Camurati-Engelmann disease

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Introduction

Camurati-Engelmann disease (CED), or progressive diaphyseal dysplasia, is a rare sclerosing dysplasia of which 250 cases have been described in the English literature.[1] The disease affects one in a million people and is autosomal dominant with variable penetrance.[2-5] It was initially described by Cockayne in 1920; Camurati was the first to suggest its hereditary nature in 1922.[6-8] A single case of muscular wasting and marked bone involvement was reported by Engelmann in 1929.[6,9] As the name suggests, there is progressive hyperostosis and predominant involvement of the diaphyses.[6,10]

The onset of the disease is usually during childhood; patients usually present by puberty and usually before age 30, with limb pain, muscular weakness, waddling gait and easy fatigue. Other symptoms and signs may include delayed growth, reduced muscle mass, anorexia and enlargement of the arms and legs.[6,11] Systemic manifestations of hepatosplenomegaly, bone marrow dysfunction (anaemia and leucopaenia) and delayed sexual development occasionally occur.[4-6,12,13] In a few patients, abnormal values of bone resorption and formation have been described.[10]

Radiologically, the hallmark of the disorder is bilateral, symmetrical cortical thickening of the diaphyses of the long bones[14,15] on both the periosteal and endosteal sides of the diaphyses. In decreasing order of frequency, the tibia, femur, fibula, humerus, ulna and radius are affected. CED results from disturbance of intramembranous ossification (Fig.1) affecting the long bones, calvaria, mandible and facial

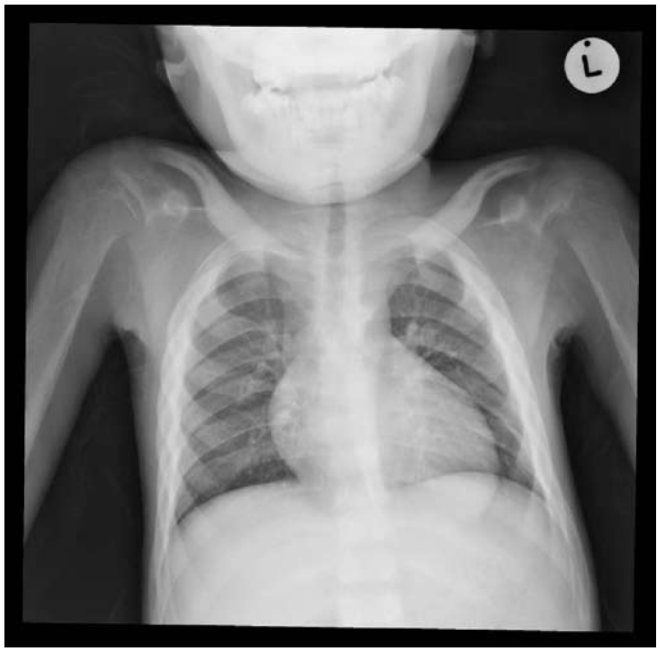
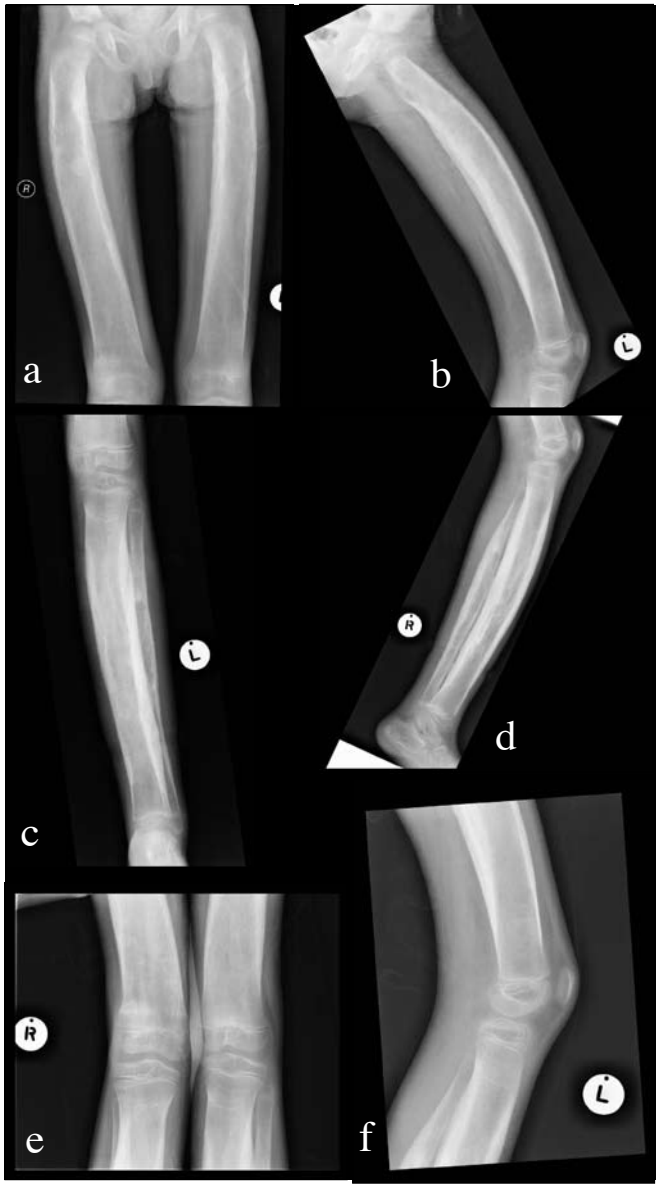
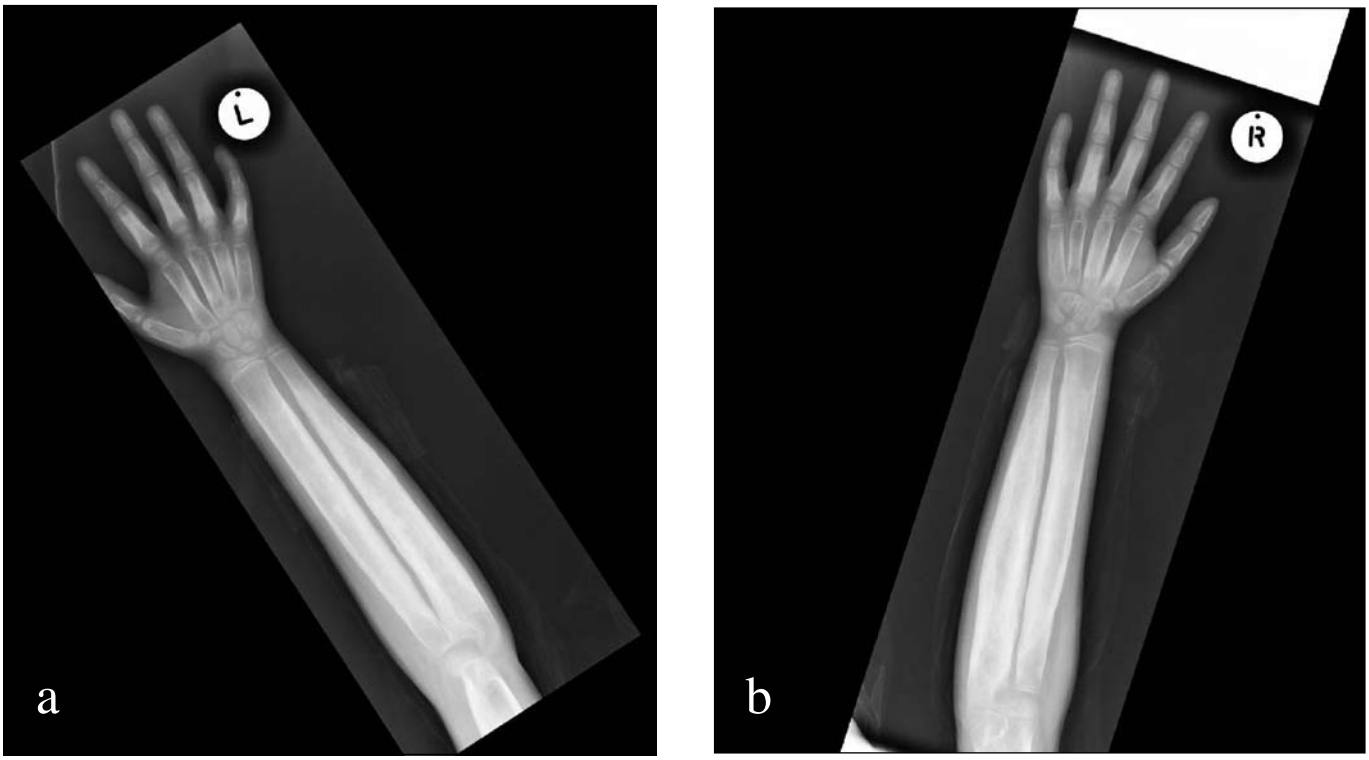


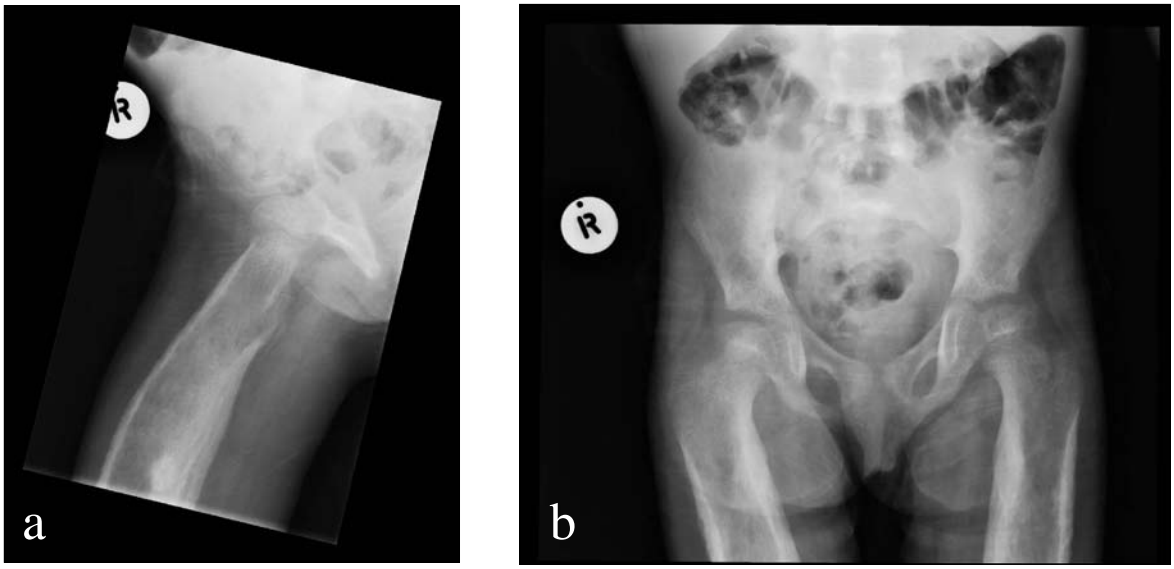
Fig. 1. Both clavicles demonstrate marked bony cortical thickening with sparing of the distal ends. The humeral epiphyses are spared.



Figs 2 a - f. The diaphyses of the long bones demonstrate endosteal and periosteal thickening with narrowing of the medullary cavity. Note the typical sparring of the epiphyses.



Figs 3a and b. The marked cortical thickening results in narrowing of the medullary cavity.



Figs 4a and b. Classical sparing of the epiphysis and metaphysis of the proximal femora.

bones.[11,16] There are a few reported cases of involvement of the skull base (a site of endochondral ossification), but these occur in advanced stages.[3,11,17,18]

Radioclinical features

According to a retrospective study of 24 families done by Janssens *et al.*,[6] clinical symptoms were documented in 74% of the patients. The most frequent clinical symptoms were pain in the extremities (63%), easy fatigue (44%), waddling gait (48%), muscle weakness (39%), reduced subcutaneous fat (21%) and hearing loss (15%).

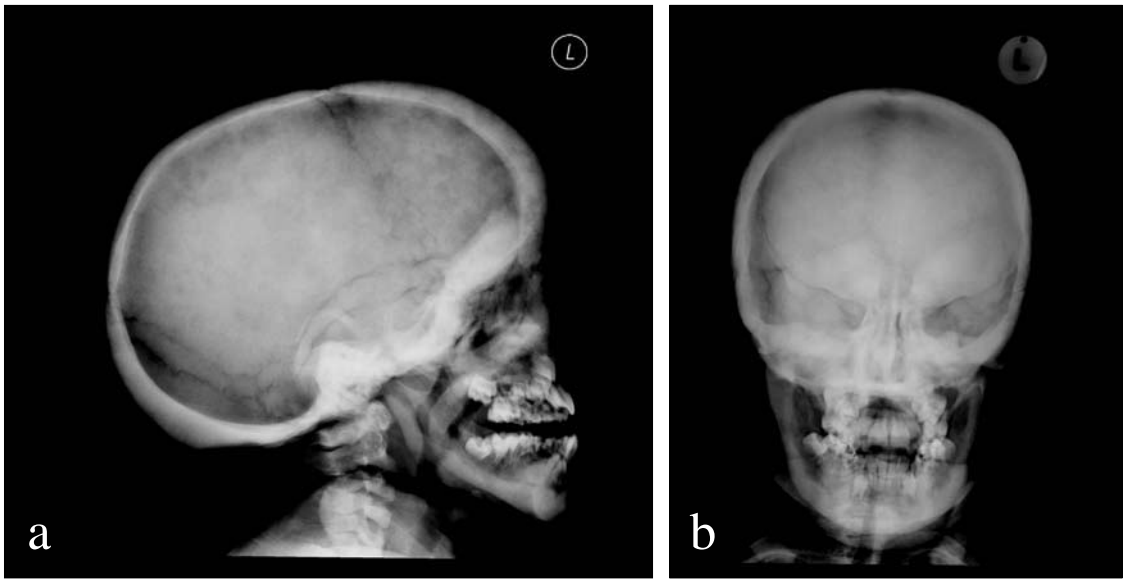
Radiographically, endosteal and periosteal thickening of the diaphyses of long bones (Figs. 2a - f) is seen in CED.[3,11,17,18] The result is narrowing of the medullary cavity (Figs 3a, b).[4] The metaphyses can become affected, but typically the epiphyses are spared (Figs 4a, b).[4,6] Sclerosis of the skull base (Figs 5a, b) can be present, leading to hearing impairment owing to progressive stenosis of the external auditory canal (EAC), and foraminal stenosis causing cranial nerve dysfunction.[6,11,19]

Increased osteoblastic activity detected scintigraphically with 99Tc-HMDP (hyfroxymethylene diphosphonate) is seen bilaterally symmetrical in the upper and lower limb long bones, longitudinally

Table I. Classification of dysplasias with increased bone density according to International Nomenclature and Classifications of the Osteochondrodysplasias (modified from Vanhoenacker FM *et al.*[13])

Disorder	Radiological pattern of sclerosis	Mode of inheritance
1. Increased bone density without modification of bone shape		
Osteopetrosis		
precocious type	Generalised	AR
delayed type	Type 1 uniform	AD
intermediate type	Type 2 endobones	
with renal tubular acidosis	Generalised	AR
	Similar other types	AR
Axial osteosclerosis		
osteomesopyknosis	Focal sclerosis in vertebrae/pelvis	AD
with bamboo hair		AR
Pycnodysostosis	Generalised	AR
Osteosclerosis Stanesu type	Cortical thickening of long bones, deficient facial sinus development	AD
Osteopathia striata	Radiodense striations on all bones	
isolated		SP
with cranial sclerosis	with cranial sclerosis	XLD
Sponastrime dysplasia	Striated metaphysis	AR
Melorheostosis	Flowing hyperostosis	SP
Osteopoikilosis	Radiodense spots	AD
Mixed sclerosing bone dysplasia	Combined pattern	SP
2. Increased bone density with diaphyseal involvement		
Diaphyseal dysplasia, Camurati-Engelmann	Craniotubular sclerosis, symmetrical	AD
Craniodiaphyseal dysplasia	Craniotubular	AR, AD
Lenz Majewski dysplasia	Craniotubular	SP
Endosteal hyperostosis	Craniotubular sclerosis, symmetrical	
van Buchem type		AR
Worth type		AD
sclerosteosis		AR
with cerebellar hypoplasia		AR
Kenny Caffey dysplasia	Diaphyseal cortex	AD, AR
Osteoectasia with hyperphosphatasia (juvenile Pagets)	Craniotubular sclerosis, bowing	AR
Diaphyseal dysplasia with anaemia	Diaphyseal cortex	AR
Diaphyseal medullary stenosis with bone malignancy (Hardcastle)	Diaphyseal cortex	AD
3. Increased bone density with metaphyseal involvement		
Pyle dysplasia	Erlenmeyer	AR
Craniometaphyseal dysplasia	Pyle-like, but cranial bones more affected	
severe type		AR
mild type		AD
other type		
Frontometaphyseal dysplasia	Frontal bones	XLR
Dysosteosclerosis	Generalised	AR
	Platyspondyly	XLR
Oculodento-osseous dysplasia	Craniotubular and mandible	AD
Trichodento-osseous	Craniotubular	AD
4. Neonatal severe osteosclerotic dysplasia		
Blomstrand	Generalised	AR
Raine dysplasia	Mild craniofacial sclerosis Undermodelled long bones	?
Prenatal onset Caffey disease	Diaphyseal cortical thickening, bowed long bones	?AR

AD=autosomal dominant; AR=autosomal recessive; SP=sporadic; XLD=X-linked dominant; XLR=X-linked recessive.



Figs 5a and b. The skull radiographs demonstrate sclerosis of the skull base and temporal bone, particularly of the external auditory canal.

along the bone cortices.[6,15] Before sclerosis is seen radiologically, increased tracer uptake can be seen and is thus valuable in the early diagnosis.[6]

Diagnosis

Ten different mutations of the TGFB1 (transforming growth factor B1) were identified in an analysis of 46 CED families.[6,20-27] The TGFB1 gene is located on the chromosomal region 19q13.1.4 All investigated mutations increase the activity of TGFB1.[6] Under physiological conditions, TGFB1 has been shown to suppress bone formation and the mutation stimulates bone formation6 thus disrupting bone turnover, causing increased bone formation. TGFB1 also inhibits myogenesis, causing muscle wasting as well as lipogensis.[6]

CED is classified as a sclerosing bone dysplasia with diaphyseal involvement (Table I). The differential diagnosis is endosteal hyperostosis – van Buchem sclerosteosis, Kenny-Caffey disease or Worth type. Owing to inheritance, one can rule out van Buchem sclerosteosis (autosomal recessive (AR)), and Worth type is a more benign form and has associated mandible enlargement.[4,13]

A combination of clinical, radiological, scintigraphic and molecular data are mandatory for a definitive diagnosis.

Treatment

Immunosuppressive agents such as anti-inflammatories and glucocorticosteroids have the negative side-effect of decreasing bone density; and this is used in CED as treatment. The role of the agents is to increase the apoptosis rate of osteoblasts and osteocytes and at the same time to suppress osteoblast proliferation, differentiation and bone matrix synthesis.[6] Further effects are to enhance proliferation and differentiation of osteoclast precursors[6] and also to decrease intestinal calcium absorption.[6] Glucocorticosteroids as well as counteracting bone formation exert a direct effect on TGFB expression. Prednisolone has been described as an effective treatment in a number of cases.[6]

Long-term treatment is not advisable owing to its unfavourable side-effects such as impaired growth and spinal osteoporosis. A good starting dose is 1mg/kg/day, but should be lowered in long-term treatment.

An alternative to medication is surgery. Reaming of the medullary cavity may be done to decrease the narrowing of the canal, or an osteotomy can be performed.[6,28] Further decompression in optic nerve compression has also been done. Gene therapy is a possibility in the future.

Conclusion

Camurati-Engelmann disease (CED), or progressive diaphyseal dysplasia, is a rare sclerosing dysplasia whose onset is usually during childhood. Patients usually present by puberty or before age 30. Radiologically, the hallmark of the disorder is bilateral, symmetrical cortical thickening of the diaphyses of the long bones occuring on both the periosteal and endosteal sides of the diaphyses.

The differential diagnosis is of CED is endosteal hyperostosis – van Buchem, sclerosteosis, Kenny-Caffey disease and Worth type. Inheritance can rule out van Buchem and sclerosteosis (AR), whereas Worth type is a more benign form and has associated mandible enlargement. A combination of clinical, radiological, scintigraphic and molecular data may be necessary for a definitive diagnosis.

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