Tooth root resorption associated with a familial bone dysplasia affecting mother and daughter

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Abstract

The dental findings are presented of a mother and daughter who suffer from an as yet unclassified bone dysplasia that shows features of both hereditary hyperphosphatasia and familial expansile osteolysis. Both patients have experienced progressive root resorption of permanent teeth, deafness, and high alkaline phosphatase levels. The mother has a more advanced bone dysplasia which has led to progressive skeletal deformity and bone pain. The kindred is consistent with an autosomal dominant pattern, and the mutation(s) is thought to be in chromosome 18q21-22 region. Conventional treatment strategies of root resorption offer only a poor prognosis for the dentition. Therapy using Alendronate, a bisphosphonate compound and a potent inhibitor of osteoclastic activity, has reduced alkaline phosphatase levels, bone pain, and may offer an effective strategy to prevent tooth root resorption in this group of diseases.(Pediatr Dent 21:363-367, 1999)

The dental findings are presented of a mother and daughter who suffer from a generalised bone dysplasia that shows features of both hereditary hyperphosphatasia, otherwise known as juvenile Paget's disease, and familial expansile osteolysis (FEO).[1-5]

There is growing recognition of a group of disorders characterised by diffuse skeletal changes, conductive hearing loss, and apical and cervical resorption of teeth due to mutations in a gene (or genes) in the chromosome region 18q21-22. The disorders include autosomal dominant forms of FEO and subgroups of hereditary Paget's disease. The gene(s) for FEO and Paget's disease has not yet been identified.[6]

Features of hereditary hyperphosphatasia include increased bone turnover, elevated alkaline phosphatase, and bone deformity with concomitant deafness. There appears to be marked variability in the severity of the disease, but the main clinical features are progressive skeletal deformities due to fragile bones, premature loss of teeth, and cranial enlargement.[1-3] The disease generally appears in infancy and transmission has been thought to be via an autosomal recessive mode.[1]

FEO is a rare and perhaps unique form of autosomal dominant bone dysplasia reported in a Northern Ireland family of five generations.[4,5] Bone involvement is typically seen from the second decade.[4,5] Progressive osteoclastic resorption , accompanied by medullary expansion and cortical thinning, leads to severe, painful, disabling deformities and sometimes pathological fracture of long bones. Serum alkaline phosphatase and urinary hydoxyproline are variably elevated, while other biochemical indices are normal. Early onset middle ear deafness is usual.[4,5]

FEO is associated with extensive external resorption affecting the cervical and apical areas of permanent teeth.[7,8] Primary teeth do not appear to be involved in the disease process. Permanent tooth root resorption leads to pain, mobility, fracture, and ultimately tooth loss. Other dental findings in FEO include a reduction in the size of the pulp chamber and root canal system.[7,8]

Linkage studies have shown that FEO is the result of a mutation on chromosome 18q, and it has been suggested that at least some patients with typical Paget's disease might have mutations in the same region of chromosome 18.[9] This was investigated by Cody et al. who studied a large kindred with a high incidence of Paget's disease and showed that the disease was linked to genetic markers in the same region of chromosome 18 as that for FEO.[10] These two studies show that FEO and inherited forms of Paget's disease are either caused by mutations in the same gene, or that the genes are closely linked.

Case Report

The patients presented in this case report are from a small family and linkage studies using markers D18S51, D18S64, and D18S69 are consistent with the causative gene being in the chromosome 18q21-22 region, but there are too few subjects available for linkage analysis to be statistically significant.

Patient A

The mother initially presented in 1971 at age 11 with long standing deafness and recent recurrent nausea, vomiting, and abdominal pain associated with intermittent hypercalcemia.[2] From age 13 she showed increasing deafness and progressive

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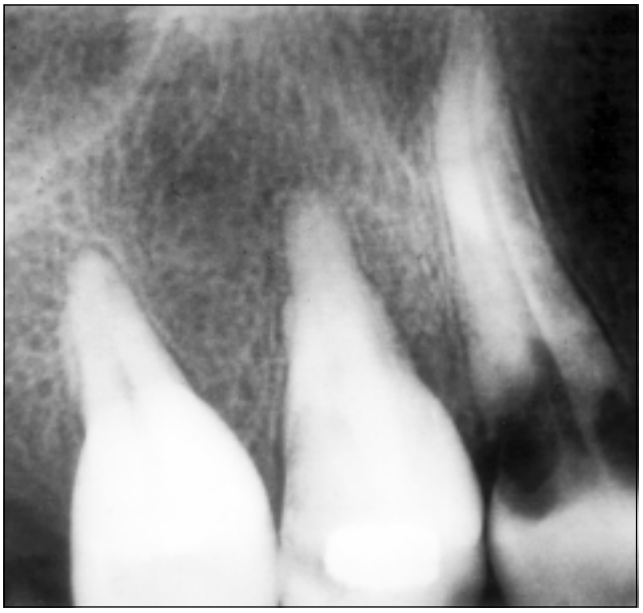

Fig 1. Maxillary periapical radiograph of patient A.

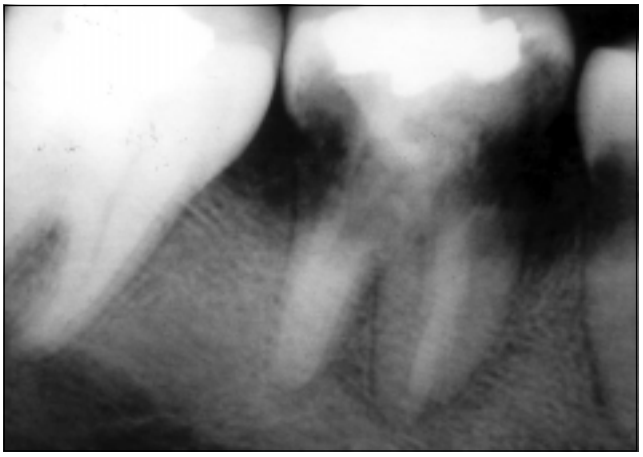

Fig 2. Mandibular periapical radiograph of patient A.

thickening and deformity of the phalanges, femora, and tibiae, with associated bone pain. Alkaline phosphatase was markedly elevated.

After an initial diagnosis of primary hyperparathyroidism was excluded by finding four macroscopically normal parathyroid glands after surgical neck exploration, the condition was initially thought to be juvenile Paget's disease. Differences from juvenile Paget's disease, which typically has an onset in infancy, included a later circumpubertal onset of clinical bone problems, supporting a less severely affected phenotype.

In 1978, at age 18 she presented to the Royal Dental Hospital of Melbourne due to pain originating from a tooth exhibiting extensive root resorption. The tooth was extracted. Biopsies of bone and tooth were diagnosed as hyperphosphatasia. Progressive root resorption led to extraction of all teeth by age 28 and subsequent provision of full maxillary and mandibular dentures, (Figs 1 & 2).

Because of varus deformity of the left femur, femoral osteotomy was performed with internal fixation in 1991 at age 30. Bleeding was profuse, but bone healing was uncomplicated.

Symptomatic hypercalcemia occurred during lactation after each of two pregnancies as previously described.[2] In 1997, she showed reduction in alkaline phosphatase from over 1000 IU/L to 85 IU/L (norm 110 IU/L) and also a marked reduction in bone pain in response to alendronate 40mg/day (a bisphosphonate) over a 12 month period. Her first daughter has similar bone and dental problems, and is deaf. A second daughter is unaffected and has normal hearing. The father is also deaf, but has no bone disease. There is no other significant family history, although the mother's half brother has been treated for pituitary dependent Cushing's disease.

Patient B

Patient B, the first daughter of patient A, presented in 1997 at 12 years of age complaining of a loose and painful tooth in the upper right quadrant after accidentally being bumped in the mouth by a friend's arm.

The daughter had been diagnosed as hearing deficit at 13 months and became totally deaf by five years. She shows early features of a bone dysplasia similar to that of her mother. She commenced treatment with oral alendronate 20 mg/day in 1998 after her mother had responded to this drug. A penicillin allergy was also documented.

Examination revealed an esthetic Class 1 early permanent dentition. Tooth 12 exhibited grade 3 mobility. All teeth exhibited a mild white opacity consistent with the appearance of mild fluorosis, no evidence of dental caries, and good oral hygiene. The patient exhibited severe anxiety concerning dental treatment.

An orthopantomogram (OPG) and periapical radiographs showed cervical root resorption in at least 13 teeth. Tooth 12 exhibited a fractured crown due to extensive cervical resorption. A tendency for reduced pulp chamber and root canal size was evident (Figs 3 & 4). A blood test at presentation revealed raised alkaline phosphatase levels 745 IU/L (norm 110 IU/L).

After liaising with medical specialists who had managed both mother and daughter, treatment options were discussed with both the patient and her mother. After appropriate medical advice, tooth 12 was extracted using local anaesthesia (Fig 5). A five-day course of erythromycin and a paracetamol/ codeine analgesic was prescribed. Subsequently, impressions were taken and a partial denture replacing tooth 12 was inserted four weeks after the extraction.

The extracted tooth was sent for examination by the University of Melbourne Oral Pathology Diagnostic Unit. Histology showed extensive external resorption, with multinucleate osteoclasts present in Howship's lacunae, particularly coronally, but with much of the resorbed areas of the root fragment having been repaired by the deposition of hard tissue (Fig 6).

A mixture of coarse-fibred woven bone and lamellar bone with multiple reversal lines typical of Paget's disease of bone was noted. A thin layer of predentine and dentine surrounded the pulp. The predentine appeared relatively resistant to resorption, though incremental lines in the dentine close to the pulp indicated a local disturbance, presumably related to the resorption. The pulp was vital and featured large vessels and a number

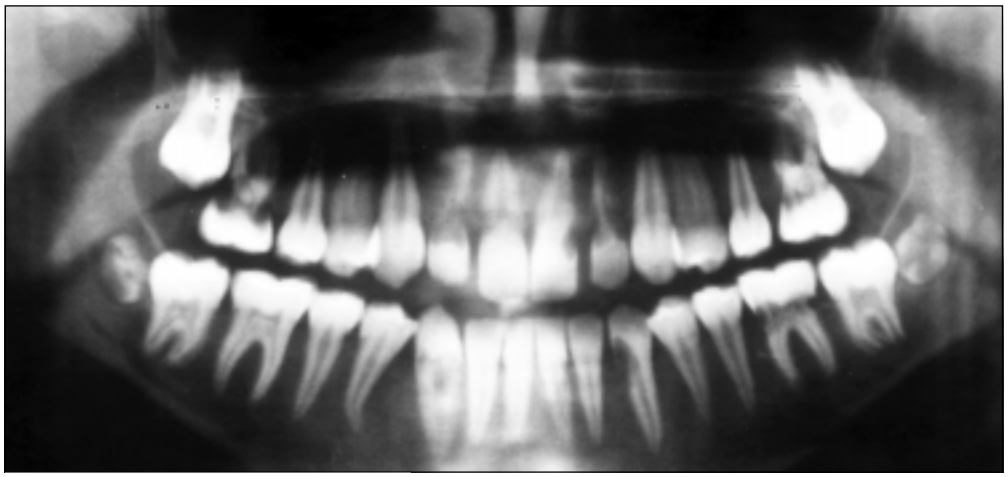

Fig 3. Orthopantomogram of patient B.

of pulp stones, some of which had a tubular structure, and others appearing as concentric lamellae. The biopsy was considered to be an example of hyperphosphatasia or juvenile Paget's disease.

Discussion

These two cases illustrate the difficulty in diagnosis and classification of uncommon bone dysplasias, which may differ markedly in severity and age of onset. The initial diagnosis of juvenile Paget's disease or hereditary hyperphosphatasia suggested a recessive inheritance, but the finding of deafness and early features of bone dysplasia in the older daughter, together with clinical similarities to the recently described entity of FEO, are consistent with autosomal dominant inheritance. Small kindreds as in these two cases make it difficult to derive an accurate diagnosis of the mode of genetic transmission. Only mother and daughter suffer from the condition. The daughter has one female sibling four years younger, who is unaffected, with no signs or symptoms of the condition. No other significant family history has been recorded. The mode of genetic transmission in this kindred is not clear, but it is consistent with an autosomal dominant pattern and the mother having acquired a de novo mutation.

A tendency for a reduction in the size of the pulp chamber and root canal systems of the incisor teeth and six year old molars was evident in the OPG of the 13-year-old daughter (Fig 3). Retrieval of archived periapical radiographs of her mother at age 18, taken over 20 years earlier, subsequently revealed clear evidence of a reduction of size of the pulp chamber and root canal systems of all teeth (Figs 1 & 2). This has been reported in FEO, rather than Paget's disease, and suggests a condition with dental findings remarkably similar to FEO. [7,8]

There is no history in either patient that the primary teeth were affected by pathological resorption, although dental records of the primary and mixed dentitions are incomplete. Perhaps primary teeth may have been affected by the resorptive process, but were exfoliated before symptoms appeared. Resorptive defects in primary teeth have not been reported in FEO, however there is no firm data concerning primary teeth.[7,8]

The pathogenesis of cervical root resorption is not fully understood.[11] The resorptive process however, is initiated by specific clastic cells which remove the organic and mineral components of dental hard tissues.[12] Clastic cell activity in root resorption has been linked to a number of factors including biomechanical forces, mechanical trauma, surgical, trauma chemical trauma, endodontic micro-organisms, and associated toxins, developmental defects, neoplasia, and hormonal disturbances.[12]

Currently available therapeutic measures which can regulate clastic activity in external root resorption include endodontic treatment, the use of specific anticlastic agents such as corticosteroid/antibiotic pastes, (e.g. "Ledermix"paste [Lederle Pharmaceuticals, Cyanamid GMBH, Wolfratshausen, Germany]), non specific necrobiotic agents such as calcium hydroxide and trichloroacetic acid, surgery, or root surface conditioners such as fluoride.[12] Equivocal experimental evidence suggests that the naturally occurring polypeptide

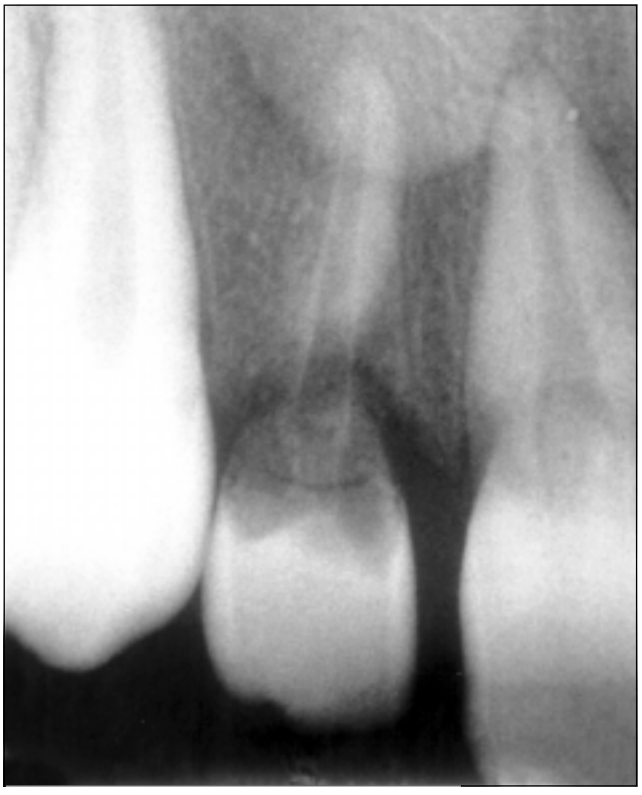

Fig 4. Periapical radiograph of tooth 12, patient B.

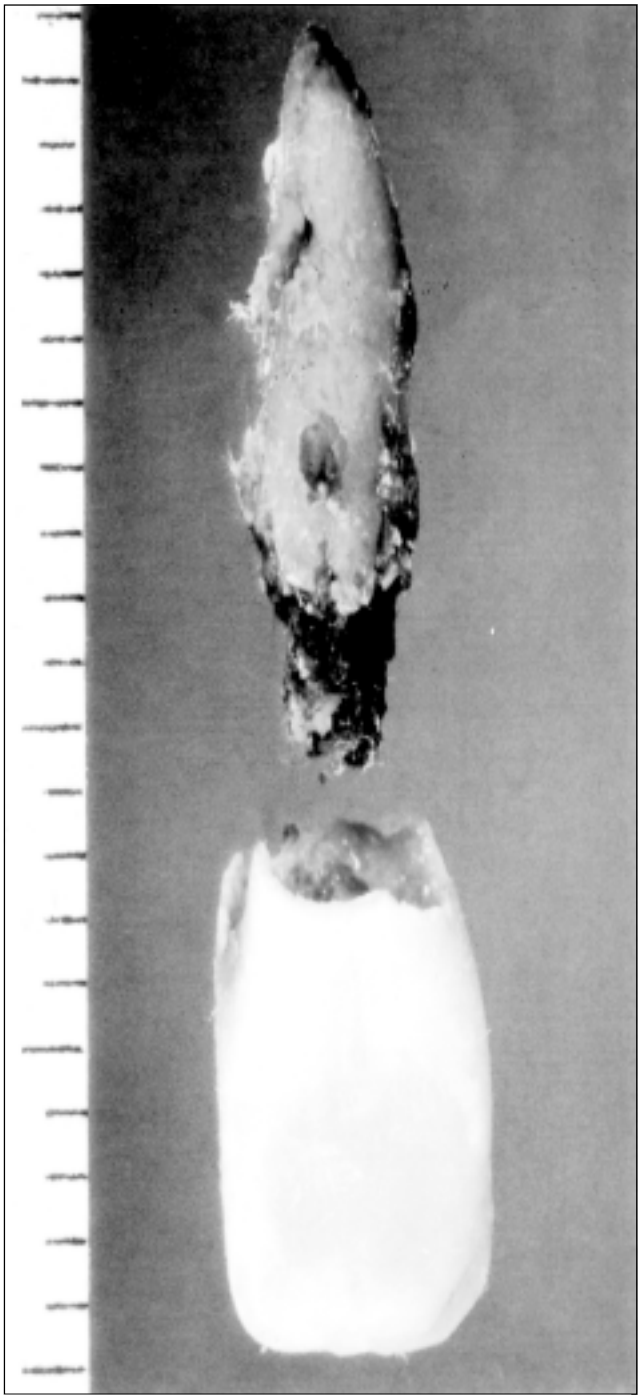

Fig 5. Extracted tooth 12, patient B (scale=mm).

hormone calcitonin, which has a regulatory function on clastic cells, may have a therapeutic effect if introduced to the root canal system of a tooth undergoing external resorption in monkeys.[13-15] This has not been substantiated clinically in humans. There is similarly limited evidence that bisphosphonates, which have been developed for use in diseases of bone and calcium metabolism, reduce or prevent resorption of human dentine in in vitro experiments, but again this has not been substantiated clinically.[16,17] Control of resorption has also been attempted by changing the composition of the tooth root surface by application of a fluoride solution, and while this appears to slow the resorptive process, it does not prevent it.[12]

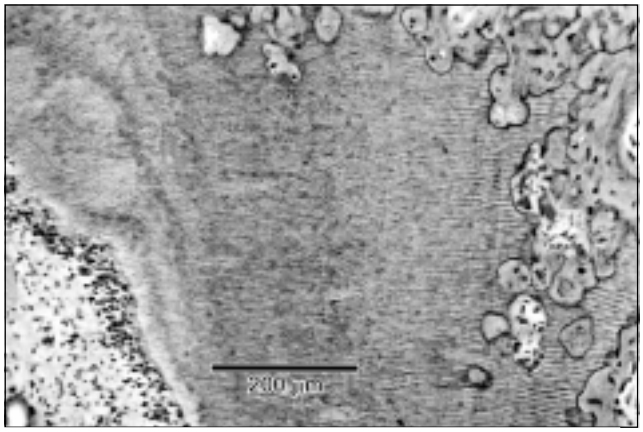

Fig 6. Photomicrograph of extracted tooth (picrothionin stain).

In both patients, root resorption occurred cervically and appeared to extend apically when the destruction became extensive. This is seen in the periapical radiographs of mother and daughter, in the OPG of the daughter, and in extracted tooth 12 of daughter (Figs 1–5). It is evident that the resorptive process in the cervical area of the tooth roots appears more severe mesially and distally compared with labial/buccal and palatal/lingual aspects, as reported in FEO, and lends weight to a disease process similar to FEO.[7,8]

In view of the dramatic response shown by the mother to alendronate in reduction of bone pain and decrease in alkaline phosphatase, it is possible that agents of the bisphosphonate group, which are potent inhibitors of osteoclastic activity, may also inhibit tooth root resorption.[16,17]

The prognosis for the dentition in the daughter is extremely poor. Resorption occurring apically is virtually impossible to arrest surgically, and intra canal endodontic procedures aimed at arresting external resorption are at best highly unpredictable.

Cervical resorption may be managed by surgical exposure or orthodontic extrusion of the resorptive defect, followed by surgical curettage of the lesion, then by chemical treatment with trichloroacetic acid and subsequent restoration, by a glass ionomer cement or a resin bonded to dentine composite resin.[12,18,19] Surgical curettage alone is usually insufficient to deactivate clastic cells and prevent recurrence or continuation of the process.[12] Use of either calcium hydroxide or corticosteroid/antibiotic paste into the root canal system of affected teeth may assist in arresting the resorptive process, but obviously condemns previously vital teeth to endodontic therapy.

In clinical practice, these traumatic and technically demanding techniques are only viable on small lesions accessible from a labial/buccal or lingual/palatal approach. These techniques are not feasible in this case because of the multiple, extensive, and inaccessible nature of the interproximal and apical lesions. In addition there currently are no available preventive strategies to stop initiation and progression of further lesions.

It is inevitable that multiple extractions will be necessary. The viability of titanium implants in such a patient remains speculative. There are no reported cases of implants being used in this type of bone dysplasia. Also little information is available on the use of dental implants with bisphosphonate therapy. Starck and Epker reported the failure of successfully integrated dental implants after bisphosphonate therapy for osteoporosis, and advised that implant placement be avoided in patients

who require bisphosphonate therapy.[20] It is felt that long-term management with removable prostheses will be required. Advances in dental management of this condition must lie in the prevention of the resorptive process. It may be speculated that this will only be achieved by systemic control of the osteolytic process, perhaps by early introduction of a bisphosphonate to inhibit osteoclastic activity, provided these agents can be shown to be safe in children.

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Abstract of the Scientific Literature

After-Hours Advice in Private and Nonprivate Pediatric Populations

This survey study compared the content of after-hours medical advice given on the telephone to private practice patients vs nonprivate practice patients. Assessment of compliance with advise resulting from those called was measured. The results showed that nonprivate patients were more likely to be referred for office care while private practice patients were more likely to be referred to the emergency room. Compliance with recommended treatment was not significantly different in both groups of patients.

Comments: Research on dental advice given by the dentist over the telephone is of unique interest to the private practioner. Yet, such data is lacking in the dental literature. AK

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After-hours telephone triage and advice in private and nonprivate pediatric populations. Baker RC, Schubert CJ, Kirwan KA, Lenkauskas SM, Spaeth JT: Arch Pediatr Adolesc Med 153:292-296, 1999.

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