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Autosomal dominant osteopetrosis
(A family study)

by

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Introduction

Osteopetrosis is a rare inherited metabolic disorder characterized by a general, increased bone density and abnormalities of bone modelling. This is the result of decreased bone resorption because of disturbed osteoclastic function (Johnston *et al.*, 1968; Marks, 1977; 1982; Key *et al.*, 1984).

Originally the disorder was described in two forms, with different modes of inheritance: An autosomal dominant type, with delayed and mainly mild symptoms; and an autosomal recessive form, with early and serious symptoms. In the latter form the patients all die in the first two decades of life from infections and anaemia.

During the last few years various intermediate forms have been described. They are characterized by mild symptoms and recessive inheritance (Beighton *et al.*, 1979; Horton *et al.*, 1980; Whyte *et al.*, 1980; Bourke *et al.*, 1981; Sly *et al.*, 1983; Kahler *et al.*, 1984).

Here the autosomal dominant form of osteopetrosis will be described based on a family study.

Materials and methods

Case history

A 61-year-old man was admitted to the ENT-department because of long-lasting, intense pain in the left lower jaw region.

Odontological, otological, neurological and otoneurological examinations did not disclose any abnormalities.

X-ray examination of the skull and spine showed universally dense, sclerosed bone compatible with osteopetrosis. CT-scan of the skull demonstrated no intracranial calcification. The left mandibular channel was very difficult to identify, compared to the right, indicating stenosis.

The patient was treated symptomatically with carbamazepine which relieved the symptoms.

The patient's family was examined.

Available X-ray pictures were reviewed, and when they were inconclusive, supplementary radiological examination was carried out.

Altogether twenty persons in four generations were examined, and the subjects with radiologically verified osteopetrosis were examined clinically.

Results

The proband (1, Fig. 1) showed no symptoms other than trigeminal neuralgia in the third branch on the left side. There was no history of fractures, and X-ray examination did not show any sign of old fractures or abnormal bone modelling.

The family pedigree (Fig. 1) showed osteopetrosis in three generations, with a pattern indicating an autosomal dominant inheritance. There were no past history or radiological signs of osteopetrosis either in the proband's mother or in his siblings or their descendants. The disorder was probably inherited from the father of the proband, who unfortunately could not be traced.

The proband's daughter (2) was known to have osteopetrosis diagnosed several years previously when she had an X-ray of the spine. One of the sons (3) and a grand-daughter (4) (Fig. 2) were diagnosed radiologically during the present study. None

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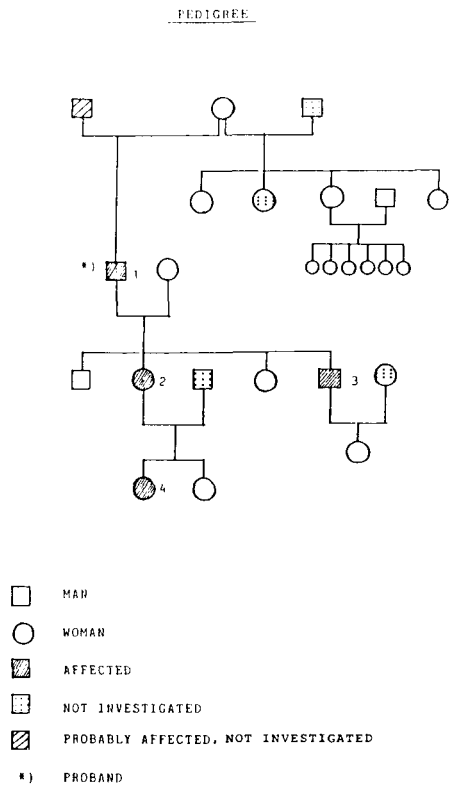


FIG. 1
Pedigree of family with dominant osteopetrosis.

of these subjects showed any clinical symptoms and none of them had ever sustained fractures.

The laboratory results are shown in Table 1. The only abnormal findings were a slightly elevated serum acid phosphatase in one subject and slightly decreased serum inorganic phosphate in two others.

Discussion

The inheritance and clinical appearance of the disease described here are compatible with the autosomal dominant form of osteopetrosis, with mild and delayed symptoms.

Characteristically, two of our subjects (3 and 4) both without any symptoms, were found during this study. The most frequent symptom of osteopetrosis is bone pain and low back pain was found in one of the subjects (2). Another typical symptom is involvement of the cranial nerves due to sclerosis around the foramina or narrowing of the intra-osseous channels; this was found in the proband. None of the patients showed the other cardinal symptom of increased frequency and delayed healing of fractures.

The majority of studies of dominant osteopetrosis have described elevated levels of serum acid phosphatase and low levels of serum phosphate (Johnston *et al.*, 1968; Horton *et al.*, 1980; Kahler *et al.*, 1984), but only one of our subjects (4) had an elevated level of acid phosphatase, two others having slightly lowered levels of serum phosphate. The other laboratory results were normal, and in particular there were no signs of metabolic acidosis.

The aetiology of osteopetrosis is unknown. Studies of spontaneous osteopetrotic mice have shown a reduced hyper calcaemic response to PTH-stimulation. This indicates that reduced bone resorption might be a pathogenic factor in those forms that have been investigated (Marks, 1977,



FIG. 2
X-ray of the skull in a 20-year-old asymptomatic woman (4) with osteopetrosis.

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TABLE I
LABORATORY RESULTS OF THE PATIENTS WITH OSTEOPETROSIS

	Ref. val.	Subjects no. 1	2	3	4
Calcitonin	<135 pg/ml.	82	86	63	75
PTH	<68 pmol/l.	39	20	82	25
Calcium	2.2–2.7 mmol/l.	2.40	2.47	2.49	2.41
Albumin	36–50 g/l.	40	42	44	45
Alk. phosph.	80–275 U/l.	198	86	162	157
Acid phosph.	1.0–4.6 U/l.	3.8	3.0	4.0	4.9
Bicarbonate	21–27 mmol/l.	26.4	24	25.1	25.9
Potassium	3.6–5.0 mmol/l.	3.7	4.4	3.8	3.8
Phosphate	0.8–1.6 mmol/l.	0.6	1.0	0.6	1.2

Subject no. refers to the pedigree (Fig. 1).

1982; Marks and Walther, 1976). An investigation of children with the malignant form of osteopetrosis showed similar results (Caniggia, 1980).

Recently it has been shown that in one of the intermediary forms of osteopetrosis, characterized by osteopetrosis, renal tubular acidosis and intracranial calcification, there is an almost complete lack of carbonic anhydrase II (Sly *et al.*, 1983, 1985) in the erythrocytes. This isoenzyme, however, has also been demonstrated histochemically in osteoclasts, but not in other bone cells (Väänanen, 1984). It has been suggested that lack of the enzyme in the osteoclasts is the cause of the defective osteoclast function and hence of this form of osteopetrosis.

No measurements of carbonic anhydrase II have been performed in the autosomal dominant osteopetrosis.

The autosomal recessive form of osteopetrosis has been treated in a few cases with bone-marrow transplantation (Sieff *et al.*, 1983; Coccia *et al.*, 1980; Sorell *et al.*, 1981) and with high doses of calcitriol (Key *et al.*, 1984), both with good results in a short follow-up.

As in our own case, the treatment of the dominant form has so far been symptomatic. These patients must be given advice about increased bone fragility and warned of the delayed symptoms.

Summary

Osteopetrosis is a rare metabolic disorder, characterized by an abnormal accumulation of bone mass probably caused by diminished bone resorption. Symptoms are directly and indirectly derived from the increased amount of bone.

A family study was made, starting with a proband presenting with symptoms of trigeminal neuralgia. The pedigree indicated an autosomal dominant inheritance through three generations, comprising four affected subjects, of whom two were free of symptoms.

References

Beighton, P., Hamersma, H. and Cremin, B. J. (1979) Osteopetrosis in South Africa. The benign, lethal and intermediate forms. *South African Medicine Journal,* **55:** 659–665.

Bourke, E., Delaney, V. B., Mosawi, M., Reavey, P. and Weston, M. (1981) Renal tubular acidosis and osteopetrosis in siblings. *Nephron,* **28:** 168–172.

Caniggia, A., Gennari, C., Lore, F., Nuti, R. and Galli, M. (1980) Effects of parathyroid hormone and calcitonin on plasma and nephrogenous cyclic adenosine – 3′, 5′-monophosphate in normal subjects and in pathological conditions. *European Journal of Clinical Investigation,* **10:** 99–105.

Coccia, P. F., Krivit, W., Cervenka, J., Clawson, C., Kersey, J. H., Kim, T. H., Nesbit, M. E., Ramsey, N. K. C., Warkentin, P. I., Teitelbaum, S. L., Kahn, A. J. and Brown, D. M.(1980) Successful bone marrow transplantation for infantile malignant osteopetrosis. *New England Journal of Medicine,* **302:** 701–708.

Horton, W. A., Schimke, R. N. and Iydama, T. (1980) Osteopetrosis. Further heterogeneity. *Pediatry,* **97:** 580–585.

Johnston, C. C. Jr., Lavy, N., Lord, T., Vellios, F., Merrit, A. D. and Deiss, W. P. (1968) Osteopetrosis. A clinical, genetic, metabolic and morphologic study of the dominantly inherited, benign form. *Medicine,* **47:** 149–167.

Kahler, S. G., Burns, J. A. and Aylsworth, A. S. (1984) A mild autosomal recessive form of osteopetrosis. *American Journal of Medicine and Genetics,* **17:** 451–464.

Key, L., Carnes, D., Cole, S., Holtrop, M., Bar-Shavit, Z., Shapiro, F., Arceci, R., Steinberg, J.,

https://doi.org/10.1017/S0022215100103287 Published online by Cambridge University Press

Gundberg, C., Kahn, A., Teitelbaum, S. and Anast, C. (1984) Treatment of congenital osteopetrosis with high-dose calcitriol. *New England Journal of Medicine,* **310:** 409–415.

Marks, S. C. Jr. (1977) Osteopetrosis in the toothless (tl) rat: Presence of osteoclasts but failure to respond to parathyroid extract or to be cured by infusion of spleen or bone marrow cells from normal littermates. *American Journal of Anatomy,* **149:** 289–297.

Marks, S. C. Jr. (1982) Morphological evidence of reduced bone resorption in osteopetrotic (op) mice. *American Journal of Anatomy,* **163:** 157–167.

Marks, S. C. Jr. and Walther, D. G. (1976) Mammalian osteopetrosis. A model for studying cellular and humoral factors in bone resorption. In: The biochemistry and physiology of bone. Vol. IV, 2nd ed. New York, San Francisco, London, pp. 227–301.

Sieff, C. A., Chessells, J. M., Levinsky, R. J., Pritchard, J., Rogers, D. W., Casey, A., Muller K., Hall, C. M. (1983) Allogenic bone-marrow transplantation in infantile malignant osteopetrosis. *Lancet,* **i:** 437–441.

Sly, W. S., Hewett-Emmett, D., Whyte, M. P., Ya-Shiou, L. Y. and Tashian, R. E. (1983) Carbonic anhydrase II deficiency identified as the primary defect in the autosomal recessive syndrome of osteopetrosis with renal tubular acidosis and cerebral calcification. *Proceedings in Natural Academy of Science, USA,* **80:** 2752–2756.

Sly, W. S., Whyte, M. P., Sundaram, V., Tashian, R. E., Hewett-Emmett, D., Guibaud, P., Vainsel, M., Baluarte, J., Gruskin, A., Al-Mosawi, M., Sakati N. and Ohlson, A. (1985) Carbonic anhydrase II deficiency in 12 families with the autosomal recessive syndome of osteopetrosis with renal tubular acidosis and cerebral calcification. *New England Journal of Medicine,* **313:** 139–145.

Sorell, M., Kapoor, N., Kirkpatrick, D., Rosen, J. F., Chaganti, R. S. K., Lopez, C., Dupon, B., Pollack, M. S., Terrin, B. N., Harris, M. B., Vine, D., Rose, J. S., Goossen, C., Lane, J., Good, R. A. and O'Reilly, R. J. (1981) Marrow transplantation for juvenile osteopetrosis. *American Journal of Medicine,* **70:** 1280–1287.

Väänänen, H. K. (1984) Immunohistochemical localization of carbonic anhydrase isoenzyme I and II in human bone, cartilage and giant cell tumor. *Histochemistry,* **81:** 485–487.

Whyte, M. P., Murphy, W. A., Fallon, M. D., Sly, W. S., Teitelbaum, S. L., McAlister, W. S. and Avioli, L. V. (1980) Osteopetrosis, renal tubular acidosis and basal ganglia calcification in three sisters. *American Journal of Medicine,* **69:** 64–74.

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