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Achondroplasia and hypochondroplasia

Comments on frequency, mutation rate, and radiological features in skull and spine

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SUMMARY An attempt was made to ascertain all the dwarfs in the State of Victoria. The incidence of achondroplasia proved to be approximately 1 in 26 000 live births in the period 1969 to 1975 when ascertainment was nearly complete. This indicates a mutation rate of $1 \cdot 93 \times 10^{-5}$ per generation in this locus. Paternal age was shown to influence mutation. Ascertainment in earlier years of the study was low despite the very great effort made to find all cases. Patients with hypochondroplasia were particularly difficult to find. However, 25 cases were found for study. Overlap between hypochondroplasia and achondroplasia was found in all features except the facial appearance (which was the basis of definition). Achondroplasia was more severe in all regards, but some individuals with hypochondroplasia were very short and some had extreme degrees of spinal canal stenosis. The classical measurements used to describe the skull changes in achondroplasia failed to distinguish this condition from hypochondroplasia. More efficient indices were devised, but visual assessment of the size of the facial region compared to that of the cranial vault proved more reliable than any index. The clinical distinction based upon facial appearance remains the arbitrary basis of definition.

Achondroplasia is now very clearly defined by clinical features (including a characteristic facies) and by radiographic criteria (Langer *et al.*, 1968). Hypochondroplasia has received less attention, but is generally defined by the presence of radiographic features similar to those of achondroplasia (but less severe) in a patient with normal facial features (Walker *et al.*, 1971). Both conditions show autosomal dominant inheritance and allelism of the genes concerned has been claimed (McKusick *et al.*, 1973). However, the hypochondroplasic patient illustrated in this crucial report appeared to have an achondroplasic facies. This seemed to indicate a need for a more objective definition.

This paper analyses certain selected features of the two conditions: the changes in the skull and pelvis by which they might be distinguished, the range of height observed, and certain epidemiological facts.

Methods

Ascertainment of cases began in 1966 within the Royal Children's Hospital and extended to all teaching hospitals, all paediatricians, all radiologists, and all orthopaedic surgeons in Victoria during 1968 to 1970. All organisations (public and voluntary) involved with handicapped children and adults were contacted, as were employment agencies. Newspaper and television publicity was used. The Little People's Association of Australasia collaborated very actively. Finally, one author (LS) visited several rural regions, calling on the district hospitals and general practitioners, and enquiring at local meeting places.

The number of young babies with achondroplasia referred to the authors has increased greatly since 1968, and it seems likely that ascertainment is nearly complete for the period 1969 to 1975, inclusive. Data from this period have been used to calculate incidence and mutation rates. The incidence in this period was used to calculate the extent of ascertainment of older patients, using the age profile of the Victorian population in 1971 (Australian Bureau of Statistics), and assuming that achondroplasics experience the same mortality rate as other members of the com-

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munity. All these calculations were confined to Victorian born patients.

Parental age was examined in all achondroplasics born to unaffected parents using two methods: simple comparison with matrices of parental ages and birth order of all Victorian births in the appropriate year, and a more efficient and powerful method recently devised (Fisher and Sheffield, 1978). The control data for both methods related to Australian births up to 1970 and to Victorian births after that year.

Height was measured standing in patients over 2 years of age and prone before that age. Results were expressed as the number of SD below the mean for each year of age (in childhood) and were then put into age groups for presentation. Normal data was that of Tanner *et al.* (1966).

The skull measurements used are displayed and can be described in terms of Fig. 1a to d. The cephalic index is $\frac{Br}{L} \times 100$. The basal angle is shown in Fig. 1c as $<XYZ$. The modulus (M) $= \frac{L+H+Br}{3}$. The ratio of length of anterior cranial fossa: total skull length = AB:L. Facial height = h. Lower face:upper face = CD:AB. Lower face:skull breadth = CD:Br. Lower face:length = CD:L.

All of these were measured on films taken at a fixed focal film distance of 90 cm.

Interpedicular distance was measured with calipers on AP films also taken at a fixed focal film distance of 90 cm (Hinck *et al.*, 1966). The AP diameter of the neural canal was measured as the shortest distance between each vertebral body and the anterior surface of the neural arch (Hinck *et al.*, 1965). Both measurements were expressed as a percentage of the normal figures of these authors for children or adults of the appropriate age.

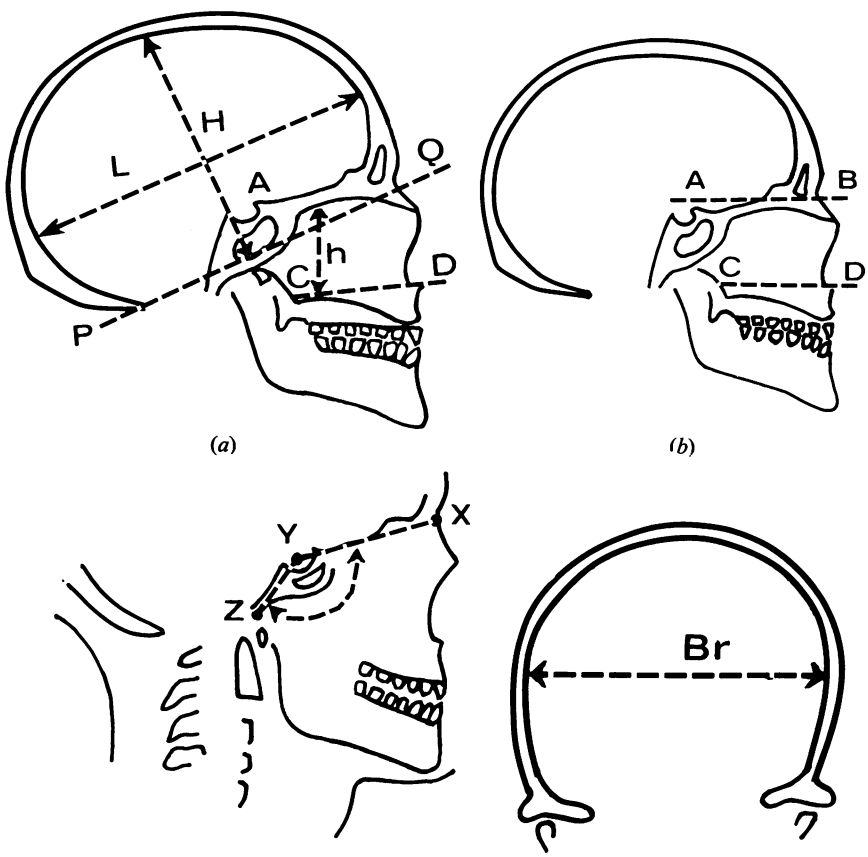

Fig. 1 a–d *Diagrams of skull x-rays showing the various measurements used and described in the text. Where not otherwise indicated, the measurement was taken to the outer cortical table of the bone at the point where the reference line intersected it. Point A is the anterior clinoid process.*

Results

INCIDENCE OF ACHONDROPLASIA AND MUTATION RATE

Nineteen of the babies found with achondroplasia were born in 1969 to 1975, inclusive. Total births in the period were 492 889. Incidence was therefore 3·855 per 100 000 live births (95% confidence limits, 2·626 and 5·084) or 1 in 25 940 (95% confidence limits, 1 in 19 670 and 1 in 38 000).

All these patients were born to normal parents so that the estimated mutation rate was $1·93 \times 10^{-5}$ per generation (SD $0·443 \times 10^{-5}$, 95% confidence limits, $1·06 \times 10^{-5}$ and $2·80 \times 10^{-5}$).

PARENTAL AGE AND BIRTH ORDER IN ACHONDROPLASIA

Simple comparison with matrices of statistics from all Victorian births in the appropriate years showed a substantial excess of older parents ($P<0·001$) (Table 1) and a higher than expected birth order ($0·1>P>0·05$). The more sophisticated analysis showed that the paternal age effect remained highly significant when maternal age was held constant ($0·02>P>0·01$), whereas the reciprocal analysis showed no residual effect of maternal age ($0·5>P>0·4$). Birth order effect also proved secondary to paternal age.

ASCERTAINMENT

Several adult dwarfs, who appeared to have achondroplasia, were sighted in the suburbs of Melbourne, but were not drawn into the study. Several teenage children and adults with achondroplasia refused to co-operate. Each visit to a major rural area identified one or two new dwarf patients. All these experiences showed that ascertainment was incomplete despite the great effort put into the search for dwarf patients.

Analysis of the age distribution of the patients who were found allowed an estimate of the completeness of ascertainment (Table 2). The calculation assumed that achondroplasics experience the same pattern of mortality as the remaining population, and used only Victorian born patients. It may be more valid to include the additional 8 patients now living in Victoria, but born elsewhere, to compensate for Victorian born patients moving out of the State. This would raise the average ascertainment to 47%. The method also ignores the massive influx of adult immigrants into Victoria over the last 30 years. Migrants have been screened medically and presumably few dwarfs have been admitted. One might, therefore, expect that the true prevalence of achondroplasia in middle aged adults may be considerably lower than that predicted from the incidence in young babies. For these reasons, the ascertainment achieved may be of the order of 60 to 70%. However, it is certainly far from complete especially in the 35 to 45-year-old group.

Table 1 *Parental age analysis*

	Age groups −24	25–29	30–34	35+	*Total*
Maternal age					
Observed	7	9	13	9	38
Expected	19·53	12·28	7·15	4·95	
	$\chi^2_3 = 17·02$, $P<0·001$				
Paternal age					
Observed	1	7	10	20	38
Expected	6·57	12·02	9·26	10·14	
	$\chi^2_3 = 16·37$, $P<0·001$				

Table 2 *Ascertainment of achondroplasia (Victorian cases only)*

Decade	*Cases found*	*Cases expected**	*Ascertainment (%)*
1961–70	19	26·4	72·0
1951–60	9	24·6	36·6
1941–50	8	21·2	37·7
1931–40	1	16·4	6·1
1921–30	5	16·8	29·8
1911–20	6	13·2	45·5
1901–10	4	9·2	43·0
Total	52	127·9	40·7

*Based on age distribution in Victoria in 1971, assuming true incidence to be that calculated for 1969 to 1975.

PROPORTION OF NEW MUTANTS

Only 2 of the 60 achondroplasics ascertained were born to affected parents. The remaining 58 were new mutants. Only 3 adult patients had any children; each produced one child, all 3 being affected (2 resident in Victoria and included in the study, one living out of Victoria).

HYPOCHONDROPLASIA STATISTICS

Twenty-five patients were found, but everything about their ascertainment suggested that they represented a very small proportion of all cases in the community. Several of the index patients regarded themselves as small normal people, and the affected relatives found from tracing the family history were especially loth to be studied, asserting their normality quite aggressively.

It would be quite misleading to calculate incidence or mutation rate. Of the 25 patients, 9 were born to an affected parent. It is more difficult to be certain that the remaining 16 patients were the result of new mutations. Two had short parents who were difficult to classify even with radiographic examination. Several others had one short parent who would not accept clinical or radiological assessment.

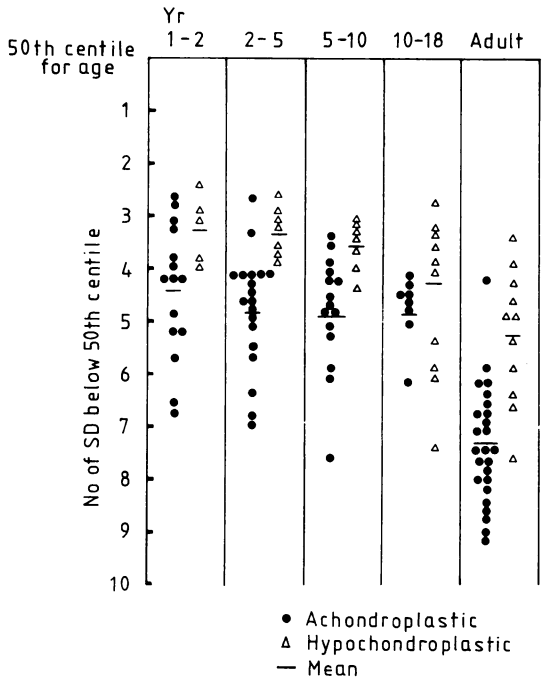

Fig. 2 *Height of patients with achondroplasia and hypochondroplasia presented as the number of SD below the 50th centile for the age of the patient.*

HEIGHT IN ACHONDROPLASIA AND HYPOCHONDROPLASIA

The information displayed in Fig. 2 shows the considerable overlap in the height recorded in the two conditions at all ages. The cumulative effect of the growth disturbance is apparent in both conditions, so that adults deviate further from the mean than young children. The difference between the two conditions also increases. There may be many more relatively tall hypochondroplasics in the community whose inclusion would alter the pattern considerably.

DISTINCTION BETWEEN ACHONDROPLASIA AND HYPOCHONDROPLASIA

This study has accepted definition by the clinical appearance of the facies (Walker *et al.*, 1971). Generally, the degree of shortening and distortion of shape of the limb bones was also distinctly different, but this was not true in all cases. A search was made for methods of distinguishing the two conditions by the radiological appearance of the skull and of the lumbar vertebrae.

SKULL *x*-RAYS

The basal angle did not distinguish between the two conditions at all satisfactorily (Fig. 3). The cephalic

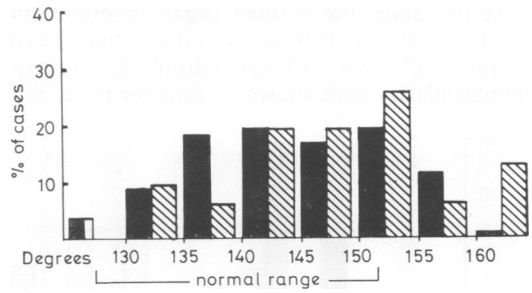

Fig. 3 *Frequency histogram of basal angle measurements in achondroplasia (solid columns) and hypochondroplasia (hatched columns).*

index and the modulus were even less satisfactory. When these classical measurements failed various other ratios were calculated (facial height/overall height : anterior cranial fossa/length of skull). These also failed to distinguish between the conditions.

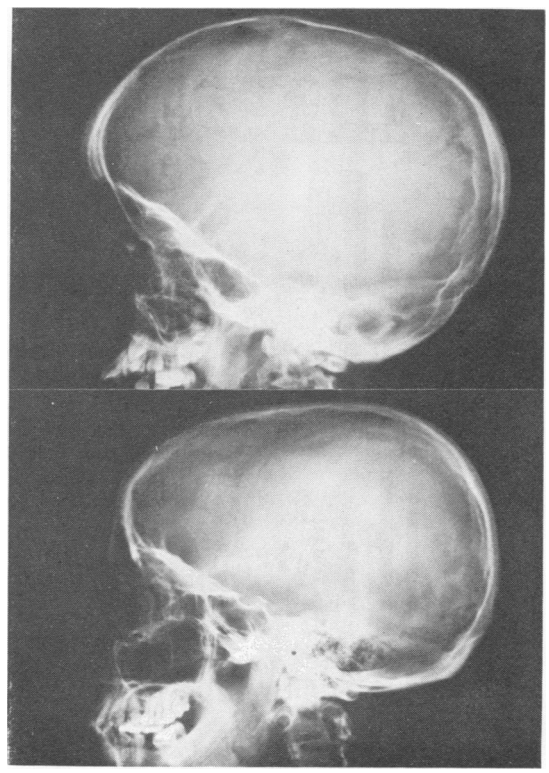

Fig. 4 *Lateral skull films of patients with (top) achondroplasia and (bottom) hypochondroplasia, showing the remarkable difference in the size of the facial bone structures.*

At this stage the authors began to doubt their belief that the skull films were distinctive. Twenty lateral skull films (10 achondroplasic, 10 hypochondroplasic) were shown in random order to an experienced radiologist who knew none of the cases. He classified all 20 correctly. The shape and size of the facial bones seemed to be critical in this distinction (Fig. 4). Ratios using this part of the skull film proved more successful. Fig. 5 shows the ratio length of lower face/breadth of skull. The ratio lower face length/skull length gave a very similar degree of differentiation.

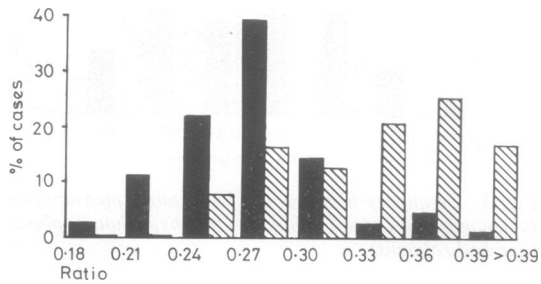

Fig. 5 *Frequency histogram of the ratio length of lower face divided by breadth of skull in achondroplasia (solid columns) and hypochondroplasia (hatched columns).*

SPINAL CHANGES

Measurements of interpedicular distance and of the saggital diameter of the neural canal in the lumbar region are displayed in Fig. 6. They confirm the often stated tendency for progressive caudal narrowing of the neural canal in both conditions, and show that this tendency is more marked in achondroplasia. The important point to note is the severe degree of spinal canal stenosis present in a minority of patients with hypochondroplasia (Fig. 7).

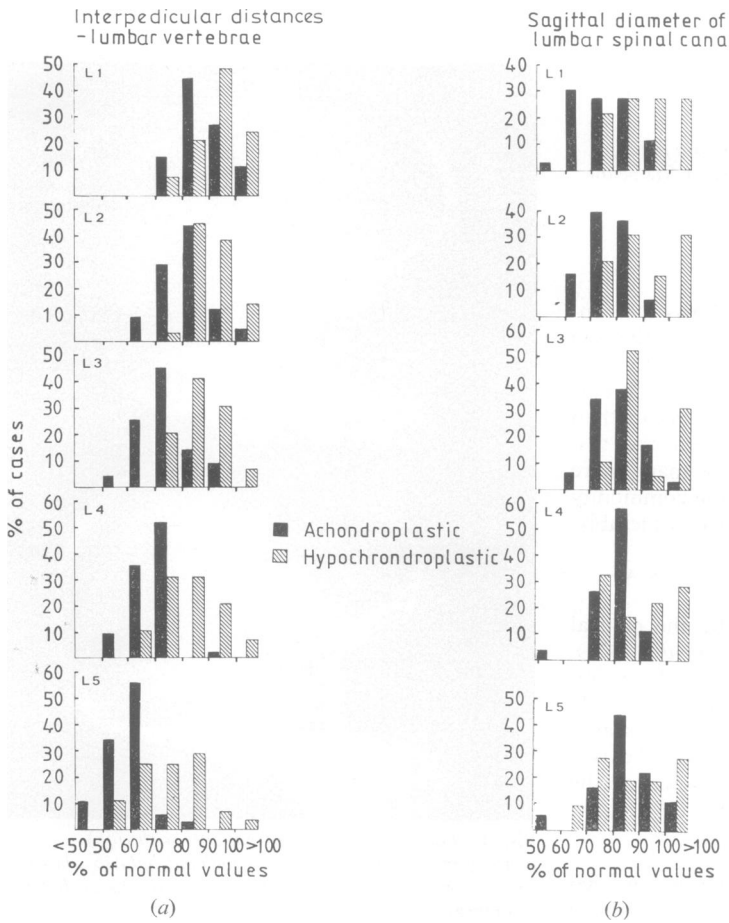

Fig. 6 *Frequency histograms of* (a) *interpedicular distance and* (b) *sagittal diameter of lumbar vertebral canal at L1 to L5.*

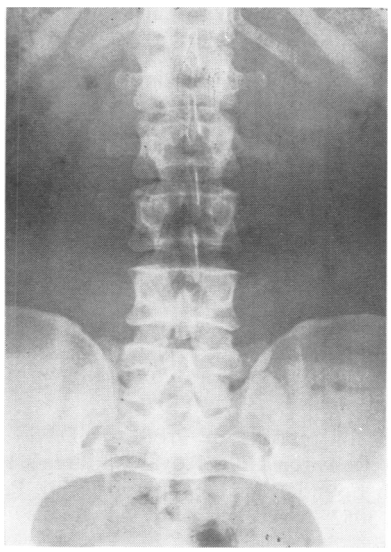

Fig. 7 *A–P view of spine of patient with hypochondroplasia showing extreme narrowing of spinal canal.*

Discussion

This paper deliberately presents several isolated fragments of information about achondroplasia and hypochondroplasia to supplement the extensive facts already well known.

The patients were discovered in the course of a very intensive programme seeking to ascertain all dwarf patients in the State of Victoria (population 3·5 million). However, analysis showed that this objective was not achieved even for the most obvious and best known of the conditions, achondroplasia. It is difficult to make an accurate assessment of the completeness of the ascertainment, but 60% is probably a reasonable estimate if allowance is made for the effects of migration upon the calculations presented in this paper. Ascertainment was particularly poor in the middle aged adults and the importance of this observation will be discussed in another paper which reports the sociological data gathered in the same survey.

The intense interest generated by the study has made ascertainment of new babies with dwarfing bone dysplasias very close to complete since 1969, allowing a reasonable estimate of the incidence and mutation rate for achondroplasia. The mutation rate calculated is similar to others calculated in man and to mutation rates found in experimental animals. The figure is much lower than that found in the classic study of Mørch (1941) in Denmark. It is well known that this study included patients with several other bone dysplasias, some of which are recessively inherited (Silverman and Brünner, 1967).

It is impossible to make a reasonable estimate of the frequency of hypochondroplasia. The 25 cases presented here represent a very large series by the standards of existing published reports, yet it is quite certain that these patients are only a small proportion of those who exist in Victoria. The taller hypochondroplasics merge in with the smallest members of the general population. Even within affected families, some of the affected individuals refused to acknowledge that they were abnormal in any way. Even when both parents of a hypochondroplasic child were examined clinically and radiologically it was sometimes impossible to reach a decision as to whether either had hypochondroplasia. It is very difficult to classify an adult who is between 2 and 3 SD below the mean adult height, has a lumbar neural canal which widens only very minimally from L1 to L5, a fibula which is marginally longer than the tibia, and rather large greater femoral trochanters. Difficulty also occurs in distinguishing between hypochondroplasia and dyschondrostenosis.

This study has clung to the definition that hypochondroplasic individuals have normal facial appearance and lack the characteristic facies of achondroplasia. It seemed useful to seek features in the skull films which could be used by radiologists without seeing the patient clinically, and also by readers of articles on hypochondroplasia. Several skull measurements and indices which are classically described in achondroplasia proved to be of no use in making this distinction. Some other indices were devised which were more valuable. However, it is important to note that these indices were devised after an experiment showed that an experienced radiologist could distinguish skull films of hypochondroplasic individuals from those of achondroplasics without making any measurements. None of the ratios devised distinguished as reliably as the experienced eye, which seemed to compare the volume of the facial bones with the size of the cranial vault. This is quite striking in the *x*-rays shown in Fig. 4.

Measurements of the neural canal in the lumbar region confirmed the belief that progressive narrowing is characteristic of both conditions and is more severe in achondroplasia. The important point behind these measurements is the severe degree of spinal canal stenosis which can be present in some patients with hypochondroplasia, and this point is further shown by the illustrative *x*-ray (Fig. 7). It is most important that clinicians caring for patients with hypochondroplasia should realise that some of these patients are exposed to the same risk of neurological complications of spinal canal stenosis as achondroplasic patients.

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