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Jacobs Journal of Anatomy

Case Report

Clinically Silent Calvarial Defects in a Dog: Developmental Failure of Endochondral and Intramembranous Ossification

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Received: 07-16-2015

Accepted: 08-07-2015

Published: 09-23-2015

Abstract

A 3-year-old Shih Tzu was examined for bilateral nasal discharge and sneezing. The dog had no apparent neurological deficits. Computed tomography (CT) of the nasal cavity and remaining head was performed. Imaging findings were consistent with a non-destructive rhinitis. Multiple well-defined, round to ovoid defects in the calvarial bones were an ancillary finding of the CT imaging. A thin layer of soft tissue attenuation was present spanning these defects. Severe hydrocephalus was also identified, with no evidence of parenchymal herniation through the calvarial defects. Findings are consistent with a congenital failure of both endochondral and intramembranous ossification involving cells from both neural crest and mesoderm origin.

Keywords: Ossification defect; Calvarial; Endochondral; Intramembranous

Introduction

The craniofacial bones of higher vertebrates form by both intramembranous and endochondral ossification. With intramembranous ossification osteoblastic differentiation from mesenchymal cells is direct [1]. Endochondral ossification begins with formation of a cartilage template, with subsequent ossification [1]. The skull is also separated into the neurocranium and the viscerocranium. The neurocranium envelops the brain and special sense organs, while the viscerocranium scaffolds the face and jaws. The neurocranium is further divided into those bones formed by intramembranous ossification, and

those formed by endochondral ossification. The membranous bones of the neurocranium compose the calvarial vault (frontal, parietal, temporal, ethmoid), and the bones formed by endochondral ossification compose the base of the skull (occipital, sphenoid, pterygoid) [2]. The viscerocranium is entirely formed by membranous bones (nasal, maxillary, vomer, palatine, mandibular) [2,3]. Craniofacial bones are also classified by their embryonic cell of origin. The bones formed from cephalic mesoderm via somitomeres include the supraoccipital, temporal, and a portion of the sphenoid. The exoccipital bone is contributed by skeletal somite cells. The remainder of the neurocranium and viscerocranium is formed from neural crest cells of ectodermal origin [2].

In the human literature, the majority of calvarial defects are described in infants. Multiple conditions, such as osteogenesis imperfecta, achondrogenesis, hypophosphatasia, and copper metabolism defects can result in diffuse thinning of other regions of the skull [3]. Many of these conditions are lethal, and are infrequently seen in adult animals. Other conditions result in focal osteopenia or calvarial defects. These conditions include iatrogenic osteotomies, traumatic fractures, osteomyelitis, metastatic neoplasia, leptomeningeal cysts, hypophosphatasia, persistent anterior fontanelle, cranium bifidum, giant frontal and parietal foramina, membranous bone dysplasia, and cleidocranial dysplasia [4,5].

The imaging findings of the patient reported here share some characteristics of these conditions, but do not match the suite of any of them completely. Imaging findings were also not supportive of aggressive bone lysis or soft tissue swelling consistent with infection or neoplasia. This report presents a dog with multiple parasagittal skull defects that appear to be secondary to failure of both endochondral and intramembranous ossification during skull formation.

Case Report

A 3-year-old, 3.5-kg, neutered male Shih Tzu dog presented for evaluation of a 2-month history of bilateral nasal discharge, sneezing, hyporexia, and lethargy. The dog had previously been treated with amoxicillin/clavulanic acid, enrofloxacin, guaifenesin, and theophylline by the referring veterinarian. Clinical signs improved on these medications, but worsened following discontinuation several days prior to presentation. The dog's physical examination was normal except for a small region of alopecia and scaling on the left lateral thorax. There was no in-depth neurologic examination of this dog because no signs were displayed suggesting the need for such. Complete blood counts, urinalysis, fecal flotation, and skin cytology were within normal limits. Blood chemistry showed a mildly increased albumin (4.1 g/dl), consistent with mild dehydration. Differential diagnoses included inflammatory rhinitis (allergic, immune-mediated), infectious rhinitis, or intranasal foreign body.

Three-view thoracic radiographs were performed, and were within normal limits. Helical computed tomography (CT) of the head was acquired in a transverse plane from the nasal planum to the occiput (1.0 mm slices thickness, kVp 120, bone and soft tissue algorithms). Adherent to the nasal mucosa bilaterally, fluid to soft tissue attenuating material (10-70 Hounsfield units) was present. This change was more severe on the left side. Portions of this material contrast enhanced, consistent with mucosal thickening. There was no evidence of nasal turbinate or paranasal bone lysis, excluding a palatine bone defect described below. Nasal findings were consistent with bilateral non-destructive rhinitis, suggesting inflammatory or infectious etiologies.

Ancillary to imaging of the nasal cavity, multiple calvarial bones contained well defined round to ovoid defects (Fig. 1-2). Bones involved in defects included the parietal, temporal, supraoccipital, presphenoid, wings of the basisphenoid, and palatine bones. Involvement of the frontal bone could not be excluded due to poor demarcation of the frontoparietal and frontosphenoidal suture lines. The majority of the defects had a general symmetry from left to right, suggesting a developmental pathogenesis. The palatine defect was bilateral, but extended across midline. A persistent midline frontoparietal fontanelle was not present. Spanning the calvarial defects, a thin, curvilinear, soft tissue attenuating (60-90 Hounsfield units) structure was present. There was no periosteal new bone identified at the margins of these defects. The lateral ventricles were severely bilaterally enlarged. No parenchymal brain herniation was present through any of the calvarial defects. Findings in the skull were consistent with a congenital failure of both endochondral and intramembranous ossification of multiple embryologic cell lines.

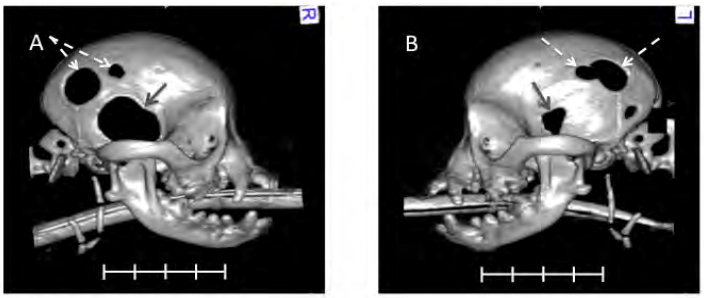

Figure 1

Figure 1. 3D reconstruction of CT data showing the multifocal calvarial defects from right lateral (A) and left lateral (B) views. Dashed arrows in panels A and B show defects sharing partial left-right symmetry by position, size and shape. The solid gray arrows show defects with symmetry by position but not by size. The scale bar divisions are 1 centimeter each.

Endoscopy of the nasal cavities was performed, and biopsy samples were obtained. Biopsy samples of the right nostril demonstrated mild, acute, multifocal, neutrophilic and hemorrhagic rhinitis. Samples of the left nostril demonstrated moderate, acute, diffuse, suppurative rhinitis with hair and plant foreign material. The dog was placed on 3.5 mg/kg doxycycline (50 mg tablets) orally every 12 hours. The owner was advised that the dog may be more prone to injury from head trauma

due to the calvarial defects, and was advised to monitor for neurologic signs.

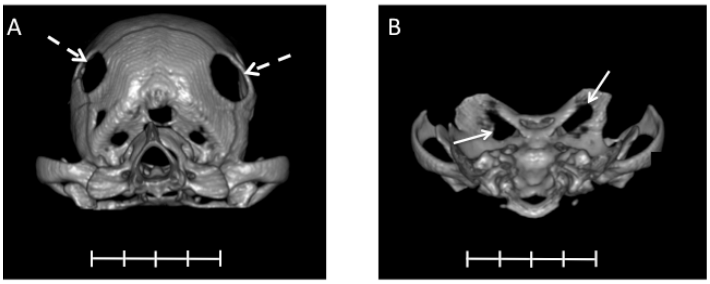

Figure 2

Figure 2. 3D reconstruction of CT data showing caudal (A) and caudodorsal to rostroventral with a portion of the calvaria removed (B) views. Dashed arrows in panel A show the same defects as indicated by dashed arrows in Figure 1. Solid arrows in panel B show bilateral, irregularly ovoid sphenoid and palatine defects. The scale bar divisions are 1 centimeter each.

Discussion

There are diverse causes of focal skull defects in mammals. Leptomeningeal cysts occur following traumatic dural lacerations [3,5]. The laceration allows cerebrospinal fluid to pulse the fracture line, resulting in widening and focal defects. Defects associated with leptomeningeal cysts may be solitary or multifocal, but require a prior traumatic fracture, which is inconsistent with the patient reported.

Hypophosphatasia is a genetic defect resulting from absent or decreased serum alkaline phosphatase. This disorder can present as calvarial bone islands or disconnected bone plates along with generalized decreased opacity of the skull and vertebrae [3]. The case described here had normal blood serum alkaline phosphatase levels. Additionally, the patient had no evidence of diffuse calvarial or vertebral osteopenia.

Persistent anterior fontanelle results in a midline defect along the fronto-parietal suture [5]. The patient presented did not have any midline defects along the fronto-parietal suture, and the calvarial defects present were parasagittal.

Cranium bifidum and giant frontal and parietal foramina are phenotypic variations of a genetic defect [6]. Cranium bifidum, also called dysraphism, results in a midline defect that predisposes to parenchymal herniation [3]. This condition has been reported in conjunction with hydrocephalus, Chiari malformation, schizencephaly, myelomeningocele, meningoencephalocele, and dermal sinus [3,7]. Giant frontal and parietal foramina are symmetrically paired defects within the frontal or parietal bones that persist in the adult [3,4,6]. These defects can extend across midline, and may assume a parasagittal location as midline ossification proceeds [3,6-8]. Of note is that these foramina may also be associated with anomalous venous drainage secondary to an absent or hypoplastic straight sinus [6]. The patient presented here had no clinical signs of elevated intracranial pressure or neurologic deficits, but did have severe hydrocephalus. Other intra-axial defects associated with these conditions in humans were not identified in this patient.

Membranous bone dysplasia, which is termed lacunar skull, results in focal calvarial defects spanned by lucent fibrous bone, and typically resolves early in life [6]. Lacunar skull occurs in association with other defects of the neural tube such as Chiari Type II malformation, myelomeningocele, and encephalocele. While the defects produced by this condition are similar to the defects reported here, this patient did not have the associated intra-axial abnormalities and was an adult at presentation.

Cleidocranial dysplasia results in widening of fontanelles secondary to a genetic mutation in the CBFA1 gene. This gene regulates differentiation of osteoblasts, but only affects membranous bone. Cleidocranial dysplasia may also be associated with other axial and appendicular skeletal defects, as well as hearing loss [3]. This condition differs from the case presented in that this patient had defects of bone derived from both endochondral and intramembranous ossification, and that the patient did not have additional axial or appendicular defects.

In addition to the above disease syndromes, genetic deficiencies of certain proteins and transcription factors have been implicated in craniofacial defects. Connexin (Cx) 43 is a gap junction protein present in neural crest cells and osteoblasts [9]. Mice that lack Cx43 have both delayed intramembranous and endochondral ossification, secondary to impaired osteoblast development and function. Interestingly, although Cx43 is present within cells of neural crest origin, mice deficient in this protein develop ossification defects in bones of both neural crest and mesodermal origin. Cx45, another gap junction protein, is up-regulated in Cx43 deficient mice. This up-regulation can mask some of the defects secondary to the Cx43 deficiency, but delayed ossification still occurs [9].

Forkhead transcription factor (Foxc1) is another regulator of calvarial development. Relating to the calvaria, Foxc1 controls signaling of fibroblast growth factor and bone morphogenic protein [10]. It is also present within the dura, which itself plays a role in normal ossification of the skull. One lethal variant of Foxc1 deficient mice not only has calvarial defects, but also develop hydrocephalus secondary to incomplete dural formation [10]. While the case reported here has some similarities to mouse models deficient in Cx43 and Foxc1, these mice also have defects in other body systems including cardiovascular, renal, and ocular [9,10]. Such defects were not identified in the patient presented here.

Focal thinning and suspected discontinuous cortical defects were reported in a case series of porencephalic dogs, but symmetric lesions were not described [11]. The case reported here did not have cervical imaging, but clinical signs of cervical hyperesthesia consistent with syrinx formation were not present. Porencephaly was not identified on CT images of the

patient reported here.

The case reported here is unique for several reasons, and is a departure from reported cases available in both human and veterinary literature. The calvarial defects involved bones of both neural crest (parietal, presphenoid, palatine, +/-frontal) and mesodermal (temporal, supraoccipital, basisphenoid) embryologic origin. The bones involved were also of separate cellular ossification pathways, namely membranous (parietal, palatine, +/- frontal) and endochondral origin (temporal, presphenoid, basisphenoid, supraoccipital). calvarial defects were relatively symmetric and parasagittal, but not mirrored exactly on contralateral sides. Hydrocephalus was present, but the patient had no related clinical signs and this is a common condition in this breed. This patient survived to adulthood, and had no clinical signs related to the ossification defects. The case presented has characteristics most closely related to giant parietal and frontal foramina, membranous dysplasia, and cleidocranial dysplasia, however with important differences previously described. As in this dog, human cases of giant frontal and parietal foramina may occur with no clinical symptoms [8]. A role for Cx43 and/or Foxc1 deficiency in this patient seems likely, but is purely speculative without genetic confirmation. In addition to genetic testing, magnetic resonance imaging and cerebrospinal flow studies may be contributory to further characterize intraxial defects and flow dynamics not possible with CT. The case reported represents a novel presentation of clinically silent calvarial defects, secondary to failure of both endochondral and intramembranous ossification.

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