Endocrine Function in Sclerosteosis

S. EPSTEIN, H. HAMERSMA, P. BEIGHTON

SUMMARY

Sclerosteosis is a rare autosomal recessive condition which is characterized by excessive skeletal overgrowth, distortion of the facies, cranial nerve abnormalities and raised intracranial pressure. Syndactyly and digital malformation are associated features.

Radiological examination reveals thickened sclerotic bone maximally involving the skull, including the pituitary fossa. Sclerosis and hyperostosis are present throughout the skeleton.

Biochemical and endocrine tests were carried out on 3 patients with sclerosteosis in an attempt to detect any dysfunction of calcium regulation of the pituitary. Results revealed no abnormality of basal parathyroid or calcitonin secretion. Histological examination revealed quantitatively increased bone resorption in comparison with normal subjects, although the pattern resembled osteosclerosis. Regulation of growth hormone, adrenocorticotrophin, gonadotrophin and thyrotrophin function were intact.

We conclude that pituitary function and calcium 'homeostasis' are normal in this disorder.


Sclerosteosis is an unusual, potentially lethal disorder, in which skeletal overgrowth leads to tall stature, distortion of the facies, cranial nerve entrapment and a rise in intracranial pressure (Figs 1 and 2). Syndactyly of the 2nd and 3rd fingers is an associated feature. Massive bony hyperostosis and sclerosis are radiographically evident (Fig. 3).

Sclerosteosis, which is inherited as an autosomal recessive, attains its maximum prevalence among the Afrikaner community of Southern Africa. In a nationwide survey we have studied 40 affected individuals and their clinical and radiological features have been published elsewhere. Three of these patients were admitted to hospital for investigation of calcium regulation, and in view of their tall stature and the radiological evidence of expansion of the pituitary fossa, pituitary function was also assessed. The results of these studies are presented and discussed in this article.

PATIENTS AND METHODS

Three patients with sclerosteosis were investigated after informed consent had been obtained. In each instance insulin tolerance tests (0.1 unit soluble insulin per kg body weight) were performed for determination of plasma growth hormone and cortisol levels; 24-hour urinary calcium on a normal diet containing 900 mg calcium per day and hydroxyproline values were also measured. In patients 1 and 2, bone specimens were taken from the anterior iliac crest after administration of tetracycline as a label. These specimens were examined histologically, both qualitatively and quantitatively.

A calcium infusion (15 mg of elemental calcium per kg body weight in 1 litre 5% dextrose water) was administered to patients 1 and 2 and venous blood was sampled serially for determination of plasma parathyroid hormone (PTH) and calcitonin, by radio-immunoassay. Total serum thyroxine (T₄) and percentage T₃ resin uptake were estimated to exclude thyroid disease. Basal testosterone, oestradiol, luteinizing hormone (LH) and follicle-stimulating
hormone (FSH) levels were determined by radio-immunoassay to exclude gonadal dysfunction. Routine hematological and 12-channel auto-analyser (Technicon) investigations were performed on blood specimens from these 3 patients, and on a further 9 adults and 9 children with the condition.

The radio-immunoassay of PTH measures human plasma PTH, using bovine antisera (AS 211/32) raised against the whole molecule of PTH which cross-react with human PTH. The sensitivity of the radio-immunoassay of human plasma calcitonin is such that normal unstimulated basal levels cannot be detected.

In order to provide a perspective of the manifestations of the condition, the clinical features of the 3 patients are described in some detail. For the sake of clarity, the investigation results are given separately.

**Case 1**

This patient, a male, was born in 1927 after an uneventful pregnancy and delivery. Apart from partial soft-tissue syndactyly of the 2nd and 3rd fingers of both hands, he was normal at birth.

He suffered from recurrent episodes of facial palsy, identical to Bell’s palsy, during early childhood. A progressive hearing defect, which became apparent at this time, was relieved to some extent by the use of a hearing aid. By mid-childhood, excessive growth of the mandible was obvious and proptosis developed in early adult life.

The fused fingers were separated surgically during childhood and an uneventful gastrectomy was performed for a perforated peptic ulcer when he was 30 years of age. His general health was good and, in particular, neither fractures nor bony infection had occurred. His elder brother, who had been similarly affected, had died suddenly at the age of 31. An unaffected sister had died during childhood from glandular fever, but both parents, who were first cousins, had lived a full lifespan. No other members of the kindred had the condition.

**Clinical examination.** When examined in November 1974, the patient was 190.5 cm in height and weighed 82 kg. He had a lean habitus, with little body fat and normal secondary sexual characteristics. His head was large, with a prominent asymmetrical mandible and marked proptosis. Bilateral facial nerve weakness contributed to the distortion of his facies. Widening of the bones, particularly the clavicles, was evident on palpation.

The hands were large and the digits were mis-shapen, with residual bilateral soft tissue fusion of the proximal regions of the 2nd and 3rd fingers. The nails of the 2nd fingers were dysplastic. The toes were normal.

Apart from facial nerve involvement, bilateral combined conductive and perceptive deafness were present. He had no papilloedema and the fundi were normal. No abnormalities were detected in the cranial nerves or other systems. There was no clinical evidence of endocrine dysfunction.

**Radiographic investigation.** Gross changes were present in the skull, the calvarium being widened and increased in density. The pituitary fossa was enlarged, with greatly thickened walls and floor. The base was similarly dense.
and the mandible was deformed. The pelvis was sclerotic but the vertebrae were relatively spared. The clavicles and ribs were widened and dense.

The cortices of the tubular bones were increased in diameter and density. Their shafts were misshapen, with loss of the normal diaphysial constriction. These changes were particularly evident in the digits. Tomography of the skull revealed bony encroachment upon the optic canals and foramen ovale.

**Case 2**

The patient, a female, was born in 1937. Syndactyly of the 2nd and 3rd fingers of each hand was evident at birth, but, at that time, she was otherwise normal. Left-sided facial palsy developed at the age of 4 and the right side became similarly affected when she was 10 years old. The paralysis fluctuated during childhood, but resulted in grossly impaired 7th nerve function in early adult life. Deafness in the left ear was first noticed at the age of 17. Temporary, partial relief was subsequently obtained by operation and a hearing aid is now worn. Facial distortion and maxillary overgrowth became increasingly evident as childhood progressed and proptosis of the left eyeball had developed by the age of 30. At this stage, the intracranial pressure became elevated due to overgrowth of the calvarium, and cranietomy was carried out.

Her younger sister had the condition, but the parents, brother, two sisters and other members of the kindred were all normal. There was no consanguinity in the family. The patient has not procreated but her menstruation had been completely regular and cyclical since the onset of menarche at 13 years of age. Her affected sister produced a normal infant after an uneventful pregnancy and delivery.

Neurological examination revealed bilateral weakness of the facial nerve, mixed deafness and some optic atrophy. In the arms, signs of cervical nerve root compression were elicited. Other systems were normal, including breasts and genitalia. Radiographic studies revealed changes in skeletal density and configuration, essentially the same as those of the previous patient, the floor and walls of the pituitary fossa being grossly thickened.

**Case 3**

Patient 3, a female, weighed 3 kg at the time of her birth in 1951, after an uncomplicated pregnancy and prolonged labour. Soft-tissue fusion of the 2nd and 3rd fingers of each hand was corrected during an uneventful operation in early infancy. Right-sided facial palsy was noted at birth. This complication resolved spontaneously but there were several transient episodes of facial paralysis during early childhood, before bilateral facial weakness became permanent by the age of 10. Maleruption of the primary teeth necessitated total dental clearance at the age of 5. Menstruation commenced at 14 years of age and remained regular.

Bilateral conductive deafness, worse on the right side, became evident in the early school years and increased in severity throughout childhood. A hearing aid was beneficial to some extent, but severe deafness persisted. The facies became progressively distorted during mid-childhood, with massive expansion of the mandible. Two operations were undertaken during the second decade in order to reduce the prognathism and improve the quality of speech.

Severe headaches began at the age of 10 and eyesight began to deteriorate in late adolescence. Craniectomy and orbital decompression, carried out when she was 19 years of age, gave relief from the headaches, but her visual defects remained unchanged. In the following year, a cerebrospinal leak was plugged and shortly afterwards sight was completely lost in the right eye.

There were no siblings and neither the parents nor any other members of the kindred were affected. There was no parental consanguinity.

In 1976, severe headache was followed by collapse and death. Autopsy was not performed.

**Clinical examination.** At the time of her admission to Groote Schuur Hospital, Cape Town, in December 1974, the patient was 175 cm in height and weighed 86 kg. She was heavily built but not obese, with massive bone structure. Her intelligence was normal but she was virtually blind and deaf and had a withdrawn personality.

The face was very abnormal, with gross asymmetrical mandibular overgrowth, irregular teeth and relative midfacial hypoplasia. Bilateral proptosis with divergent strabismus and bilateral facial paralysis contributed to her abnormal appearance.

The 2nd and 3rd fingers of both hands bore surgical scars and the shafts of the digits were malformed. All finger nails were dystrophic, those of the 2nd and 3rd fingers being most severely affected. The toes were normal. Examination of the cranial nerves revealed unreactive pupils, bilateral optic atrophy and divergent squint. Proptosis, worse on the right side, was very obvious. Bilateral mixed deafness and bilateral facial palsy could be demonstrated.

The other cranial nerves and central nervous system were normal and the remainder of the general physical examination, including the genitalia, revealed no abnormality.

**Radiographic investigation.** Changes were present throughout the skeleton, being most marked in the skull. The calvarium was widened and sclerotic, with a frontal defect from the previous craniectomy. The base of the skull was dense, and the floor and walls of the pituitary fossa were sclerotic. The radiological features were generally similar to those of case 1.

**RESULTS**

The biochemical and endocrine data of the 3 patients investigated in detail are shown in Tables I and II. No obvious endocrine abnormality involving growth hormone, ACTH, thyroid or gonadotrophic hormones was detected. The 24-hour urinary hydroxyproline and calcium values were normal. Basal plasma calcitonin and PTH levels were not abnormal but, despite hypercalcaemia, calcitonin remained undetectable during the calcium infusion (Table II). Plasma PTH, however, was suppressed to undetectable levels by hypercalcaemia for most of the infusion period.
TABLE I. ENDOCRINE AND BIOCHEMICAL INVESTIGATIONS IN SCLEROSTEOSIS

<table>
<thead>
<tr>
<th>Insulin tolerance test</th>
<th>Growth hormone (ng/ml)</th>
<th>Plasma cortisol (µg/ml)</th>
<th>Blood sugar (mg/100 ml)</th>
<th>Urinary hydroxyproline (mg/24 h)</th>
<th>Urinary calcium (mg/24 h)</th>
<th>Serum T₄ (µg/100 ml)</th>
<th>T₃ resin uptake (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Time</td>
<td>Time</td>
<td>Time</td>
<td>Time</td>
<td>Time</td>
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<td>0' 20' 60'</td>
<td>0' 20' 60'</td>
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<td>8,6 11,6 29,7</td>
<td>80 48 38</td>
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<td>186</td>
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<tr>
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<td>1,2 4,6 17,4</td>
<td>10,0 15,2 29,5</td>
<td>84 42 40</td>
<td>28</td>
<td>169</td>
<td>9,7</td>
<td>30,2</td>
</tr>
</tbody>
</table>

Normal values: growth hormone 0-5 ng/ml; plasma cortisol 8-25 µg/ml; urinary hydroxyproline <50 mg/24 h; urinary calcium <200 mg/24 h; serum T₄ 5,4-13,7 µg/100 ml; T₃ resin uptake 25-37%.

TABLE II. PLASMA PARATHYROID HORMONE AND CALCITONIN VALUES BEFORE AND DURING CALCIUM INFUSION IN SCLEROSTEOSIS

<table>
<thead>
<tr>
<th>Parathyroid hormone (pg/ml)</th>
<th>Calcitonin (pg/ml)</th>
<th>Serum calcium values during calcium infusion (mg/100 ml)</th>
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<tbody>
<tr>
<td>Patient</td>
<td>Time</td>
<td>Time</td>
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<tr>
<td></td>
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<tr>
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<td>9.2</td>
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<tr>
<td>2</td>
<td>30</td>
<td>10.8</td>
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</table>

--- = not detectable.
Normal values: parathyroid hormone 100-730 pg/ml; calcitonin undetectable — 100 pg/ml; serum calcium during infusion 8.6-10.8 mg/100 ml.

No abnormality in the haematological and 12-channel auto-analyser results, including calcium, phosphorus and alkaline phosphatase levels, was found.

The histological bone pattern resembled osteosclerosis, with thicker than normal trabeculae and cortices. This is compared with normal bone in Fig. 4. The quantitative data in patient 1 revealed an obvious difference in percentage bone resorption, but not in formation or osteoid width, compared with those in normal males (Table III).

![Fig. 4. The histological appearance of a bone biopsy specimen from patient 1 (A). The cortices and trabeculae are thicker than those of the normal control subject. (B).](image)

The values for alkaline phosphatase, calcium and phosphorus in the 9 other adults and 9 children are given in Tables IV and V. As several individuals had elevated levels of creatine phosphokinase (CPK), these findings are also shown in the tables. Biochemical values, including those for sodium, potassium, urea and uric acid, were consistently normal, and for this reason they have not been tabulated. Skin biopsy specimens from 2 patients have been cultured in the Department of Human Genetics, University of Cape Town. The fibroblasts obtained were morphologically normal and did not stain metachromatically.

Cytogenetic studies of leucocytes from 6 patients revealed a normal karyotype in each instance.

**DISCUSSION**

Our investigation of 3 patients with sclerosteosis revealed no endocrine dysfunction which could account for the increased height and grossly thickened sclerotic bones, which are features of this disease. In addition, despite the radiological abnormalities of the pituitary fossa, pituitary function was normal.

The serum alkaline phosphatase levels, although normal in all 3 patients, were raised in each of the 9 children and in 8 of the 9 affected adults who underwent 12-
TABLE IV. BIOCHEMICAL FINDINGS IN ADULTS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Alkaline phos. (KA units)</th>
<th>Phosphorus (mg/100 ml)</th>
<th>Calcium (mg/100 ml)</th>
<th>CPK (IU)</th>
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</tbody>
</table>

Normal serum concentrations: alkaline phosphatase 30 - 85 KA units; phosphorus 2.5 - 4.5 mg/100 ml; calcium 8.6 - 10.8 mg/100 ml; CPK 10 - 110 IU.

TABLE V. BIOCHEMICAL FINDINGS IN CHILDREN

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Alkaline phos. (KA units)</th>
<th>Phosphorus (mg/100 ml)</th>
<th>Calcium (mg/100 ml)</th>
<th>CPK (IU)</th>
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<td>253</td>
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<td>9,2</td>
<td>110</td>
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</table>

Normal serum concentrations: alkaline phosphatase 30 - 85 KA units; phosphorus 2.5 - 4.5 mg/100 ml; calcium 8.6 - 10.8 mg/100 ml; CPK 10 - 110 IU.

channel auto-analyser screening (Tables IV and V). It was noteworthy that the concentrations were highest in the children. This may merely represent the influence of growth on the alkaline phosphatase levels, or alternately it may be consistent with the hypothesis that the condition is a progressive metabolic disorder which becomes static during adulthood.

The creatine phosphokinase levels were also elevated in 5 of the children and 3 of the adults. The significance of this observation is not clear, although it may be a reflection of increased muscle bulk.

The bone pattern was compatible with osteosclerosis, but the quantitative data showed an increased percentage of bone resorption. This finding is difficult to explain and to reconcile with the clinical, biochemical and radiological features of the disease; an explanation may well be that we only measured bone resorption surface and not bone resorption rate, which might have reflected dynamic changes in bone turnover more accurately.

Basal calcitonin and PTH values were normal. It can be argued that lack of stimulation of calcitonin by hypercalcaemia (Table II) may reflect abnormal calcium homeostasis. This failure to stimulate calcitonin may have a technical basis, especially since we did not use an alternate stimulus such as pentagastrin. Therefore, PTH values were normal at the start of the calcium infusion and then became undetectable for most of the infusion period, demonstrating that the parathyroid glands responded appropriately to hypercalcaemia. Serum calcium values were normal in all patients and urinary calcium values in 3 patients in whom it was measured. This, in conjunction with the calcitonin and PTH values, leads us to believe that this disease is not primarily a disorder of calcium regulation. Measurements of calcium absorption and calcium balance, however, are probably required to confirm this belief.

Sclerosteosis, unlike the osteopetrosis which occurs in the grey lethal mouse, does not appear to be characterized by elevated levels of calcitonin.

We believe that our conclusions are of value and that they reflect the endocrine status of these persons. Owing to the rarity of the condition and the geographical scatter of these patients, it would be impossible to undertake hospital investigation of a larger group of affected individuals, in order to substantiate our findings.

In view of the progressive course, it is likely that some facet of bone metabolism is at fault in sclerosteosis. Identification of a biochemical abnormality would be of great importance from the diagnostic and therapeutic point of view and would permit the development of techniques for heterozygote detection and antenatal diagnosis.

As the minimum prevalence of sclerosteosis in the Afrikaner community is 1 in 60,000, this problem is of considerable practical significance and warrants further attention.
We are grateful to Dr Jennifer Jowsey, Mayo Clinic, Rochester, Minnesota, for the bone histological studies, to Dr L. Galante, Royal Postgraduate School of Medicine, Hammersmith, London, for the parathyroid hormone and calcitonin assays, and to Dr M. Nelson for the cytogenetic investigations.

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REFERENCES

Review Article

Which Benzodiazepine, Why and How?

J. L. STRAUGHAN

SUMMARY

While no major differences with regard to psychopharmacological actions are to be found among the benzodiazepines, certain pharmacokinetic differences are known. These differences allow the benzodiazepines to be classified as cumulative or non-cumulative; the differences between these two groups are further dissected and evaluated, in an attempt to rationalize therapy with these agents.


Rational use of drugs demands a certain minimum base of hard data. The enquiring prescriber will hunt out such data as he thinks pertinent and useful, but the vast majority of prescribers require reviews to enable them to obtain with relative ease and in a minimum of time the essentials of the relevant information.

This review aims to draw some distinctions between the various benzodiazepines, which hopefully may be of value in an area of therapeutics that seems beset with a superfluity of agents looking for conditions to treat!

Anxiety is the most common 'dis-ease' encountered in medical practice; this has ensured that pharmaceuticals promising respite from this experience find a ready market. For several decades the barbiturates were widely used as sedative, anti-anxiety agents. Nothing really new was forthcoming until about 1960, when the benzodiazepines appeared on the pharmacotherapeutic scene.

The benzodiazepines were innovative, particularly with regard to their safety, both in normal doses and in large overdoses. They have several other advantages over the barbiturates: by careful adjustment of dosage, the anti-anxiety effect may usually be obtained with minimal sedative effect; tolerance and dependence are less prevalent; and there is no significant induction of hepatic microsomal enzymes, and thus no accelerated biotransformation of endogenous substances or other exogenous substances also metabolized by these enzymes.

Thus, it is easy to understand why this group of drugs has become a worldwide best-seller. Nevertheless, it is salutary to bear in mind that the therapeutic spectrum of the benzodiazepines is not very different from that of the barbiturates.

ARE THE BENZODIAZEPINES A HOMOGENEOUS GROUP?

With regard to their pharmacological actions, there is very little of major importance to differentiate the various benzodiazepines on the market in the Republic of South Africa. Once variations in potency and dosage have been taken into account, these agents have remarkably similar