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Review

An update on the pathogenesis of syringomyelia secondary to Chiari-like malformations in dogs

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ABSTRACT

Syringomyelia (SM) is a spinal cord disease that can cause neuropathic pain in dogs. The pathogenesis of SM secondary to Chiari-like malformation (CM) has been the focus of intense research in recent years. The gulf in our understanding of CM/SM in dogs relative to the analogous human condition has progressively narrowed. CM is primarily a disease of abnormal geometric morphometry affecting the caudal cranial fossa and the brain parenchyma contained within it. This review describes how advanced imaging techniques have revealed a series of morphometric abnormalities associated with CM/SM. The series is presented in a logical order to help describe the pathogenesis of CM and the subsequent formation of syringes, with particular reference to the concepts of craniospinal compliance and cerebrospinal fluid pulse pressure timing.

Introduction

Syringomyelia (SM) is an enigmatic disease in dogs characterised by fluid-cavitation of multiple spinal cord segments (Rusbridge et al., 2000; Loderstedt et al., 2011). Cavitation and damage to the spinal cord, typically the dorsal horn, results in abnormal processing of sensory information that manifests clinically as pain and dysaesthetic behaviour (Rusbridge et al., 2007; Hu et al., 2011a). SM occurs in dogs secondary to congenital and acquired neurological disorders such as craniocervical malformations, subarachnoid diverticulae, intervertebral disc disease and intra-cranial neoplasms. These diseases share reduced cross-sectional area of the subarachnoid space (SAS) and altered cerebrospinal fluid (CSF) hydrodynamics as common features. Alteration in CSF flow is suspected to drive the accumulation of fluid in the spinal cord causing central canal dilation and eventually parenchymal cavities (Bhadelia et al., 1995; Panigrahi et al., 2004).

Chiari type 1 and Chiari-like malformation

Human Chiari type I malformations (CMI) are associated with reduced posterior fossa volume (Milhorat et al., 1999) and caudal descent of the cerebellar tonsils (Milhorat et al., 2010). The prevalence of SM secondary to CMI is high (Speer et al., 2003) as altered CSF hydrodynamics occur at the level of the foramen magnum and the cranial cervical spinal cord (Levine, 2004; Greitz, 2006). Similarly, SM commonly co-exists with craniocervical malformations in dogs, but dogs lack cerebellar tonsils (Rusbridge et al., 2000; Rusbridge and Knowler, 2003).

The term *Chiari-like* malformation (CM) in Cavalier King Charles spaniels (CKCS), as defined by an international working group (Capello and Rusbridge, 2007), encompasses a mismatch between caudal cranial fossa (CCF) volume and the brain parenchyma within, leading to a caudal herniation of part of the cerebellum and brainstem into or through the foramen magnum. This terminology is advantageous in the CKCS where all these features are typically present and are somewhat analogous to CMI, for which the disease serves as a naturally occurring model (Driver et al., 2012a). A further advantage of studying the disease in CKCS is the high prevalence of CM (Couturier et al., 2008; Carrera et al., 2009); in one study 92% of CKCS had at least one morphological abnormality consistent with CM on magnetic resonance imaging (MRI; Cerda-Gonzalez et al., 2009a).

Diagnosis of CM requires MRI, with indentation and herniation of the cerebellar vermis most commonly cited as key diagnostic features (Lu et al., 2003; Cross et al., 2009). These features can be seen in Fig. 1, in comparison to a brachycephalic dog without CM.

Syringomyelia secondary to Chiari-like malformation

Unlike human medicine, there is debate in the veterinary literature regarding whether CM alone causes clinical signs (Lu et al.,

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2003; Cerda-Gonzalez et al., 2009a; Driver et al., 2012b). Conversely, SM has been associated with neurological signs and neuropathic pain in CKCS (Rusbridge et al., 2007; Cerda-Gonzalez et al., 2009a; Rutherford et al., 2012), with large and asymmetric syringes being the strongest predictors of pain (Rusbridge et al., 2007).

The mechanisms by which SM leads to neuropathic pain have been reviewed previously (Rusbridge and Jeffery, 2008) and updated by Hu et al. (2011b). SM secondary to CM is a complex oligogenic trait in CKCS with a moderately high estimate of heritability (Lewis et al., 2010). Preventative breeding schemes have existed for several years with some recent success in reducing the disease prevalence (Knowler et al., 2011). It is from these breeding schemes that estimates of the prevalence of asymptomatic SM have been made; 25% of CKCS aged 12 months have SM, increasing to 70% in CKCS aged 72 months or more (Parker et al., 2011). This phenomenon is evident radiologically in dogs with SM, as sequential MRI scans reveal that the cavity width increases with time (Driver et al., 2012a).

It is difficult to predict which dogs will develop clinical signs following incidental diagnosis, and this is a source of concern and frustration for dog owners, breeders and veterinarians. It appears that following a clinical diagnosis of SM, signs of neuropathic pain can be progressive in some cases despite medical and surgical intervention (Vermeersch et al., 2004; Dewey et al., 2005, 2007; Rusbridge, 2007; Plessas et al., 2012).

CM/SM is also observed in an increasing number of other small or 'toy' dog breeds, including the French bulldog, Griffon Bruxellois, Chihuahua, Pomeranian, Maltese terrier, Pug and Yorkshire terrier (Dewey et al., 2005). CM is an important risk factor for the development of SM in the Griffon Bruxellois, however SM does occur in dogs without apparent cerebellar herniation (Rusbridge et al., 2009). Moreover, other morphological abnormalities affecting the volume of the subarachnoid space in the craniocervical region, such as atlantooccipital overlapping, might contribute to the disease and should possibly be included as defining features of CM (Marino et al., 2012). The pathogenesis of canine SM secondary to CM (in its broadest sense) is therefore likely to be complex.

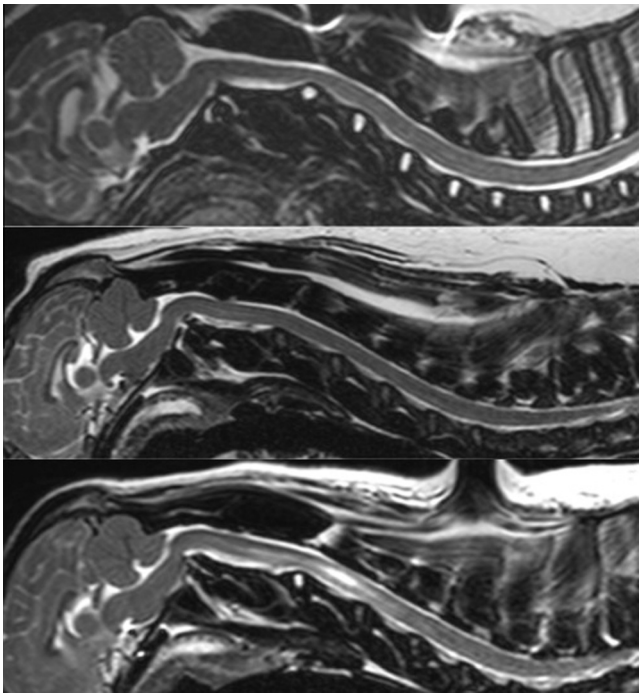

Fig. 1. Sagittal T2-weighted MRI scans of the brain and cervical spine in a flexed position from (top to bottom) of a brachycephalic (Pug) dog with a normal cervicomedullary junction, a Cavalier King Charles spaniel (CKCS) with Chiari-like malformation (CM; indentation of the cerebellum by the occipital bone and herniation of the cerebellar vermis into the foramen magnum) and a CKCS with CM that has developed syringomyelia in the cervical spinal cord.

Morphometric analysis of CM/SM

Morphometric studies can be used to study the relationships of certain highly variable anatomical features with particular diseases. There are several examples of morphometric studies in veterinary medicine pertaining to musculoskeletal disorders, such as cranial cruciate disease (Mostafa et al., 2010; Ragetly et al., 2011) and neurological disorders such as cervical spondylomyelopathy (Da Costa et al., 2006; De Decker et al., 2012). Individual anatomical features can be measured in two or three dimensions. As shortening of a particular anatomical feature might be associated with compensatory increase in another dimension, three-dimensional studies are preferred where possible, although they require advanced multi-planar imaging techniques (Driver et al., 2010a).

In canines, breed selection pressure has resulted in a vast variation of skull shape and size. In particular, canine brachycephaly is related to paedomorphosis (Goodwin et al., 1997), as in certain dog breeds it is considered desirable (for various functional and aesthetic reasons) to retain the shorter skull confirmation that is common to all juvenile dogs. Brachycephalic dogs have rounded, relatively broad heads with shortened facial bones (Evans, 1993). This process has led to the alteration of other cranial features, for example the virtual abolition of frontal sinuses (Scrivani et al., 2007) and morphological differences in the neurocranium, specifically a large cephalic index (Roberts et al., 2010). Brachycephalism also has effects on cerebral tissue, such as a more ventral pitch of the primary longitudinal brain axis and ventral shift in the position of the olfactory lobe (Roberts et al., 2010; Hussein et al., 2012).

At a basic level, CM is a disease of abnormal geometric craniocerebral morphology that could also be associated with brachycephalism and miniaturisation. The traditional view of human CMI is that occipital bone hypoplasia facilitates the caudal descent of the cerebellum (Vega et al., 1990; Nishikawa et al., 1997; Milhorat et al., 1999, 2010). Occipital bone hypoplasia has been proposed as a cause of CM in dogs (Rusbridge et al., 2000; Rusbridge and Knowler, 2004). However, abnormalities of the occipital bones in isolation are not consistent with the observation that dogs with CM display shortening of the entire basicranium (Rusbridge et al., 2009). Given the wide braincase of CKCS, the aetiology of CM could be associated with a higher grade of the brachycephalic phenotype (Schmidt et al., 2011).

Caudal cranial fossa morphology

The CCF is the intra-cranial compartment that contains the cerebellum, pons and medulla oblongata. Internally, it is delineated dorsally and rostrally by the tentorium cerebelli and ventrally it extends from the petrosal crests and dorsum sellae to the foramen magnum (Evans, 1993). It is defined externally by the pyramidal occipital bones; the supraoccipital, basioccipital and paired exoccipitals (Evans, 1993; Rusbridge et al., 2006). The volume of the posterior fossa plays a role in CMI (Trigylidas et al., 2008), which is significantly smaller in children with both CMI and SM (Sgouros et al., 2006).

It is conceivable that more severe morphological abnormalities affecting the CCF might be associated with a more severe disease phenotype in dogs, in particular CCF volume and the presence of clinically significant SM. However, initial studies failed to associate CCF area or volume with SM (Carruthers et al., 2009; Cerda-Gonzalez et al., 2009a; Schmidt et al., 2009; Driver et al., 2010a). A