Clinical Genetics 1984: **25**: 175–181

The syndromic status of sclerosteosis and van Buchem disease

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We have examined 50 persons with sclerosteosis in the Afrikaner community of South Africa and 15 individuals with van Buchem disease in Holland. The clinical and radiographic manifestations of these conditions are very similar, the only notable differences being greater severity and syndactyly in the majority of the patients with sclerosteosis.

The Afrikaners have Dutch antecedants and it seems likely that these autosomal recessive disorders result from homozygosity of the same faulty genes. The phenotypic variation may be due to the epistatic effect of modifying genes in the Afrikaner population.

Received 6 July, accepted for publication 27 September 1983

Key words: Autosomal recessive inheritance; craniotubular hyperostoses; sclerosing bone dysplasias; skeletal dysplasia.

Sclerosteosis and van Buchem disease are inherited sclerosing bone dysplasias which are classified as craniotubular hyperostoses. We have examined 50 patients with sclerosteosis in the Afrikaner community of South Africa (Beighton et al. 1976, Beighton & Hamersma 1979) and 15 individuals with van Buchem disease in Holland. The two conditions have many clinical and radiographic features in common, and as the Afrikaners are largely of Dutch descent, it seems possible that there is a fundamental genetic link between these disorders.

The syndromic status and inter-relationship of sclerosteosis and van Buchem disease are reviewed in this paper. We postulate that they are both the consequence of homozygosity for the same pair of abnormal genes, and that superficial phenotypic differences are due to the epistatic influence of additional modifying genes which are present in the Afrikaner population.

Material and Methods

Every known patient with sclerosteosis in South Africa has been examined and investigated and a total of 40 persons have been seen since 1972, of whom 5 are now deceased. In addition, medical records, photographs and radiographs facilitated the diagnosis of sclerosteosis in a further 10 deceased Afrikaners. The present analysis is based upon firm evidence available for 42 of these patients.

During a visit to Holland the 12 surviving Dutch patients known to have van Buchem disease (van Buchem et al. 1955, van Buchem et al. 1962, van Buchem 1971) were examined (P.B. and H.H.). Three additional previously unreported affected children

were also recognized in the consanguineous community of Urk in the Zuider Zee.

Radiographs were available for the 42 sclerosteosis patients, while details of those of several persons with van Buchem disease had been described in the literature. Recent hand radiographs from 8 Dutch patients with van Buchem disease were provided by Dr. van der Wouden.

Two families in Britain, one in Canada and one in the U.S.A. who had been previously diagnosed as having van Buchem disease were also seen by H.H. or P.B. These patients proved to have the autosomal dominant type of endosteal hyperostosis. This disorder is readily differentiated from the preceding conditions by virtue of its mild clinical and radiographic features, benign course and dominant mode of inheritance (Eastman & Bixler 1977) and it will not be given further consideration in this article.

Results

The 42 Afrikaner patients with sclerosteosis were members of 27 separate families, while the 15 Dutch individuals with van Buchem disease came from 8 kindreds, 10 being members of the consanguineous community of Urk in the Zuider Zee. In each instance, pedigree data was consistent with autosomal recessive inheritance.

Basic information concerning sclerosteosis and van Buchem disease and the patients who form the subject of this study is given in Table 1.

Clinical Features

As both conditions are progressive, meaningful comparison of manifestations is difficult in childhood. The clinical features of 25 adults aged 20 and over with sclerosteosis and 10 adults with van Buchem disease, which are of value in distinguishing between these disorders are shown in Table 2.

Table 1

	Sclerosteosis	van Buchem disease
Adults:	25	10
Children:	17	5
Total patients:	42	15
Location:	South Africa	Holland
Age of presentation:	Early childhood	Mid childhood
Prognosis:	Potentially lethal	Relatively benign
Genetics:	autosomal recessive	autosomal recessive

Table 2

Sclerosteosis and van Buchem disease: distinguishing features in adulthood

Clinical	Sclerosteosis	van Buchem disease
Tall stature (over 180 cm):	18/25–72%	4/10–40%
Syndactyly:	19/25–76%	0 0
Nail hypoplasia:	20/25–80%	0 0
Severe facial distortion:	20/25–80%	3/10–30%
Mild facial distortion:	5/25–20%	7/10–70%
Fadial palsy:	22/25–88%	6/10–60%
Deafness:	23/25–92%	4/10–40%
Raised intracranial pressure:	20/25–80%	2/10–20%

Radiographic Features

The age-related radiological manifestations were similar in both groups of patients. The major changes were present in the skull, where massive hyperostosis of the calvarium and mandible and sclerosis of the base invariably occurred. The spine showed mild sclerosis, especially the vertebral pedicles, while the pelvis was sclerotic, without alteration of the bony contours. Increased radiological density and cortical widening was a major feature of the long bones of the limbs.

The only real difference between the conditions was in the hands, where some degree of syndactyly and radial deviation of terminal phalanges was seen in the majority of sclerosteosis patients (Beighton et al. 1976). By contrast, none of the persons with van Buchem disease had changes of this type.

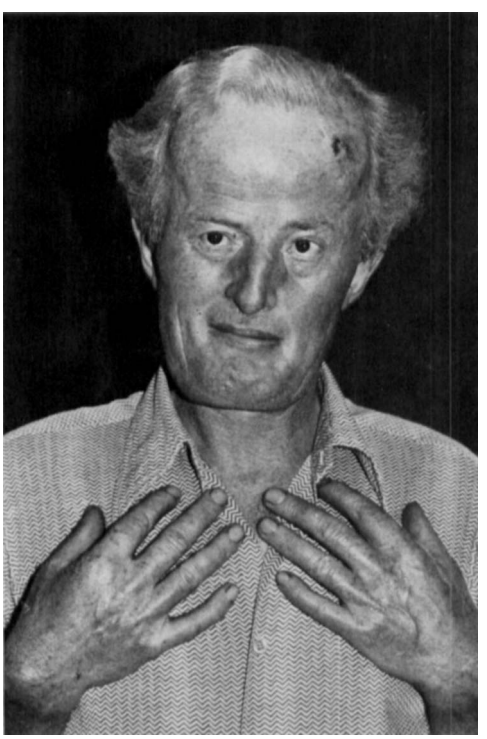

Fig. 1. Van Buchem disease: moderate craniofacial involvement, no syndactyly.

Fig. 2. Van Buchem disease: severe craniofacial involvement. This patient has no syndactyly.

Under-modelling of the shafts of the tubular bones of the digits was present in both disorders but consistently more pronounced in the sclerosteosis group, even in the individuals who lacked syndactyly. Irregularity of the cortices of phalanges was age-related, and was encountered in both sets of patients.

Discussion

In view of the similarity of clinical and radiographic features, it is tempting to postulate that sclerosteosis and van Buchem disease are the same disorder, and that their separation is an artificial concept based upon clinical differences which are really reflections of varying expression of the same abnormal genotype.

A patient with sclerosteosis of moderate severity, with most or all of the features

listed in Table 2, would usually be readily distinguishable from an individual with van Buchem disease of the same degree. However, there is certainly overlap and a sporadic individual with mild sclerosteosis, and without syndactyly or other digital changes would be difficult to distinguish clinically and radiographically from a severely affected patient with van Buchem disease. To emphasise these points, mild and severely affected adults with sclerosteosis and van Buchem disease are depicted in Figures 1–5 and hand radiographs are shown in Figures 6 and 7.

Some degree of syndactyly of the fingers was present in 76% of our adult sclerosteosis patients and several others had radial deviation of terminal phalanges and ungual hypoplasia. Conversely, none of the van Buchem patients we examined had any digital changes, other than thickening of the shafts of the phalanges. However, of the 31 sclerosteosis patients of all ages with syndactyly, 4 had affected siblings with normal

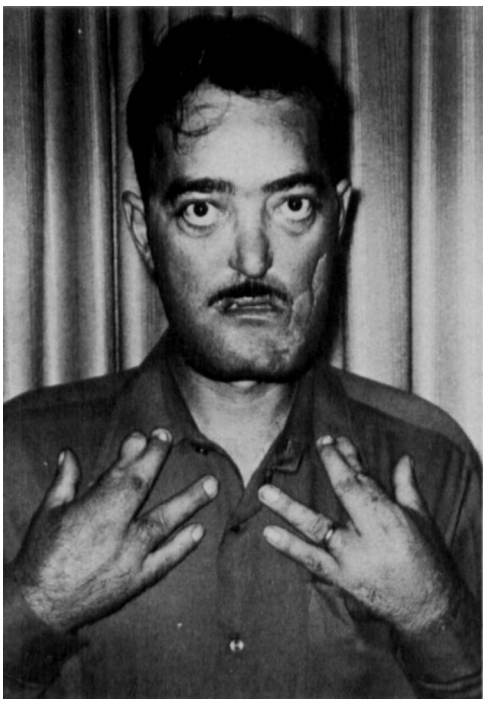

Fig. 4. Sclerosteosis: Severe craniofacial involvement, marked syndactyly.

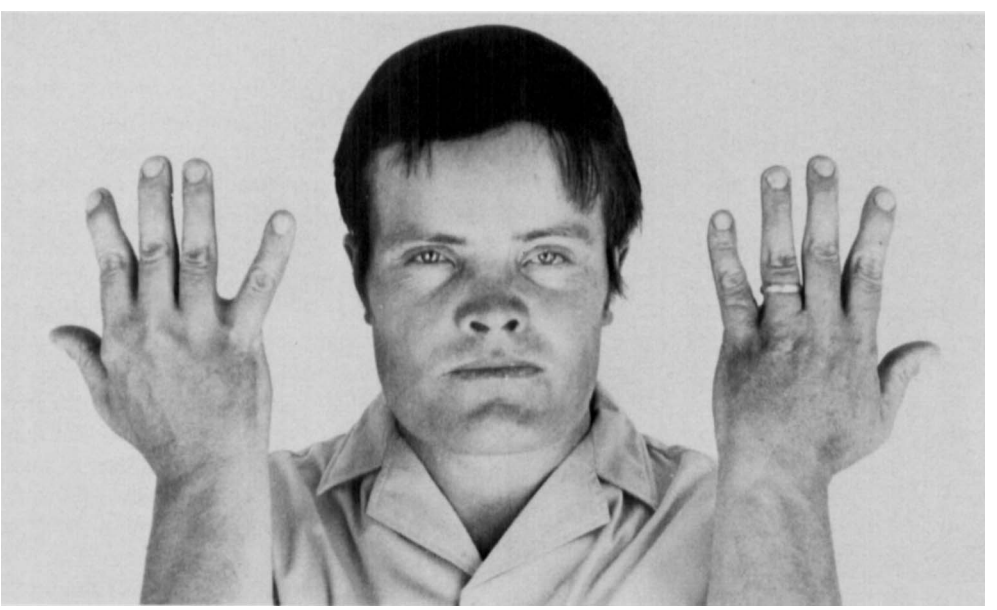

Fig. 3. Sclerosteosis: Mild craniofacial involvement, no syndactyly. The clinical and radiographic features of this patient are indistinguishable from those of van Buchem disease.

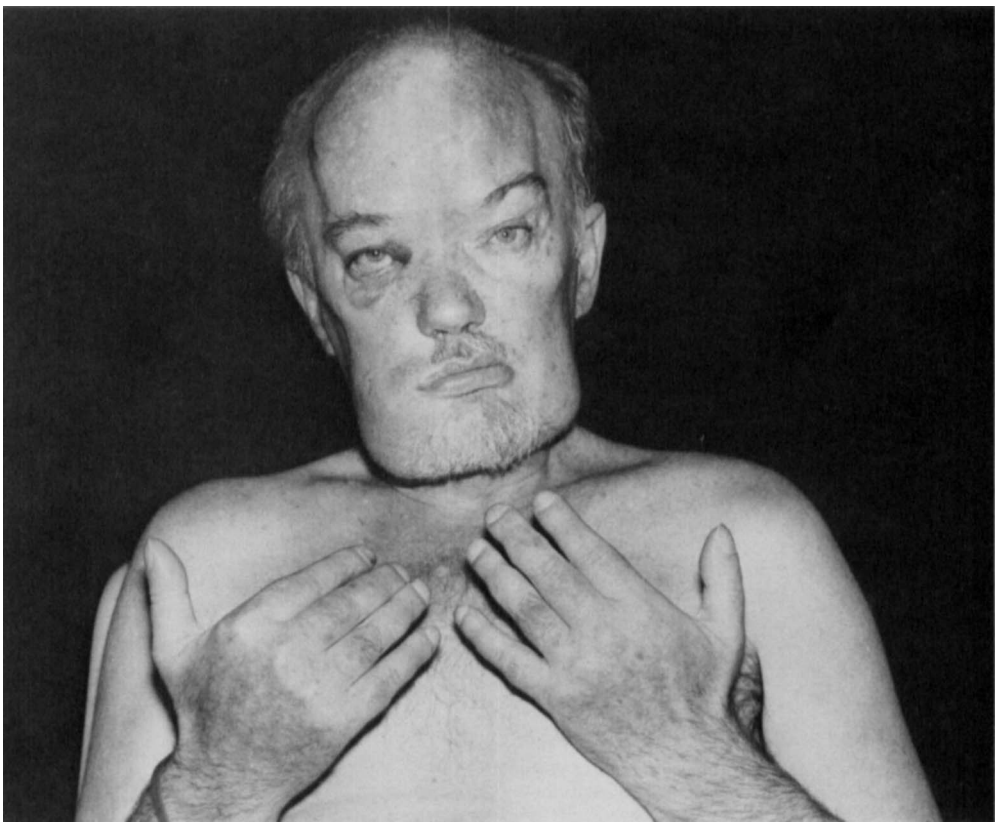

Fig. 5. Sclerosteosis: Severe craniofacial involvement, no syndactyly.

fingers; on this basis, the presence or absence of syndactyly is not an absolute diagnostic discriminant.

Stature is another possible point of differentiation, but although 72% of adult sclerosteosis patients had excessive height, the remainder were normal in this respect. Moreover, in two sets of affected siblings, one was very tall, while the other had normal stature. In the same way, although stature was generally normal in the van Buchem patients, three out of ten adults were unusually tall. One of these was a female, whose affected brother was of normal height.

Excessive height and digital abnormalities were the most important additional manifestations in sclerosteosis. However, these changes were not directly related to each other and some very tall individuals had relatively normal hands, and vice versa.

Laboratory studies are unhelpful in differentiation. In particular, serum alkaline phosphatase has previously been shown to be elevated in all children and most adults with sclerosteosis and in van Buchem disease. Other routine biochemical parameters are normal and the fundamental defect has not been elucidated in either condition (Epstein et al. 1979).

Both conditions are inherited as autosomal recessive traits (Beighton et al. 1977) and as the present-day Afrikaners of South Africa have close ancestral links with the

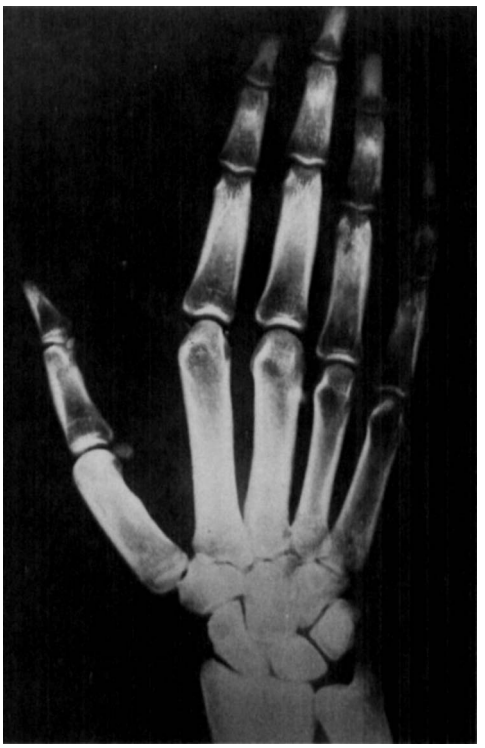

Fig. 6. Van Buchem disease: Hand radiograph of an adult female showing cortical sclerosis undermodelling of the tubular bones.

Dutch, it is tempting to speculate that sclerosteosis and van Buchem disease are the consequence of homozygosity for the same abnormal gene.

Apart from the Afrikaners, cases recognisable as sclerosteosis have only been reported in two kindreds in North America (Kelley & Lawlah 1946, Higinbotham & Alexander 1941), a consanguineous family of Dutch ancestry in Brazil (de Paes Alves et al. 1982), and a sporadic girl in Japan (Suguira & Yasahura 1975). Equally, the only report of van Buchem disease occurring outside Holland concerns affected siblings in Scotland (Dixon et al. 1982). In view of the dramatic syndromic stigmata it is unlikely that many cases have gone unnoticed, and it is reasonable to assume that these conditions are excessively rare. This fact gives further support to the concept of fundamental syndromic homogeneity in the closely related Afrikaans and Dutch populations.

In spite of the foregoing, it is an inescapable fact that the majority of sclerosteosis patients have some degree of syndactyly and nail hypoplasia, together with tall stature. Conversely, these features are not usual manifestations of van Buchem disease. The most logical explanation of this anomalous situation would be that the Afrikaners possess an additional epistatic gene. This hypothetical gene must present in relatively high frequency in the South African population and its presumptive mode of action would be in developmental regulation during early embryogenesis. If this is indeed the true state of affairs, the separate syndromic status of sclerosteosis and van Buchem disease becomes a matter of semantics.

Acknowledgments

We are grateful to R. C. de Mèneaud for preparing the illustrations and to Gillian Shapley for typing the manuscript. The investigation was supported by the Mauerberger Foundation, The South African Medical Research Council and the University of Cape Town Staff Research Fund.

This article is based upon a paper presented by PB at the 1983 Congress of the European Society of Human Genetics, Nijmegen, Holland.

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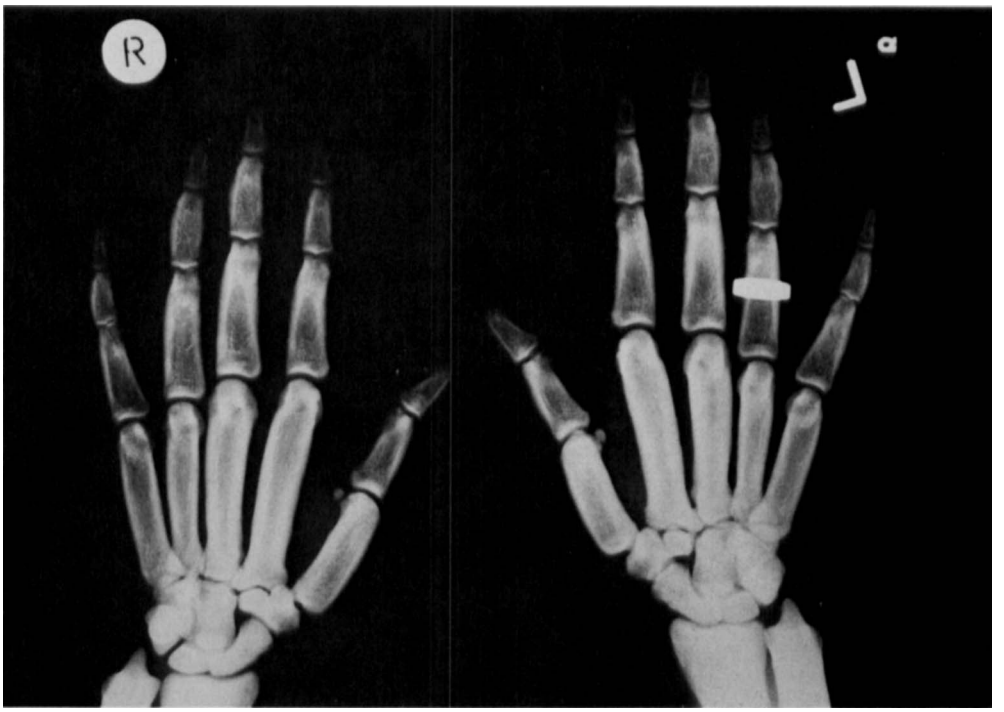

Fig. 7. Sclerosteosis: Hand radiograph of an adult female showing changes similar to those in Fig. 6. Soft tissue syndactyly is present in patient.

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