

The Clinical Features of Sclerosteosis

A Review of the Manifestations in Twenty-Five Affected Individuals

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Sclerosteosis is a unique autosomal recessive condition in which skeletal overgrowth is associated with syndactyly and digital malformation. Analysis of the course and clinical features in 25 affected individuals showed that the condition is progressive and potentially lethal. Facial palsy and deafness are common complications and raised intracranial pressure may develop. The clinical and radiographic stigmata of sclerosteosis permit differentiation from the other disorders of the "osteopetrosis" or "Albers-Schönberg disease" group, in which bony thickening and cranial nerve palsy occur.

SCLEROSTEOSIS is a rare genetic disorder in which syndactyly is associated with thickening and overgrowth of the bones (1). The condition is of considerable practical significance as deafness and facial palsy are common complications, while compression of other cranial nerves may occur. Sudden death may be a consequence of raised intracranial pressure.

We have personal knowledge of 25 affected individuals in 15 kindreds in South Africa. The clinical manifestations of sclerosteosis, based upon our studies of these patients, are reviewed in this paper.

Investigation Procedure

We have attempted to investigate every affected individual in South Africa. Many of the patients with sclerosteosis had been referred to one of the authors (H. H.) for assessment and treatment of deafness or for facial nerve decompression, while others were traced as part of a nationwide survey of various forms of "osteopetrosis."

We were able to undertake clinical, radiologic, and biochemical studies on each of the 21 living patients. Medical case notes and family photographs provided adequate data concerning a further 4 deceased individuals who were affected siblings of patients in our series.

Extensive investigations in the relatives of our patients have led to the accumulation of radiologic and biochemical data. Using this material, we are at present endeavouring to devise a method for detection of the clinically normal heterozygous carrier of the gene.

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Clinical Features

The clinical features of the patients in our series are shown in Table 1. In view of the progressive nature of the disorder, the findings in children and adults have been tabulated separately.

GENERAL COURSE AND PROGRESSION

Affected individuals may be recognised at birth by the presence of variable degrees of syndactyly, usually of the second and third fingers, associated with dysplasia of the nails and radial deviation of the terminal phalanges (Figure 1).

Palsy of the facial nerve may also be evident at birth, or may occur episodically throughout infancy or childhood. Unilateral or bilateral facial paralysis or paresis frequently becomes permanent in late childhood. Conductive deafness due to impaired mobility of the middle ear ossicles, usually necessitating the use of a hearing aid, often becomes apparent when schooling commences.

In early adult life, the optic nerves may be compressed, and papilloedema consequent upon raised intracranial pressure may develop. However, complete loss of vision seldom occurs. Compression of the olfactory and trigeminal cranial nerves is a less common complication.

Apart from the changes in the digits, abnormalities of the skeletal configuration are not apparent during infancy. However, generalised bony overgrowth and progressive enlargement of the mandible and forehead usually become noticeable after the age of 4. Facial distortion is very obvious by the age of 10 and considerable deformity of the facies is present by the time that progression ceases at the end of the third decade. At this stage, in addition to the clinical consequences of their cranial nerve palsies, the majority of affected individuals have proptosis, malalignment of the teeth and relative midfacial hypoplasia (Figure 2A and B).

Gigantism is evident in childhood and many affected adult men exceed 198 cm (6 ft, 6 in) in height, while adult women may be more than 183 cm (6 ft) tall. Patients are unusually heavy, due to excessive skeletal mass; and widening of the bones, particularly the clavicles, can be recognised on palpation.

General health is good and intellectual capacity is normal, as evidenced by the way that one of our patients

Table 1. Sclerosteosis—Clinical Features

Patient	Kindred	Sex	Birth Year	Height	Weight	Syndactyly, second and third fingers	Cranial Nerve Compression				Deafness		Prop- tosis	Head- ache	Date of Death
							Optic		Trigeminal		L	R			
							L	R	L	R					
				cm	kg										
Adults															
1	1	M	1943	203	118	+		+	+	+	+	+	+		
2	2	M	1949	200	91	+		+	+	+	+	+	+		
3	3	F	1942	182	69	+++		+	+	+	+	+	+		
4	3	F	1940	185	73	+				+	+				
5	4	F	1956	177	95				+	+	+	+			
6	5	M	1945	200	86	+++			+	+	+	+	+		
7	5	F	1934			++			+	+	+	+	+		
8	5	F	1937			?			+	+	+	+	+		1965
9	6	F	1951	177	86	++	+	+	+	+	+	+	+		1964
10	7	F	1954	182	63				+	+	+	+	+		
11	8	M	1927	198	82	++			+	+	+	+	+		
12	8	M	1925	200	84	+			+	+	+	+	+		1960
13	9	F	1940	167	85	+++			+	+	+	+	+		
14	9	M	1947	177	79	+			+	+	+	+	+		
15	10	M	1920	180	82				+	+	+	+	+		
16	10	M	1900	202	98	?				?	+	+	+	+	1944
Children															
17	11	M	1965	139	27	++			+		+	+			
18	11	F	1970	109	18	++			+						
19	12	F	1970	91	14	+			+	+					
20	13	F	1964	129	25	+			+	+	+	+			
21	13	M	1970	104	16	+				+					
22	14	F	1964	152	45	++				+	+				
23	15	M	1959	182	52	+++	+	+	+	+					
24	15	F	1966	134	23	++			+						
25	15	M	1967	129	25	+++			+	+					

became an amateur boxing champion while another gained a university degree in metallurgy. However, psychological difficulties are commonplace and social life may be disrupted.

The bones are not fragile and there is no undue liability to osteomyelitis or dyshaemopoiesis, as occurs in some forms of osteopetrosis.

Headache is a common complaint in early adult life and craniotomy has been required for the relief of raised intracranial pressure in several patients. Four individuals known to us died suddenly in early adulthood. In one, autopsy showed that acute medullary compression had oc-



Figure 1. Digital deformity and nail dysplasia. Soft tissue syndactyly has been corrected at operation.

curred. It is noteworthy that only two of our patients are more than 35 years of age. On this basis, sclerosteosis must be regarded as a potentially lethal condition.

NEUROLOGICAL MANIFESTATIONS

Facial Nerve Palsy: In view of the clinical importance of the neurological complications, these are considered in greater detail in this section. Unilateral facial palsy was present at birth in 4 patients, and developed during the first 5 years of life in 12 others.

These children had frequent attacks of facial paralysis, identical to Bell's palsy, and it is of considerable significance that disturbed function of the facial nerve occurred before overgrowth of the skull severely constricted the neural foramina. However, with thickening of the cranial bones and occlusion of the foramina in later childhood, the facial nerve compression produced permanent paralysis, which was usually partial in extent. These changes were bilateral in 11 of the 16 affected adults and in 4 of the affected children, and unilateral in all but 1 of the other patients in the series.

Deafness: Conductive deafness due to immobilisation of the ossicles of the middle ear was bilateral in all adults. Three children also had bilateral deafness, while the majority of the others were below the age at which this complication usually develops. One 14-year-old boy, who had normal hearing, was an exception in this respect. Impairment of the inner ear function, as measured by means of bone conduction, may develop in adulthood, probably as

a result of compression of the vestibulocochlear nerve in the internal auditory canal, or due to interference of the oval and round windows of the cochleae.

Visual Impairment: The fundal changes of optic atrophy were observed bilaterally in one adult and unilaterally in two others, while an adolescent boy also had bilateral changes. Of these individuals, significant visual impairment was present in one young man who had unilateral blindness following optic nerve decompression and in a woman who had lost the sight in one eye after craniotomy and orbital decompression. In three other patients, visual defect due to papilloedema was completely relieved by craniotomy.

From our experience, it appears that involvement of the optic nerves is a late feature of the condition, and that total blindness from this cause is unlikely to occur. However, longstanding raised intracranial pressure and papilloedema certainly pose a threat to vision.

Involvement of Other Nerves: Impairment of sensation in the areas of the face supplied by the first and second divisions of the trigeminal nerve was shown in six of our patients. This abnormality was limited in degree and of little clinical consequence. However, in a middle aged man, severe unilateral pain in the jaw has been attributed to involvement of the second and third divisions of the trigeminal nerve.

No patient complained of symptoms that could have been related to involvement of the vestibular or olfactory nerves.

Bilateral pain and paresis in the arms, from cervical plexus involvement, incapacitated a woman. At operation, which was technically difficult and produced only partial relief, the roots of the plexus were found to be compressed by bony overgrowth in the intervertebral foramina.

Radiological Features

Apart from digital malformations, the skeleton is radiologically normal at birth. Changes become apparent in early childhood and increase in severity until progression ceases at the end of the third decade.

By late childhood, gigantism is apparent, with overgrowth of all bones. Increased radiologic density is particularly obvious in the skull and pelvis, while involvement of the spine is relatively mild. The cortices of the tubular bones becomes dense and the normal diaphyseal constrictions are lost (Figure 3A and B, Figure 4A and B).

The radiologic features of our patients will be reported in greater detail elsewhere.

Laboratory Investigations

Routine biochemical investigations were undertaken in all living patients. The only significant abnormality was in the serum alkaline phosphatase, which was persistently elevated in all but four of the patients. In particular, levels exceeded 200 King-Armstrong units (normal range 30, 85 King-Armstrong units) in each of the children.

Other biochemical parameters, including serum calcium, phosphorus, and acid phosphatase concentrations were normal in all instances.

Standard haematologic investigations yielded consistently normal results, and there was no anaemia or evidence of bone-marrow dysfunction in any of the patients.

Genetics

Previous reports have indicated that sclerosteosis is inherited as an autosomal recessive (2). Several of our pa-

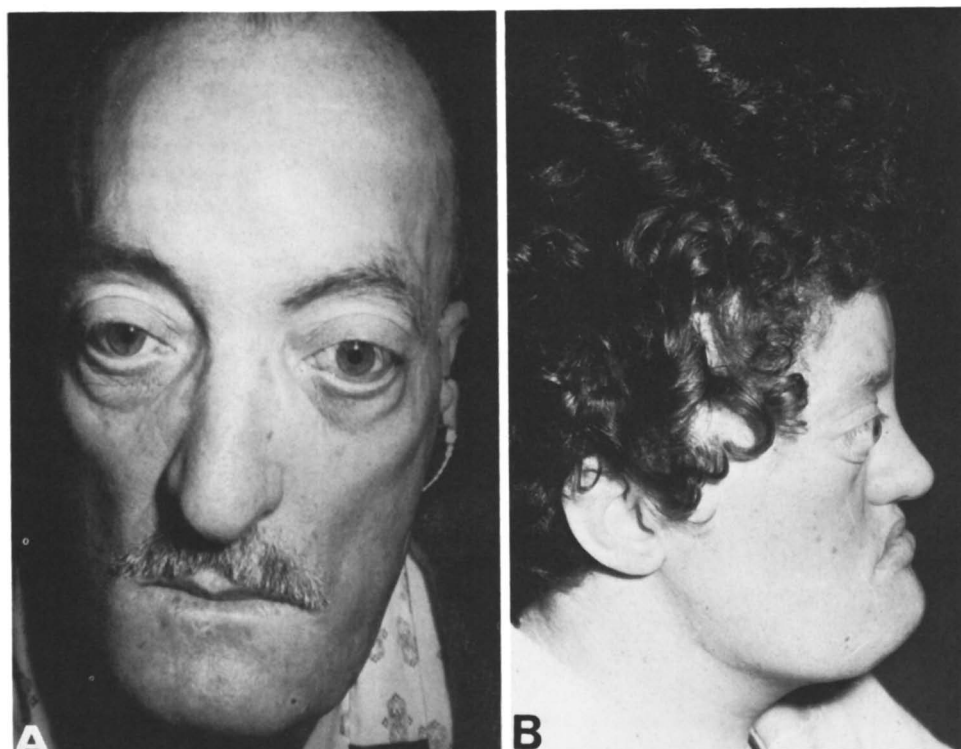


Figure 2A. Characteristic facies—mandibular overgrowth and asymmetry. **B.** Typical profile—mandibular distortion and proptosis.

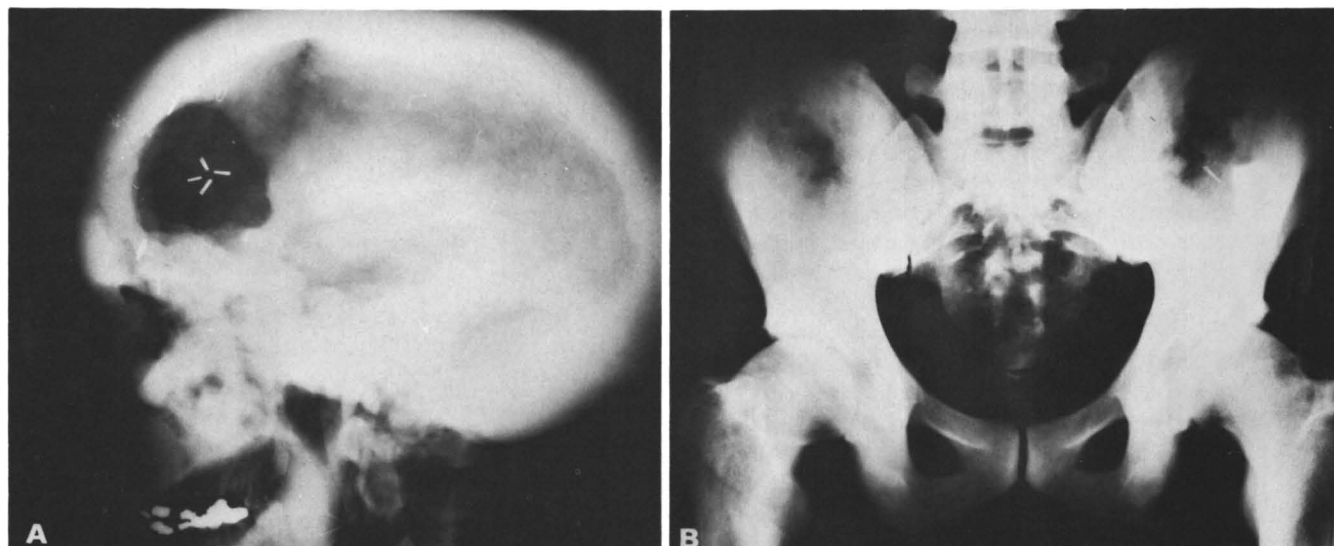


Figure 3A. Lateral skull radiograph. Gross sclerosis and hyperostosis. The frontal defect is the consequence of craniotomy. **B.** Anteroposterior radiograph of pelvis.

tients had affected siblings, and parental consanguinity was present in five of the kindreds. There were no instances of parent-to-offspring transmission, and our pedigree data is entirely consistent with autosomal recessive inheritance.

In several of the clinically normal parents of affected individuals, minor degrees of thickening and loss of tabulation of the calvarium was apparent on lateral skull radiographs. It is possible that these observations may permit recognition of the asymptomatic heterozygous carrier of the gene (3).

All our patients were of Afrikaner stock, predominantly of Dutch descent, and thus, the prevalence of the disorder here can be estimated at about 1 in 100 000.

Management

The most important facet of the management of affected individuals is surgical relief of cranial nerve compression and raised intracranial pressure.

Structural abnormalities of the digits will usually require correction, while retrusion of a prognathic mandible and tarsorrhaphy or orbital decompression for proptosis may be indicated. Malalignment of the teeth necessitates regular dental treatment.

Deafness is a particularly intractable problem. However, a hearing aid provides relief for the conductive element of the auditory deficit.

In view of the grotesque appearance, it is not surprising

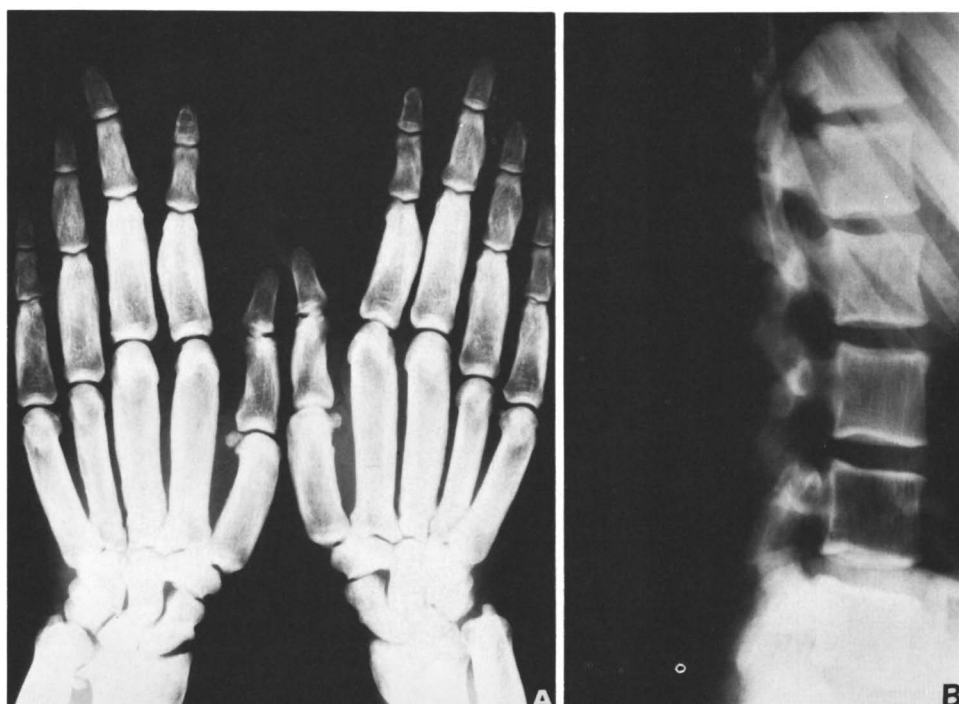


Figure 4A. Radiograph of hands. Defective bony modelling. **B.** Lateral radiograph of lumbar spine. In contrast to other forms of osteopetrosis, the vertebral bodies are comparatively normal.

that many affected individuals have considerable psychosocial problems and psychotherapy may well have an important part to play in the overall management of the disorder.

Recognition of the autosomal recessive nature of the condition permits accurate genetic counselling, and there is considerable potential for future control on a basis of heterozygote detection. In view of the digital malformations, prenatal diagnosis may be possible when the technique of foetoscopy becomes available.

Discussion

Sclerosteosis was first recognised as a distinct entity in 1958 when Truswell (4) described two unrelated South African girls. Hansen (1) (1967) used the designation "sklerosteose," and the term "sclerosteosis" has subsequently been used in other reviews and textbooks (2, 5, 6).

In the past, patients with sclerosteosis have featured in reports that have been concerned with "osteopetrosis," and in general they have not been separated from individuals with other forms of this disorder (7-12). The majority of these articles have emanated from South Africa, and several of the affected individuals have been restudied in the present investigation. The only convincing case reports from other parts of the world concern a kindred in New York (9) and a Japanese girl (13).

Conditions characterised by bony sclerosis and hyperostosis are generally grouped together under the designation "osteopetrosis" or "Albers-Schönberg disease" (14, 15). Sclerosteosis must be distinguished from these various forms of osteopetrosis and from the conditions that have been classified as "osteosclerosis," "cranio-tubular dysplasias," and "cranio-tubular hyperostoses" (2). Camurati-Engelman disease or progressive diaphyseal dysplasia bears some resemblance to sclerosteosis, in that diaphyseal hyperostosis is present, and cranial nerve problems may occur. However, the gross skeletal changes and digital malformations in sclerosteosis, together with the absence of muscular involvement in this condition are obvious points of difference.

There are some similarities between sclerosteosis and van Buchem's disease (16, 17) (hyperostosis corticalis generalisata), and it is of interest that this latter disorder was described in the population of Holland, with whom the Afrikaners share a common genetic heritage. However, gigantism and syndactyly are not features of van Buchem's disease and the radiographic changes in sclerosteosis are of greater severity. In three of our patients with sclerosteosis, syndactyly was not present, but the abnormal modelling of their metacarpals and phalanges permitted differentiation from van Buchem's disease.

It is noteworthy that none of the nine affected children lacked syndactyly. As this abnormality is often the pre-

senting feature of the condition, it is possible the patients with minor degrees of syndactyly have so far remained undiagnosed.

The distinctive clinical features of sclerosteosis permit diagnostic precision. The accurate delineation of this disorder is of considerable importance, in view of the mode of progression, distressing complications and genetic implications.

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