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Original Article

The natural history of sclerosteosis

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Sclerosteosis (SCL) is a severe, progressive, autosomal-recessive craniotubular hyperostosis (MIM 269500). The determinant gene (*SOST*) has been isolated, and genotype–phenotype correlations, as well as the elucidation of pathogenetic mechanisms, are dependent upon the documentation of the natural history of the condition. For this reason, the course and complications in 63 affected individuals in South Africa, seen over a 38-year period, have been analyzed. Thirty-four of these persons died during the course of the survey, 24 from complications related to elevation of intracranial pressure as a result of calvarial overgrowth. The mean age of death in this group of individuals was 33 years, with an even gender distribution. Facial palsy and deafness, as a result of cranial nerve entrapment, developed in childhood in 52 (82%) affected persons. Mandibular overgrowth was present in 46 (73%) adults and syndactyly in 48 (76%). In South Africa in 2002, 29 affected persons were alive, 10 being $\leq$20 years of age. It is evident that sclerosteosis is a severe disorder which places a considerable burden upon affected individuals and their families.

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Sclerosteosis (SCL) (MIM 269500) is an autosomal-recessive disorder in which progressive bone overgrowth leads to gigantism, distortion of the facies, and entrapment of cranial nerves. Syndactyly, usually of the index and middle fingers, is a variable syndromic component. Potentially lethal elevation of intracranial pressure is a frequent complication which has been recognized in children as young as 5 years of age. The condition is rare, but reaches a comparatively high prevalence in the Afrikaner community of South Africa (1, 2).

The sclerosteosis gene (*SOST*) has been mapped to 17q12–21, and a single specific mutation in the Afrikaner population has been identified (3–5). Documentation of the evolution of the phenotype is necessary for establishment of genotype–phenotype correlations and elucidation of the pathogenetic process. In this article we document the course and outcome of the disorder in 63 affected persons in South Africa, studied over a 38-year period.

Patients and methods

The 63 affected persons were members of the Afrikaner community of South Africa. Together with their families, they have been in contact with the authors since before 1964 and they have been seen on many occasions. Detailed records have been maintained and these were analyzed for the purposes of this investigation.

In order to provide a perspective of the course of the disorder, photographs of siblings in early childhood and in adulthood are presented (Figs 1–6). The characteristic radiographic appearances of digital hyperostosis and gross calvarial thickening are depicted in Figs 7 and 8.

Results

Family data

The 63 affected persons were members of 38 families, of which eight were known to be consanguineous. Thirty-four males and 29 females were affected, and pedigree data were entirely in keeping with the established autosomal-recessive mode of genetic transmission (6).

Year of birth

One or two affected children are born into the Afrikaner population each year. The actual incidence is falling because the average family size is diminishing, although the Afrikaner population

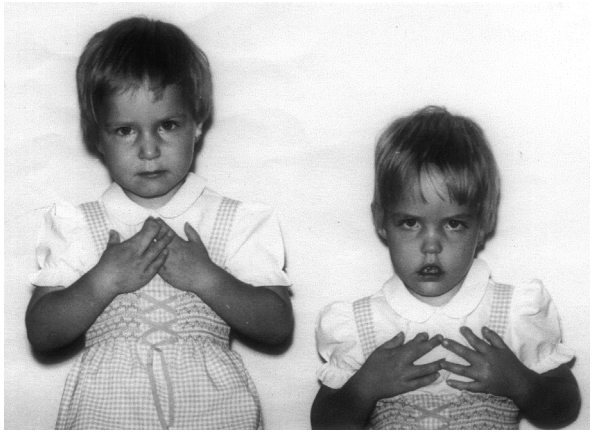

Fig. 1. Two affected sisters, R.H. (age 3–on the left), and N.M. (age 4). Both have experienced intermittent facial palsy. Syndactyly of the 2nd and 3rd fingers is evident.

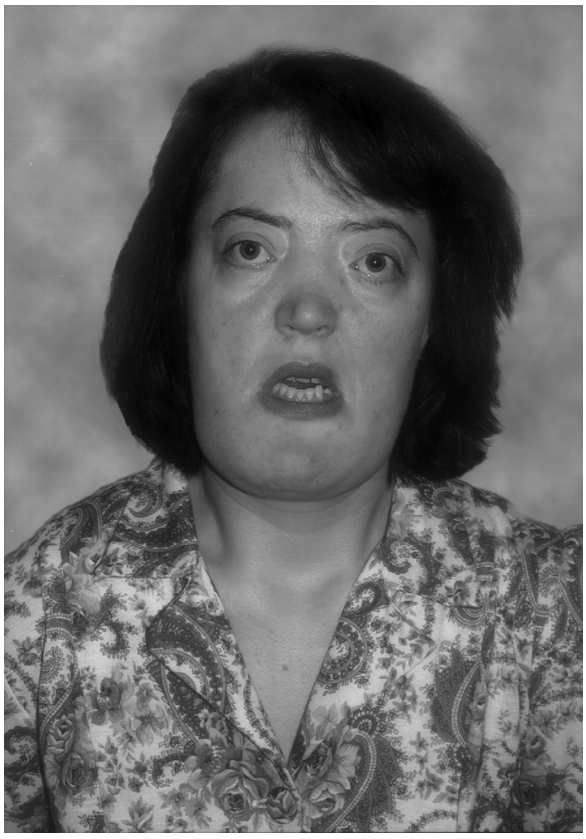

Fig. 2. Patient R.H. of Fig. 1 at 26 years of age: full face. Gross overgrowth of the mandible, proptosis, moderate bilateral deafness and bilateral partial facial palsy are present.

(currently about 4 million) has expanded during the 38-year duration of the investigation.

Stature

Affected individuals have tall stature with an increased head circumference and excessive weight.

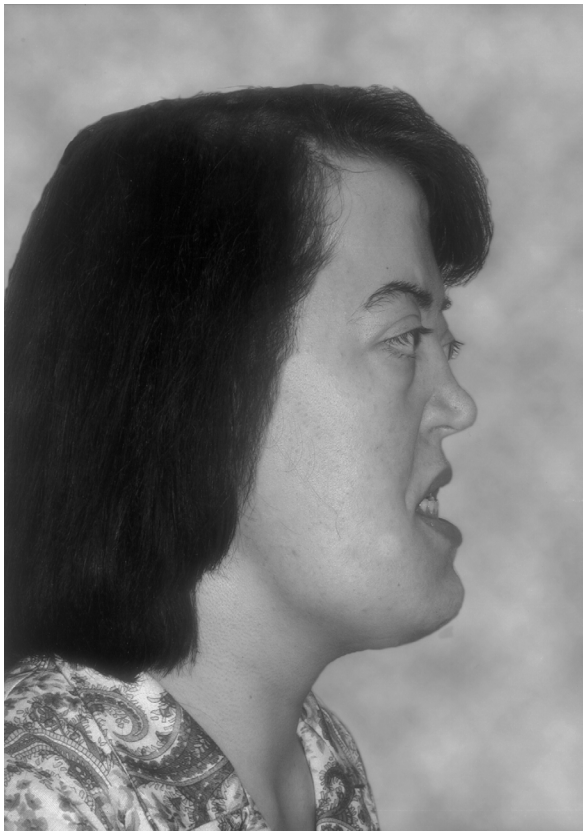

Fig. 3. Patient R.H. at 26 years of age: profile. Relative mid-facial hypoplasia and proptosis are evident. Craniectomy for elevated intracranial pressure and attempted mandibular reduction operations have been undertaken.

Fig. 4. Affected siblings: B.E. at 6 and A.E. at age 4. Both have partial facial palsy, hearing loss and mild mandibular overgrowth.

The average height of adult males (n = 14) was 194 cm (range: 178–207 cm). The average height of adult females (n = 11) was 180 cm (range: 168–190 cm). Mean head circumference in adult males

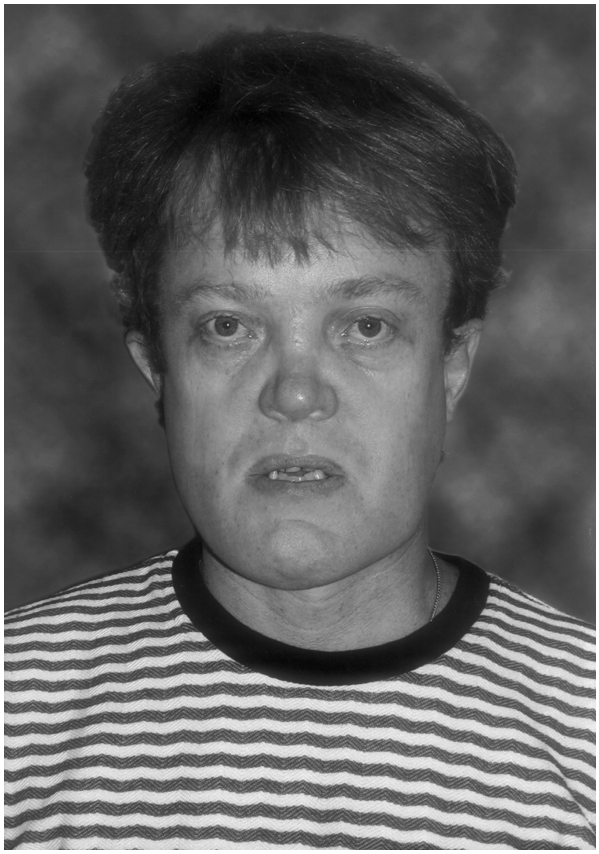

Fig. 5. Patient B.E. of Fig. 4 at 35 years of age. He has deafness, bilateral partial facial palsy and mandibular overgrowth. At this time, he was 190 cm in height and weighed 90 kg. Craniectomy had been undertaken in early adulthood.

Fig. 6. Patient A.E. of Fig. 4 at 30 years of age with facial weakness on the left side only. Syndactyly has been repaired, craniectomy undertaken and mandibular reduction attempted. She is 175 cm in height and weighs 85 kg. Prophylactic nerve decompression on the right prevented facial palsy.

was 61 cm and in adult females 58 cm. Mean adult weight for males was 85 kg, and for females 83 kg. In general, affected persons were not obese and weight was apparently related to increased skeletal size. The age of inception of puberty was similar to that of the general population. As yet, sequential measurements of growth during childhood have not been documented.

Syndactyly

Of the 63 affected persons, 48 had syndactyly of a greater or lesser degree. The index and middle fingers were involved in 41 of the 48 persons, with considerable but not absolute bilateral symmetry. The extent of the syndactyly ranged from minor soft tissue webbing to complete bony union. Radial deviation of the terminal phalanges of the affected digits was usual. The toes were not usually involved but occasionally the nails were dysplastic, especially on the great toes. The presence or absence of digital changes is important in the clinical differentiation of SCL from other sclerosing bone dysplasias (7).

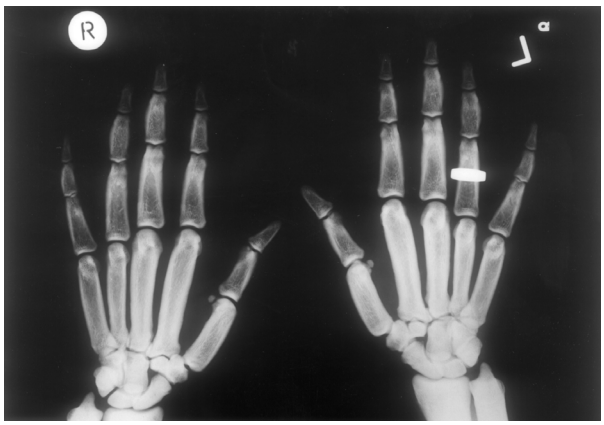

Fig. 7. Antero-posterior radiograph of the hands of an affected adult. The shafts of the tubular bones are widened and irregular, with marked cortical hyperostosis.

Mandibular overgrowth

Massive asymmetrical mandibular enlargement and relative mid-facial hypoplasia, which contribute to the facial distortion, was evident in 46 persons. The mandibular overgrowth generally

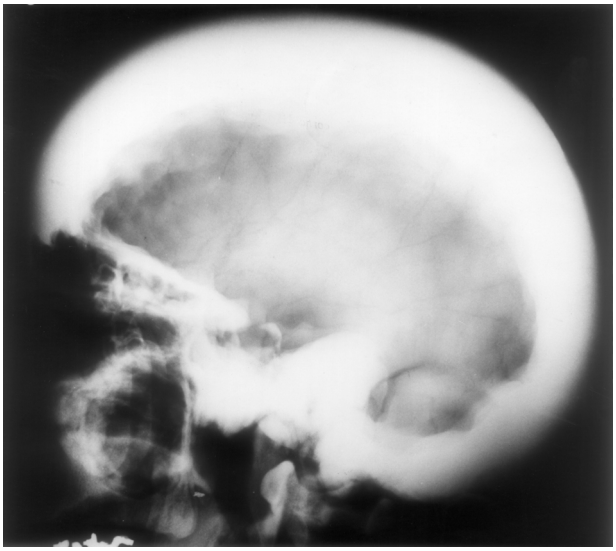

Fig. 8. Lateral skull radiograph of an adult with sclerosteosis. Gross calvarial thickening is evident.

became apparent by mid-childhood and progressed into adulthood. The teeth were morphologically normal, but dental extraction was difficult (8). Mandibular resection for cosmetic reasons or impaired mouth closure has been undertaken. Osteomyelitis of the mandible, which occurs in some forms of osteopetrosis, has not been recorded in sclerosteosis.

Facial palsy

Acute recurrent attacks of facial palsy (similar to Bell's palsy), owing to compression of the 7th cranial nerves in the bony foramina, were recorded in 52 of the 63 affected persons. The average age of presentation was 4 years, ranging from the neonatal period in 12 persons to adolescence in 40. The facial weakness, which was initially episodic but subsequently permanent, was unilateral in 17 and bilateral in 35 persons. Surgical decompression was undertaken in 22 affected individuals, with good results obtained in 15.

Hearing loss

Significant deafness necessitated the provision of a hearing aid in 29 of the 63 subjects. In these individuals, the average age of diagnosis was 6 years, ranging from infancy to young adulthood. Hearing loss was rarely complete, but eight affected children had been educated at special schools for the partially deaf. The deafness was predominantly conductive in the early stages, mainly owing to impairment of movement of the middle-ear ossicles. Closure of the round window niche also contributed a sensorineural component in some instances. Compression of the 8th cranial nerves in the internal auditory canals was sometimes a late complication.

Speech

Speech was frequently impaired owing to a combination of hearing loss, mandibular overgrowth and dental malalignment. Compression of the 7th cranial nerves, resulting in facial weakness and disturbed lip closure, was an important additional factor.

Age at diagnosis

The presence of syndactyly of the index and middle fingers in a neonate of Afrikaner stock raises a high index of suspicion, especially if there is an affected sibling. In the absence of significant or recognized syndactyly, the onset of facial palsy or hearing loss in mid-childhood usually leads to radiological investigations, which provide diagnostic confirmation. It is relevant that overgrowth of the mandible and distortion of the facies is not usually apparent before the age of 5 years. Equally, radiographic evidence of skeletal hyperostosis is rarely evident before this age (9). Sclerosis of the calvarium and base of the skull are the usual presenting radiological features. In this context, it has become apparent that conventional radiological investigations are superior to other imaging techniques for revealing early skeletal changes in the disorder. In the previous generation, accurate diagnosis was delayed until adulthood in 14 persons, but with increasing medical knowledge of the presence of the condition in the Afrikaner community, early diagnosis is now usual.

Elevation of intracranial pressure

Elevation of intracranial pressure owing to progressive calvarial overgrowth was diagnosed in 24 of the 63 affected persons. The mean age of diagnosis was 29 years, but this complication was recognized in children as young as 5 years of age. Intractable headaches were the commonest presenting feature, usually starting in the second decade of childhood. Previously, recognition of this complication was sometimes delayed or missed, but current awareness has redressed this situation. Craniectomy has been undertaken in 12 persons with elevated intracranial pressure while re-operation was carried out in eight. The initial results of craniectomy were good, but five persons died in the post-operative period. The average age of

death in the persons with elevated intracranial pressure was 33 years, the youngest being 16 years of age.

Other surgical procedures

Severe backache in adulthood may necessitate surgical decompression. Likewise, facial pain may be alleviated by decompression of the trigeminal nerve. Attempts at surgical reduction of proptosis have been unsuccessful.

Age and cause of death

Since 1968, 34 persons with SCL have died in South Africa. By 2002, 29 affected Afrikaners were alive, of whom 10 were 20 years of age or younger. Prior to prophylactic craniectomy, sudden death in early adulthood, as a result of impaction of the brainstem in the foramen magnum, was frequent.

Four affected persons have survived beyond the age of 70 years, with and without craniectomy (10). The oldest survivors were a male subject who died at 85 years of age, and a female subject who was 80 years of age. Others who have now reached middle age have remained in good health and, apart from the potentially lethal elevation of intracranial pressure, there are no inherent features of SCL which contribute to mortality. Nevertheless, the quality of life is severely compromised and two affected individuals are known to have committed suicide. Four persons died from causes which were apparently unrelated to SCL (myocardial infarction at 70 years of age, Hodgkin's disease at 10 years of age, malaria at 49 years of age and hepatic cirrhosis at 36 years of age).

Marital circumstances

The facial appearance and disability consequent upon elevated intracranial pressure prejudice social circumstances and marital relationships. Information was available concerning 48 affected adults: of 27 males, 14 had remained single and 13 had married (one of whom became divorced); and of 21 adult females, 12 had remained single and nine had married (three of whom became divorced). The fact that more than 50% of adults with SCL remained unmarried is indicative of the impact of the condition upon affected persons.

Other significant clinical factors

The natural history of SCL is similar in males and females, and there is no evidence of any gender influence on morbidity or longevity.

The hyperostotic skeleton is very resistant to trauma and no affected person is known to have suffered a fracture. Radiologically, the calvarium of the skull of a proportion of first-degree relatives of affected individuals is widened, with some increased density (9). These changes are not sufficiently consistent, however, to permit recognition of heterozygous carriers of the determinant gene. Anecdotally, the bones of the obligatory heterozygous gene carriers are relatively resistant to fracture.

There is no clinical or radiological evidence of any involvement of the central or peripheral cardiovascular system and no evidence of any endocrine disturbance. Equally, degenerative osteoarthropathy is not a feature of the disorder.

Discussion

In addition to the Afrikaners with SCL, the condition has been recognized in isolated individuals or families in several other populations: Spain (11); Brazil (12); the USA (13–15); Germany (16); Japan (17); and Senegal (18). The case descriptions in these reports are comparatively consistent and there is nothing to suggest that there are significant differences in the course and progression of SCL in these different communities. This observation may become relevant to genotype–phenotype correlations when the mutations in all of these groups have been characterized.

In terms of differential diagnosis, SCL must be distinguished from van Buchem disease (VBD) (OMIM 239100), which is present in $\approx$20 affected persons in Holland. In general, the clinical and radiological manifestations of SCL are more severe in SCL compared with VBD, and digital malformations are lacking in VBD. It is of interest that both conditions map to the same chromosomal region – 17q12–q21 – although the persons with VBD do not have mutations in the SCL gene (4, 5, 19, 20).

The severe manifestations of SCL greatly compromise the quality of life of persons with the disorder (21). The availability of surgical decompression of the skull and cranial foramina during the past two decades has improved the duration and quality of life (22); nevertheless, the condition still places a considerable burden on the affected individuals and their families (23).

The localization and characterization of the SCL gene now permits recognition of heterozygous gene carriers; antenatal diagnosis in pregnancies, which are known to be at risk, is feasible. These measures have not yet been implemented but they may become available in the future.

Parents of affected children, potential gene carriers, and their medical attendants will then be in a position to make choices; the availability of information concerning the course and the complications of the condition will be crucial in this respect.

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