Idiopathic Hyperostosis of the Calvaria in Five Young Bullmastiffs

A new calvarial hyperostotic syndrome (CHS) in young bullmastiffs is described. Calvarial hyperostotic syndrome clinically resembles canine craniomandibular osteopathy (CMO) and human infantile cortical hyperostosis (ICH), but it is unique in that there is progressive and often asymmetric skull bone involvement, and the population affected appears to be only young, male bullmastiff dogs. Characteristic radiographic findings consist of cortical thickening of the calvaria with irregular, bony proliferation over the frontal, temporal, and occipital bones. Histopathological examination shows that the trabeculae of the calvarial diploë are thickened and contiguous with a sunburst-like pattern of subperiosteal trabeculae composed of woven and lamellar bone tissue, accompanied by loose fibrovascular tissue and a variable inflammatory response comprised predominantly of neutrophils. In 80% of the cases presented, the lesion was self-limiting. The etiology remains unknown; however, traumatic, neoplastic, and degenerative conditions do not appear to be primary factors in the etiopathogenesis of the syndrome. It may be that this syndrome has a familial component, similar to that described for CMO and ICH. **J Am Anim Hosp Assoc 2000;36:439–45.**

Karen F. Pastor, DVM

James P. Boulay, DVM, MS, Diplomate ACVS

Scott H. Schelling, DVM, Diplomate ACVP

James L. Carpenter, DVM, Diplomate ACVP

Introduction

This report documents a nonneoplastic, proliferative bone disease of the skull in five male bullmastiffs, aged five to 10 months, presented to Angell Memorial Animal Hospital (AMAH) between 1976 and 1994. This distinct osteoproliferative disease, termed calvarial hyperostotic syndrome (CHS) in this report, has similar clinical and histopathological characteristics to both canine craniomandibular osteopathy (CMO) and human infantile cortical hyperostosis (ICH).[1] Both CMO and ICH are nonneoplastic, proliferative bone diseases affecting primarily the flat bones of the skull. The mandible is frequently affected in CMO. Both diseases have been reported to affect the appendicular skeleton as well.[2–7] In both of these conditions, clinical signs generally appear in the first few weeks to months of life, and the lesions tend to be bilaterally symmetrical.[2–7] Both CMO and ICH have been reported to be genetically transmitted, and the signs tend to be self-limiting as closure of the growth plates occurs.[3,6] The purposes of this report are to describe the clinical manifestation of CHS in five bullmastiffs presented to AMAH and to compare and contrast the clinical, radiographic, and histopathological appearances of this syndrome with CMO and ICH.

Case Reports

Case No. 1 (See Tables 1 and 2 for Case Summaries)

An eight-month-old, male bullmastiff was presented to AMAH with a history of three seizures during the preceding month. In addition to the seizures, the owner had noticed that a mass had developed over the dog's left eye and that the dog showed signs of pain. On physical examination, a firm mass was present over the left frontal sinus. A complete blood count (CBC), serum biochemical profile, and serum lead concentration were within reference ranges for the AMAH. Radiographs of the skull revealed periosteal proliferation and thickening of the dorsal calvaria and left temporal region.

From the Angell Memorial Animal Hospital, 350 South Huntington Avenue, Boston, Massachusetts 02130.

Doctor Pastor's current address is the VCA South Shore Animal Hospital, 595 Columbian Street, South Weymouth, Massachusetts 02190.

Cerebrospinal fluid collected from the atlanto-occipital space was within reference ranges, and a trephine biopsy of the bony mass revealed benign, subperiosteal bone proliferation. The trabeculae of bone were comprised of cores of woven bone covered by narrow seams of lamellar bone. The bony interstices contained loose, minimally cellular, fibrovascular tissue devoid of inflammation. Computed tomography of the skull revealed severe hydrocephalus with thickening of the dorsal rostral calvaria on the left side only [Figures 1, 2]. Both lateral ventricles and the mesencephalic aqueduct were dilated. The dog was treated with phenobarbital (1.1 mg/kg body weight, per os [PO] *bid*) after having two seizures while hospitalized. Four months after the initial presentation, the dog had been seizure-free on the phenobarbital therapy, and on physical examination there was no change in the size of the skull mass. No other clinical problems were noted. The dog was subsequently lost to follow-up.

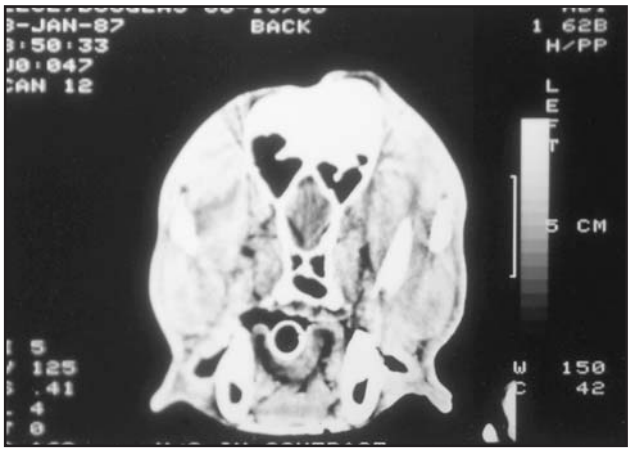

Figure 1—Computed tomography (transverse plane) of the skull of an eight-month-old, male bullmastiff with a mass over the left eye (case no. 1). Note the thickening of the left dorsal rostral calvaria.

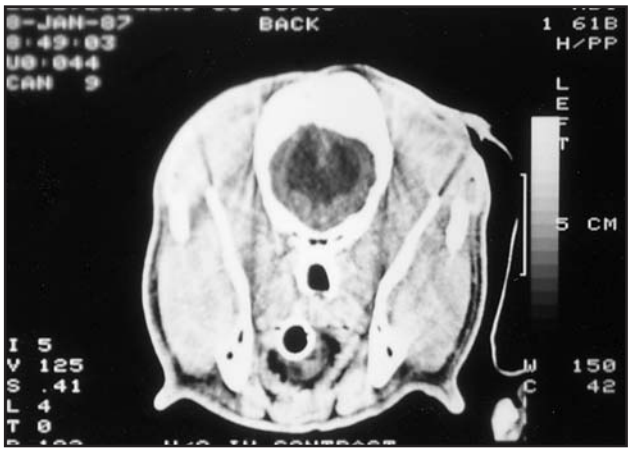

Figure 2—Computed tomography (transverse plane) of the skull of the dog from Figure 1, revealing severe hydrocephalus. Again, note the thickening of the left dorsal rostral calvaria.

Case No. 2

A seven-month-old, male bullmastiff was presented to AMAH for evaluation of a mass located on the dorsal aspect of the head. The mass initially became apparent to the owner four weeks prior to presentation at AMAH. Physical examination revealed two, discrete, firm masses, one located above the left eye at the level of the frontal sinus and the second over the right temporal region. Skull radiographs demonstrated a chronic-active periosteal bone proliferation of the majority of the dorsal aspect of the skull. The periosteal new bone was asymmetric, thickest over the caudal left frontal sinus and right temporal region. A Jamshidi needle biopsy of both bony masses revealed remodeled, reactive, woven bone. The intertrabecular spaces contained a loose, fibrous, fibrovascular tissue and a sparse, attendant, neutrophilic infiltrate. Despite the absence of mandibular involvement, a clinical diagnosis of atypical CMO was made. Because CMO is self-limiting, no therapy was administered. Six months later on physical examination, the masses were significantly reduced in size, but there was still a noticeable asymmetry to the head. No other clinical problems were noted at that time. The dog was subsequently lost to follow-up.

Case No. 3

A 10-month-old, male bullmastiff presented to the referring veterinarian for evaluation of a firm mass located over the left temporal area of the skull. The dog appeared to be in pain and resented palpation of the mass. The owner had first noted the mass four months earlier. The referring veterinarian initially prescribed methocarbamol (22 mg/kg body weight, PO *tid*) and phenylbutazone (5 mg/kg body weight, PO *tid*) for one week, but there was no apparent improvement. In the subsequent two weeks, the mass enlarged to involve the left temporal and occipital regions of the head. Routine laboratory findings (i.e., CBC and serum biochemical profile) were within reference ranges. Skull radiographs demonstrated proliferative periosteal new bone deposition over both frontal sinuses and the dorsal aspect of the calvaria, but it was more severe on the left side. A trephine biopsy of the left temporal bony mass was performed and histopathologically consisted of new periosteal bone formation intermixed with granulation tissue. The proliferative bone tissue was intermixed with a few neutrophils, lymphoid cells, and giant cells. The appearance was thought to be consistent with a diagnosis of osteomyelitis; however, no bacteria were isolated from routine aerobic and anaerobic cultures. The dog was empirically treated with chloramphenicol (30 mg/kg body weight, PO *tid*) for 14 days. The mass remained the same size, but the dog showed minimal signs of pain over the ensuing two weeks. Thereafter, despite continued antibiotic therapy, the dog showed signs of increasing pain. On physical examination, the skull mass had progressed to involve the right side of the head as well. A debulking biopsy, using an osteotome and mallet, was performed of the newly involved right frontal swelling. Histopathology revealed reactive new

bone formation. The bony tissue was composed of a lattice of roughly parallel trabeculae of woven and lamellar bone tissue. The intertrabecular spaces contained a loose, fibrovascular tissue and an attendant, neutrophilic infiltrate [Figures 3A, 3B].

Six weeks after the initial presentation to the referring veterinarian, the dog was referred to AMAH. At that time, a firm, asymmetric, bilateral bony mass was appreciated involving the skull. The mass appeared to be larger on the left side of the skull. The dog had a prominent right forelimb lameness. The right forelimb lameness was localized to the right shoulder, but radiographs of the right humerus were unremarkable, and a definitive cause was not found. Radiographs of the skull demonstrated exuberant, chronic-active, asymmetrical, periosteal new bone deposition along the dorsal surface of the calvaria extending from the frontal sinuses to the occipital crest [Figure 4]. The dog was discharged without any specific therapy. The skull mass appeared to completely resolve over the next six months. There was no recurrence of the mass for two years, at which time the dog was euthanized for aggressive behavior. The dog was unavailable for postmortem examination.

Table 1

Summary of Age at Onset, Age at Diagnosis, Clinical Signs, Location, and Radiographic Findings in Five Male Bullmastiffs with Calvarial Hyperostotic Syndrome (CHS)

Case No.	Age at Onset	Age at Diagnosis	Clinical Signs	Location of CHS	Radiographic Findings
1	7 mos	8 mos	Painful, firm calvarial mass; seizures	Left frontal bone; left temporal bone	Periosteal proliferation and thickening of dorsal calvaria and left temporal region
2	6 mos	7 mos	2 painful, firm calvarial masses	Left frontal bone; right temporal bone	Chronic-active periosteal proliferation of the majority of dorsal calvaria
3	6 mos	10 mos	Painful, firm calvarial mass	Right and left temporal, frontal, and occipital bones	Chronic-active periosteal proliferation of dorsal calvaria extending from frontal bone to occipital crest
4	9 mos	9 mos	Painful, firm calvarial masses	Right and left frontal bones; right and left occipital bones	Periosteal proliferation of dorsal calvaria extending from the frontal sinus to occipital protuberance
5	5 mos	5 mos	Painful, firm calvarial mass; fever; joint effusion	Right and left frontal bones; tympanic bullae	Periosteal proliferation of left frontal bone, dorsal aspect of calvaria, ventral margin of

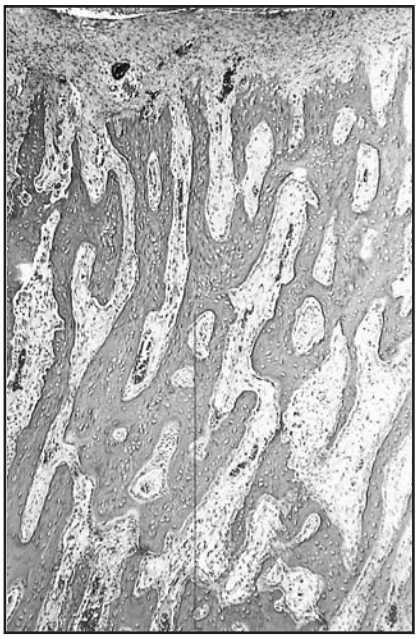

Figure 3A

Figures 3A, 3B—Photomicrograph of a debulking bone biopsy taken from the right frontal bony mass of a 10-month-old, male bullmastiff (case no. 3), demonstrating (**A**) remodeled subperiosteal trabeculae of woven and lamellar bone (50X) and (**B**) remodeled subperiosteal trabeculae of woven and lamellar bone with locally extensive, neutrophilic inflammation and necrosis (200X) (Hematoxylin and eosin stain).

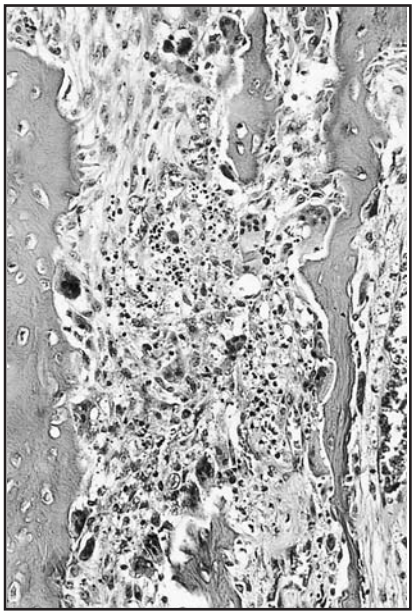

Figure 3B

Case No. 4

A nine-month-old, male bullmastiff was presented to AMAH for evaluation of firm, painful masses on both sides of the skull. Skull radiographs revealed bilateral, proliferative, active new bone deposition extending from the frontal sinus to the occipital protuberance. A trephine biopsy of the mass was interpreted as reactive, subperiosteal new bone formation with no specific etiological agent identified. No specific treatment was instituted. The dog was lost to follow-up.

Case No. 5

A five-month-old, male bullmastiff was presented to AMAH for evaluation of a swelling located over the right frontal sinus, which had been noted one week prior to admission. Physical examination revealed a palpable mass overlying the right frontal sinus. Radiographs of the skull demonstrated proliferative, periosteal new bone overlying the right frontal sinus. The puppy was discharged with no specific therapy, and the owner was instructed to monitor the mass for enlargement. Two weeks later, the puppy was readmitted because the mass had doubled in size. In addition to the puppy being febrile (103º F), digital palpation of the mass and an attempt to open the puppy's mouth elicited signs of pain. A CBC and serum biochemical profile demonstrated a mild leukocytosis with a left shift (white blood cell count [WBC], 17.6 $x10^3/\mu l$ with 2% bands; reference range, 4.0 to 15.5 $x10^3/\mu l$). A trephine biopsy and culture of the bony mass were performed under general anesthesia. Histopathologically, the appearance of the lesion revealed chronic osteomyelitis, although no bacteria were isolated from aerobic or anaerobic cultures. The puppy was treated with intravenous (IV) lactated Ringer's solution (maintenance rate of 60 to 80 ml/kg body weight, per day) and ampicillin (10 mg/kg body weight, IV *tid*). Two days following the biopsy, the puppy developed pain and effusion in both carpal and stifle joints. Arthrocentesis of both carpi and stifles indicated nonseptic, neutrophilic inflammation (actual values not available). Radiographs of the stifles revealed proliferative new bone involving the metaphyseal-diaphyseal junctions of the distal femora and proximal tibiae, as well as sclerosis of the proximal aspect of the tibial crests. Two days later, the joint effusion began to resolve, although the puppy remained febrile and had a persistent leukocytosis as well as an elevated serum alkaline phosphatase (222.4 U/L; reference range, 5 to 13 U/L) and cholesterol (690 mg/dl; reference range, 92 to 324 mg/dl). Seven days following the biopsy, the fever resolved, the puppy's appetite improved, and he was discharged on amoxicillin (10 mg/kg body weight, PO *bid* for six wks). Two weeks following discharge, the puppy was reevaluated because he had developed subcutaneous [SC] nodules over both shoulders and a new mass over the left frontal sinus. Radiographs of the right shoulder demonstrated new bone deposition

along the caudal humeral cortices as well as sclerosis of the nutrient canal and a discrete, soft-tissue swelling. The new bone deposition in the humerus was similar in appearance to the radiographic changes seen in the distal femora and proximal tibiae. Radiographs of the skull revealed exuberant, proliferative new bone deposition involving the left frontal bone, dorsal aspect of the calvaria, and the ventral margin of the tympanic bullae. Biopsies of the left frontal bony mass and SC nodules over the shoulder were performed. Trephine biopsy of the left frontal bony mass revealed reactive new bone formation. A diagnosis of calcinosis circumscripta was made from the excisional biopsies of the SC nodules over the shoulders. Two days following the biopsies, the puppy was depressed, had a dome-shaped skull, ptyalism, and was unable to completely open his mouth. The animal was euthanized at the owner's request.

Gross lesions noted at necropsy included generalized lymph node enlargement, SC edema over the nasal planum and calvaria, a thickened calvaria, a seroma where one of the shoulder nodules had been excised, cecocolonic trichuriasis, multifocal endocardial mineralization, proliferative and sclerotic bone lesions involving multiple bones, and an incomplete fracture of the left femoral neck.

Histopathologically, there was suppurative osteomyelitis involving the frontal and parietal bones and suppurative pachymeningitis that involved the cerebral dura mater between the frontal and parietal bones. Coagulase-positive *Staphylococcus aureus* was cultured from the cerebral dura mater. The trabeculae of the calvarial diploë were thickened and contiguous with a sunburst-like pattern of subperiosteal trabeculae composed of woven and lamellar bone tissue. The intervening spaces were infiltrated with predominantly neutrophils. Changes in the long bones (femur, tibia, and humerus) were characterized by intramedullary fibrosis and proliferation of woven bone on the periosteal and endosteal surfaces of the cortices. Histopathological changes in the soft tissues included mineralization of the endocardium, kidneys, lung, and the pulmonary, coronary, and gastric arteries. Villous synovial proliferation and mild neutrophilic and lymphoplasmacytic synovitis were identified in the left coxofemoral and right scapulohumeral joints. There was a generalized reac-

Table 2

Summary of Histopathological Findings, Other Related Pathology, Time of Follow-up, and Outcome in Five Male Bullmastiffs With Calvarial Hyperostotic Syndrome (CHS)

Case No.	Histopathological Findings	Other Related Pathology	Time of Follow-up	Outcome
1	Benign, subperiosteal bone proliferation; devoid of inflammation	Hydrocephalus demonstrated on computed tomography	4 mos	Partial resolution
2	Remodeled, reactive new bone; sparse, neutrophilic infiltrate	None	6 mos	Partial resolution
3	Remodeled, reactive new bone; neutrophilic infiltrate	Right forelimb lameness (no definitive cause found)	2 yrs	Complete resolution
4	Reactive, subperiosteal new bone; devoid of inflammation	None	None	Unknown
5	Reactive, subperiosteal new bone; predominantly neutrophilic infiltrate	Calcinosis circumscripta; mineralization of soft tissues; periosteal and endosteal proliferation of woven bone of femora, tibiae, humeri; suppurative osteomyelitis and pachymeningitis of frontal and parietal bones; coagulase-positive *Staphylococcus aureus*	3 mos	Euthanized

tive lymphadenopathy.

Discussion

Calvarial hyperostotic syndrome in bullmastiffs shares clinical and histopathological similarities with CMO and ICH.1 However, differences between CHS and these syndromes suggest that CHS is a distinctive osteopathy.

Canine craniomandibular osteopathy is a nonneoplastic lesion that is characterized pathologically by bilaterally symmetrical, periosteal deposits of woven bone with irregular resorption of underlying, preexistent, cortical lamellar bone. As the syndrome progresses, the medullary cavities of the affected bones (i.e., mandible, tympanic bullae, and occipital bones) become filled principally with woven bone. As the dogs reach skeletal maturity, the woven bone may be partially replaced by lamellar bone, but the affected bone rarely reverts to its normal architecture.[8] Although calvarial hyperostosis has been reported as a component of CMO in some canine breeds, to the authors' knowledge there has only been one previous report describing CMO in the bullmastiff.[2] Like CMO, CHS tends to affect young dogs from five to 10 months of age and has a predilection for the flat bones of the skull. Histopathologically, both CMO and CHS appear to be nonneoplastic, proliferative, osseous abnormalities, and radiographically the type of bone reaction appears similar. Both syndromes tend to be self-limiting in nature. Unlike CMO, however, CHS does have a definite sex and breed predilection; namely, only young, immature, male bullmastiffs have been reported to be affected to date. The skull lesions of CHS are frequently not bilateral and symmetric as they tend to be in the typical case of CMO, and the mandible tends to be unaffected in CHS.

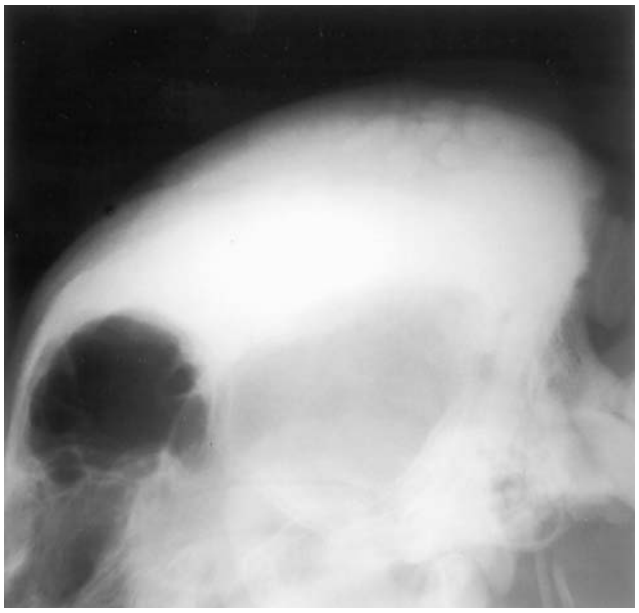

Figure 4—Lateral radiograph of the skull of the dog from Figures 3A, 3B. Note the proliferative, periosteal new bone deposition along the dorsal surface of the calvaria, extending from the frontal sinus to the occipital crest.

Human infantile cortical hyperostosis is a disease characterized by bilateral, symmetrical, subperiosteal new bone formation, most commonly involving the mandible (80% of infants) and appendicular skeleton. It is a heritable disease, which primarily affects infants from the ages of 10 weeks to five months.[3,4] Like ICH, CHS is manifested in the first few months of life and has a predilection for the flat bones of the skull. Calvarial hyperostotic syndrome and ICH share similar radiographic and histopathological features, and both conditions tend to be self-limiting.[1] Unlike ICH, CHS does not usually appear as a bilateral, symmetrical condition and does not affect the mandible.

The fact that only male bullmastiffs seem to be affected by CHS suggests that there may be an underlying heritable basis. The condition could be due to a sex-linked gene. Of course, the limited sample size makes it difficult to make major conclusions at this time. The main argument against a possible heritable basis for CHS centers on the failure to document involvement of littermates and certain bullmastiff lineages in a predictable Mendelian fashion. Further prospective studies would necessitate breeding trials of affected bullmastiff lines in order to document and characterize gene involvement. In the only other citation to bony proliferation of the calvaria in bullmastiffs, the two dogs described were of unspecified sex and not genetically related.[1]

Case no. 5 is problematic. This was the first case recognized at AMAH, and it was included because the osteoproliferative calvarial lesion was histopathologically similar to that of the other four cases. Unlike the other cases, the puppy had clinical signs that were consistent with a bacterial infection (e.g., fever, pain, joint effusion, leukocytosis). No bacteria were isolated antemortem, but on postmortem *Staphylococcus aureus* was isolated. A positive culture on a postmortem examination does not provide enough evidence to refute or support the possibility of a concurrent bacterial infection. In addition, the puppy had calcinosis circumscripta and at necropsy had evidence of a disseminated visceral mineralization and a pathological fracture of the left femoral neck. The puppy had no clinical or laboratory evidence of renal disease or perturbation of calcium-phosphorus homeostasis. The possibility exists that this puppy had multifocal bacterial osteomyelitis in addition to CHS or that sepsis is somehow related to this syndrome. It is unclear at this time exactly how the calvarial hyperostosis, lesions of the appendicular skeleton, and widespread dystrophic mineralization are related in this animal.

Several questions remain unanswered with respect to CHS: 1) Why are bullmastiffs the only canine breed seemingly affected by this syndrome? 2) Is there a sex-linked genetic basis that may explain, in part, why only male dogs are affected? 3) Could there be a common etiopathogenesis for CHS and other osteopathies such as CMO? 4) Is sepsis involved in the etiology? Unfortunately, given the paucity of CHS cases that have been reported, these questions remain unanswered. As more cases are recognized, it may be possi-

ble to better understand CHS and ways by which it might be differentiated from other osteopathies like CMO. It does not appear likely that traumatic, neoplastic, or degenerative conditions are responsible for the etiopathogenesis of CHS. It seems likely that the etiology of CHS is multifactorial, thereby explaining the protean clinical presentations of the syndrome. Possible factors include infectious, nutritional, and metabolic processes.

Conclusion

Calvarial hyperostotic syndrome of male bullmastiffs is a newly described hyperostotic syndrome, which shares some common clinical features with CMO and ICH. It does, however, possess some distinctive features. All the dogs presented here had similar radiographic findings—namely, thickened calvaria with irregular, chronic-active, bony proliferation over the frontal sinus, temporal, and occipital bones. The lesions typically were not bilaterally symmetric as in the other similar syndromes (i.e., CMO, ICH), nor were the mandibles involved. The histopathological findings at biopsy were similar. Bony trabeculae of the calvarial diploë were thickened and contiguous with a sunburst-like pattern of subperiosteal trabeculae of woven and lamellar bone tissue accompanied by loose, fibrovascular tissue and a variable inflammatory response comprised predominantly of neutrophils. The clinical signs improved partially or completely by the time of physeal closure. At this time the underlying etiopathogenesis remains unknown, but given the similarity of CHS to CMO and ICH, etiologies to be considered include infectious, nutritional, genetic, and metabolic disorders. The underlying etiopathogenesis may be multifactorial. A bone biopsy is recommended at this time to definitively diagnose and document this newly recognized syndrome. In four of the five cases reported in this article, the lesions were self-limiting. Because the condition appears self-limiting, no specific therapy can be recommended at this time. Calvarial hyperostotic syndrome may be hereditary. Until additional information on the etiology is available, the authors do not recommend breeding affected dogs.

References

1. Muir P, Dubielzig RR, Kenneth KA, Shelton GD. Hypertrophic osteodystrophy and calvarial hyperostosis. Comp Cont Ed Pract Vet 1996;18(2):143–50.
2. Watson ADJ, Adam WM, Thomas CB. Craniomandibular osteopathy in dogs. Comp Cont Ed Pract Vet 1995;17(7):911–21.
3. Newburg AH, Tampas JP. Familial infantile cortical hyperostosis: an update. Am J Roentgenol 1981;137:93–6.
4. Faure C, Beyssac JM, Montagne JP. Predominant or exclusive orbital and facial involvement in infantile cortical hyperostosis. Pediatr Radiol 1977;6:103–6.
5. Baker JR. Bone disease in a dog similar to infantile cortical hyperostosis (Caffey's disease). Vet Rec 1975;97:74–5.
6. Padgett GA, Mostosky UV. Animal model: the mode of inheritance of craniomandibular osteopathy in west highland white terriers. Am J Med Gen 1986;25:9–13.
7. Riser WH, Parkes LJ, Shiver JF. Craniomandibular osteopathy. J Am Vet Radiol Soc 1967;8:23–31.
8. Manley PA, Amundson Romich J. Miscellaneous orthopedic diseases. In: Slatter D, ed. Textbook of small animal surgery. 2nd ed. 1993;2:1991–2.