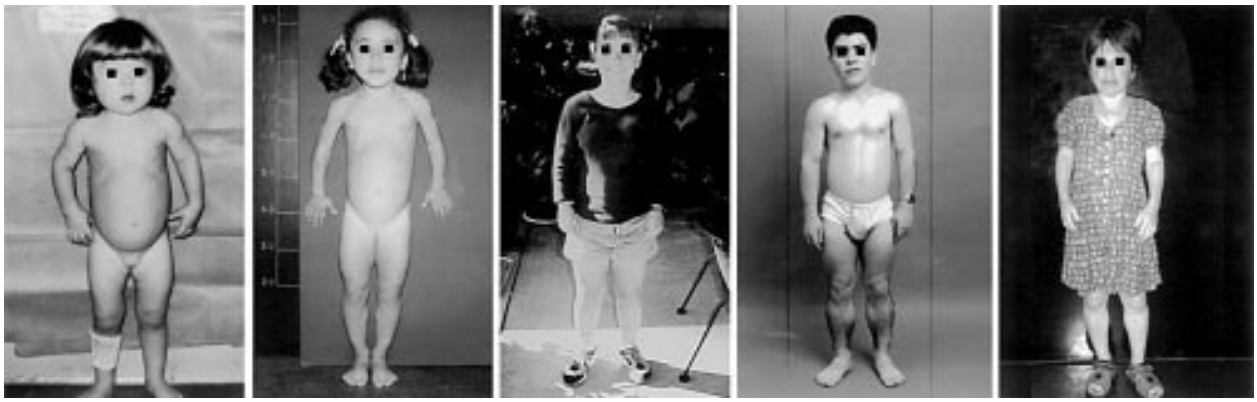

Figure 3 Front views of five acromicric dysplasia patients. The limbs, hands, and feet were short and well developed muscles were noted in several patients.

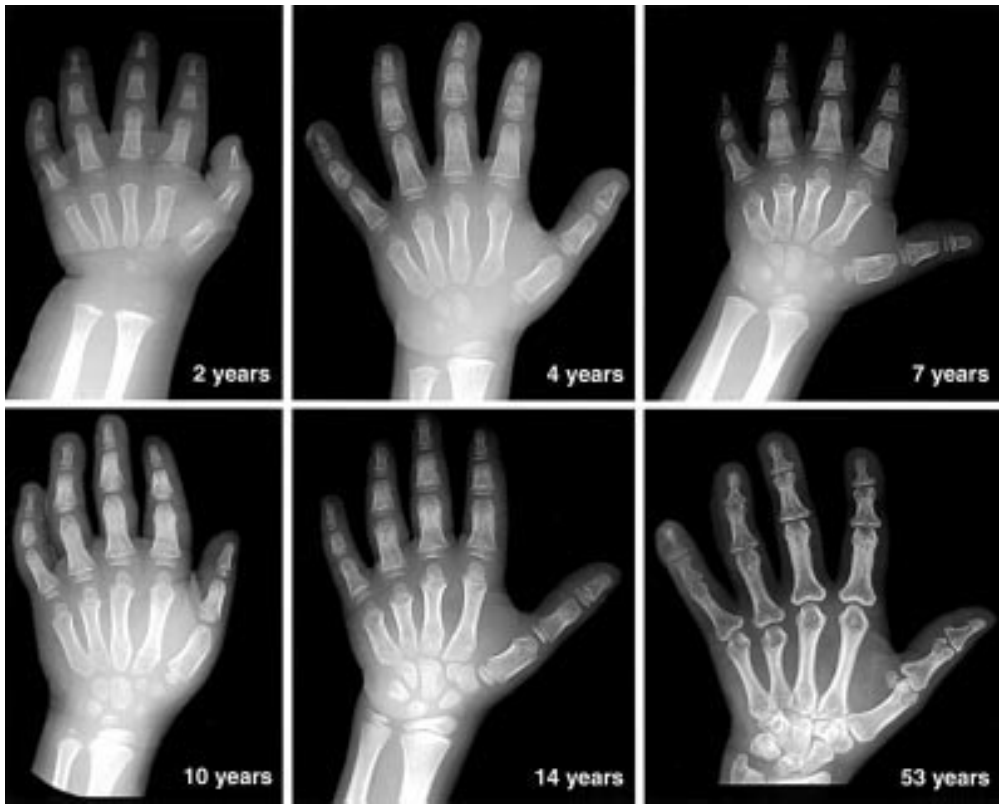

Figure 4 X rays of the hands in acromicric dysplasia. Note the short metacarpals and phalanges, the internal notch of the second metacarpal and the external notch of the fifth metacarpal, short fourth and fifth metacarpals, mild pointing of the second to fifth metacarpals, and markedly delayed bone age. Note that hand notches disappeared in adulthood.

and hepatomegaly are features of both geleophysic dysplasia and Moore-Federman syndrome, but are never observed in acromicric dysplasia. Second, cardiac valve dysplasia is observed in geleophysic dysplasia only.[5] Third, while life expectancy and functional prognosis are good in acromicric dysplasia and Moore-Federman syndrome, they are poor in geleophysic dysplasia.[6] In addition, the internal notch of the femoral heads is specific to acromicric dysplasia. Also, histological signs of storage disorder have been found in geleophysic

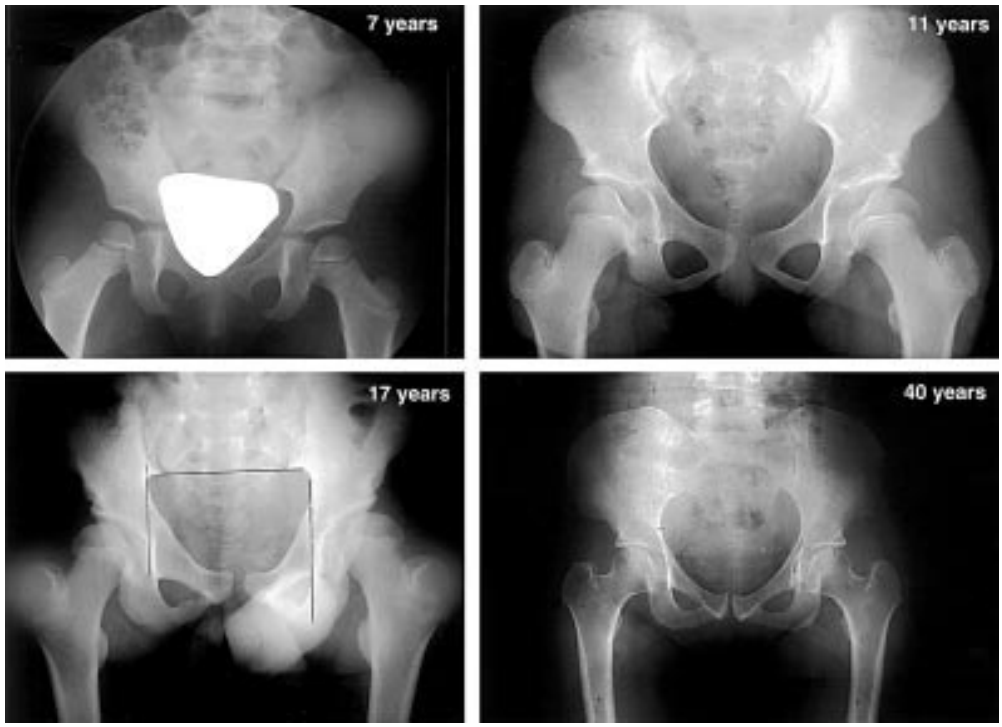

Figure 5 X rays of the pelvis in acromicric dysplasia. Note the internal notch of the femoral heads. This notch did not disappear with age.

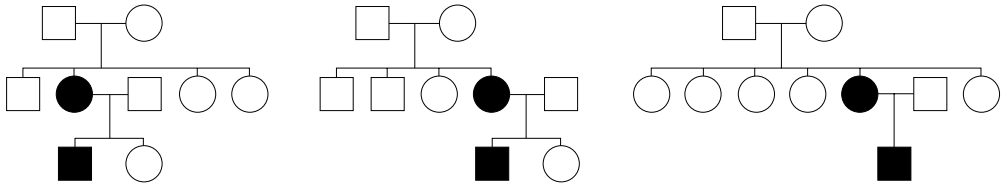

Figure 6 Vertical transmission of the disease in the three familial cases of acromicric dysplasia.

dysplasia.[4 7 8] Finally, the mode of inheritance is different in the three conditions: autosomal dominant in acromicric dysplasia and Moore-Federman syndrome[9 10] and autosomal recessive in geleophysic dysplasia.[11 12] We therefore believe that at least geleophysic dysplasia is a distinct entity from acromicric dysplasia. The differences between acromicric dysplasia and Moore-Federman syndrome are minor and the existence of only two reports of Moore-Ferderman syndrome limits the knowledge of the disease.[3 9] However, the hypothesis of clinical variability of the same entity with hepatomegaly and thickened skin being more obvious with age is not supported by the long term follow up of four patients aged 33 years or more in our series.

The pathogenesis of the disease is unknown. Cartilage histology was performed in two of the first six cases with acromicric dysplasia[1] and showed some disorganisation of the growth zone with islands of cells, some of them degenerated, an abnormal organisation of collagen forming thick rims around the cells, and wide fibres in the inter-territorial matrix, and a large accumulation of glycogen in most chondrocytes. These results do not suggest which are the candidate genes in this disorder.

In conclusion, we believe that acromicric dysplasia is a genuine entity, distinct from geleophysic dysplasia and, here, we provide additional support for the autosomal dominant inheritance of acromicric dysplasia. It is hoped that further familial cases will help in the mapping and identifying of the disease gene.

Table 2 Similarities and differences between acromicric dysplasia, Moore-Federman syndrome, and geleophysic dysplasia

	Acromicric dysplasia	*Moore-Federman*[10]	*Geleophysic dysplasia*[5]
Major distinctive features			
Thickened skin	−	+	+
Cardiac valve disease	−	−	+
Prognosis	Good	Good	Poor
Femoral heads	Notch	Deformed	Dysplastic
Histology	Normal	NR	Storage
Inheritance	AD	AD	AR
Minor distinctive features			
Joint contractures	Mild - 13/20	Moderate - 10/11	Severe - 21/23
Hepatomegaly	0/22	5/11	14/21
Height <3rd centile	22/22	11/11	16/21
Speech delay	0/22	NR	4/14
Voice	Hoarse	Hoarse	High pitched
Eye abnormalities	8/20	9/11	Possible
Similarities			
Birth length	Often normal	Often normal	Often normal
Reduced postnatal growth speed	+	+	+
Delayed bone age	Consistent	NR	Frequent
Susceptibility to ENT and respiratory infections	+	NR	+

NR: not reported.
ENT: ear, nose, and throat.

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