Diagnosis: Infantile cortical hyperostosis (Caffey's disease). Radiographs showed diffuse periosteal reaction and subperiosteal bone formation of the mandible, right clavicle, femora, tibiae, humeri, radii, and ulnae (Fig). There was no evidence of fracture.

BACKGROUND

Caffey's disease is a self-limiting disease of uncertain etiology that occurs in infancy or early childhood and is characterized by periosteal reaction. The entity was first described by Roske in 1930 and further delineated by Caffey and Silverman in 1945. After additional reports in the 1950s and 1960s with a peak incidence of 3 cases per 1000 patients <6 months of age, there has been a decrease in the worldwide number of cases throughout the past two decades, particularly of the nonfamilial subtype.

DISEASE CHARACTERISTICS

Manifestations of Caffey's disease usually occur within the first 6 months of life at an average age of 9 weeks, but may develop in utero or during later childhood. Both sexes are equally affected. Symptoms typically include the acute onset of low-grade fever and hyperirritability associated with swelling, erythema, and tenderness on palpation of the limbs.

Radiographically, diffuse polyostotic periosteal elevation and subperiosteal bone formation is apparent in the metaphysis and diaphysis of involved bones, with sparing of the epiphyses. Cortical thickening may be seen as layers of subperiosteal new bone coalesce with the underlying cortex. Areas most commonly involved include the mandible, tibia, clavicle, and ulna. Involvement of the vertebral bodies and the phalanges of the hand and feet has not been described.

Laboratory studies may be normal or demonstrate an elevated erythrocyte sedimentation rate, leukocytosis, thrombocytosis, elevated immunoglobulins, elevated alkaline phosphatase, and anemia. Histologic evaluation of areas of involved bone reveals hyperplastic immature lamellar bone with periosteal thickening, proliferation of subperiosteal cells, and marrow fibrosis.

The differential diagnosis (Table) is broad and includes disorders characterized by periosteal reaction and bone formation in infancy and early childhood. After work-up, the differential often focuses on infection, trauma, child abuse, and Caffey's disease.

CLINICAL COURSE

Caffey's disease is usually self-limited with resolution of symptoms and radiographic findings but has a variable course ranging from a few weeks to several months. Cases of recurrent disease or residual involvement are unusual but have been described. Normal growth rates and the reestablishment of normal bony morphology are expected. However, sequelae including radioulnar synostosis, tibiofibular synostosis, facial asymmetry, pleural effusion from rib involvement, exophthalmos, and leg-length discrepancy have been reported.

Observation, reassurance, and symptomatic pain relief are the usual mainstays of treatment due to the self-limited nature of the disease. Steroids, calcitonin, and immunoglobulin have been used anecdotally; however, definitive clinical trials are lacking because of the rarity of the disease.

ETIOLOGY

The etiology of Caffey's disease remains unknown. Infectious, inflammatory, immunologic, metabolic, vascular, nutritional, gestational, and genetic causes have been implicated. Cases have been reported as early as the 20th gestational week and as late as age 11 years. Although intrauterine or neonatal infection has been suggested as the cause of Caffey's disease, no bacterial or viral agent has been proved.

There appear to be two subtypes of infantile cortical hyperostosis: a familial type and a spontaneous type. Investigators have suggested an autosomal...
dominant gene with reduced penetrance; however, definitive genetic transmission has not been proved.18-21 Several authors have reported a familial background, while others have described cases without a familial background.19,20,22,23 Thus, some investigators have suggested the possibility of multiple heterogeneous causative agents with a syndrome of common clinical manifestations: cortical hyperostosis and periostitis.

A Caffey disease-like syndrome of cortical hyperostosis and periostitis has been described in patients receiving prostaglandin E1 or E2 therapy, particularly in infants treated for patent ductus arteriosus.24-26 This has raised the possibility of a therapeutic role for prostaglandin inhibitors in treating symptoms and shortening the course of Caffey’s disease.13

REFERENCES

Section Editor: Terrence C. Demos, MD

| TABLE |
| Differential diagnosis of periostal reaction and cortical thickening in infancy and early childhood |

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Characteristics</th>
</tr>
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<tbody>
<tr>
<td>Genetic Menkes (kinky-hair) syndrome</td>
<td>X-linked defective copper absorption, newborns, failure to thrive, males, central nervous system degeneration, metaphyseal fractures, kinky hair</td>
</tr>
<tr>
<td>Engelmann-Camurati disease</td>
<td>Autosomal dominant, diaphyseal long-bone thickening, waddling gait, neuromuscular degeneration</td>
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<tr>
<td>Infectious Osteomyelitis</td>
<td>Metaphyseal lytic lesion, fever, leukocytosis, elevated erythrocyte sedimentation rate, positive cultures</td>
</tr>
<tr>
<td>Congenital syphilis</td>
<td>Metaphyseal lytic lesion, &gt;3 months, osteochondritis, positive serology</td>
</tr>
<tr>
<td>Trauma Fracture/child abuse</td>
<td>Multiple fractures in various stages of healing, corner fractures, inconsistent history</td>
</tr>
<tr>
<td>Burns Metabolic Hyperphosphatemia</td>
<td>Hypertrophic osteoarthropathy</td>
</tr>
<tr>
<td>Metabolic Hyperparathyroidism</td>
<td>Elevated serum vitamin A level, &gt;9 months, abnormal liver function tests, skin rash, bleeding gums, long-bone periostal reaction (ulnae and metatarsals), ossification abnormalities</td>
</tr>
<tr>
<td>Scurvy</td>
<td>Decreased vitamin C levels, &gt;9 months, subperiosteal hemorrhage</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Elevated serum phosphorus, calcified soft-tissue masses</td>
</tr>
<tr>
<td>Neoplastic Leukemia</td>
<td>Diffuse osteopenia, &gt;2 years, metaphyseal bands</td>
</tr>
<tr>
<td>Retinoblastoma/neuroblastoma</td>
<td>Osteopenia, &lt;2 years, metaphyseal lucency</td>
</tr>
<tr>
<td>Etiology Physiologic</td>
<td>Usually at age 2-3 months, most pronounced in premature infants</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Secondary to prostaglandin therapy</td>
</tr>
</tbody>
</table>
Eight-week-old female dizygotic twin infants presented with a 3-week history of low-grade fever and fussiness, particularly while their legs were being held during diapering. There was no history of trauma. The family history was significant for leg pain and periostitis in the mother, which was detected at 6 months of age and resolved by age 1 year. Ultrasound of the hips, complete blood cell count, and erythrocyte sedimentation rate were normal. Physical examination reveals generalized irritability, mild erythema and warmth of the lower limbs, and pain on manipulation of the knees and palpation of the tibiae, femora, and humeri. Radiographs of twins showed the same abnormalities (Fig). Your diagnosis?

(See page 707 for answer.)