

Clinical Commentary

Vertebral embryology and equine congenital vertebral anomalies

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Introduction

A variety of congenital vertebral defects is seen in horses and their diagnosis is dependent on a sound clinical examination combined with ancillary diagnostic techniques. Cervical vertebral malformation or stenosis (CVM/S) is relatively common (Mayhew 2008) and, although the aetiology remains unclear, genetic, nutritional and environmental causes have been implicated (Falco *et al.* 1976; Mayhew *et al.* 1993; Levine *et al.* 2008). A number of rarer abnormalities are reported, however, associated with typically more severe defective vertebral anatomy such as the foal described by Crochik *et al.* (2009) in this issue. The following article describes the relevant embryology of mammalian vertebrae and associated structures and reviews the recognised congenital vertebral defects reported in horses.

Mammalian vertebral embryology

During early mammalian gestation a trilaminar embryonic disc forms consisting of 3 germ layers - endoderm, mesoderm and ectoderm (Larsen 2001). Cells of mesodermal origin are responsible for formation of the prechordal plate and notochordal process, with the latter developing into the notochord (Kaplan *et al.* 2005). Either side of the notochord, the mesoderm further differentiates into paraxial, intermediate and lateral mesoderm. The paraxial mesoderm then forms a series of spherical structures in a craniocaudal sequence known as somitomeres. With the exception of the most cranial somitomeres, the remainder develop into pairs of somites (Larsen 2001).

Each somite then differentiates into: 1) sclerotome that gives rise to the vertebral bodies and arches; 2) dermomyotome that forms the overlying dermis; and 3) the myotomes that develop into the musculature (Larsen 2001; Kaplan *et al.* 2005) (Fig 1). The first 4 somites contribute to the occipital bone of the skull and other

muscles and bones of the head, and the following 8 somites generate the cervical vertebrae and muscles and dermis of the neck. The cranial portion of the most cranial cervical somites also contributes to occipital bone formation (Larsen 2001).

The notochord is closely related and contributes to somite development and the early formation of the vertebrae (Nolting *et al.* 1998). Gastrulation produces the early embryonic body plan (Iimura and Pourquie 2007), which is further modified by the expression of combinations of genes that define the somites' positional identities and instigate construction of the body's 3D segmental structure (Kessel and Gruss 1991). The pathways involved are highly complex but involve differential expression and regulation of, among others, the Hox genes and involve a variety of pathways, including Wnt, retinoic acid (RA) and fibroblast growth factor (FGF) signalling (Iimura and Pourquie 2007). Defects in molecular and cellular signalling and variations in spatial expression of Hox genes may result in malformations and abnormalities of the axial skeleton and vertebrae during sclerotome differentiation, chondrification and ossification (Nolting *et al.* 1998; Kaplan *et al.* 2005).

The spinal cord is ectodermal in origin. Neurulation occurs during somatogenesis with folding of the neural plate into a hollow neural tube. The lateral lips of the folds meet dorsally as the surface ectoderm fuses and the neural tube separates enclosing a space that becomes the neural canal (Larsen 2001); associated structures subsequently form into the spinal cord. Neurulation is induced through the expression of several genes and molecular signalling pathways derived from both the notochord and the associated mesoderm (Kaplan *et al.* 2005).

Congenital malformations

Spinal malformations can be classified according to their aetiology: 1) neural tube defects; 2) defects of segmentation; and 3) defects of formation. Spinal dysraphism is the term used to describe failure of closure of the neural tube and typically involves disruption of central

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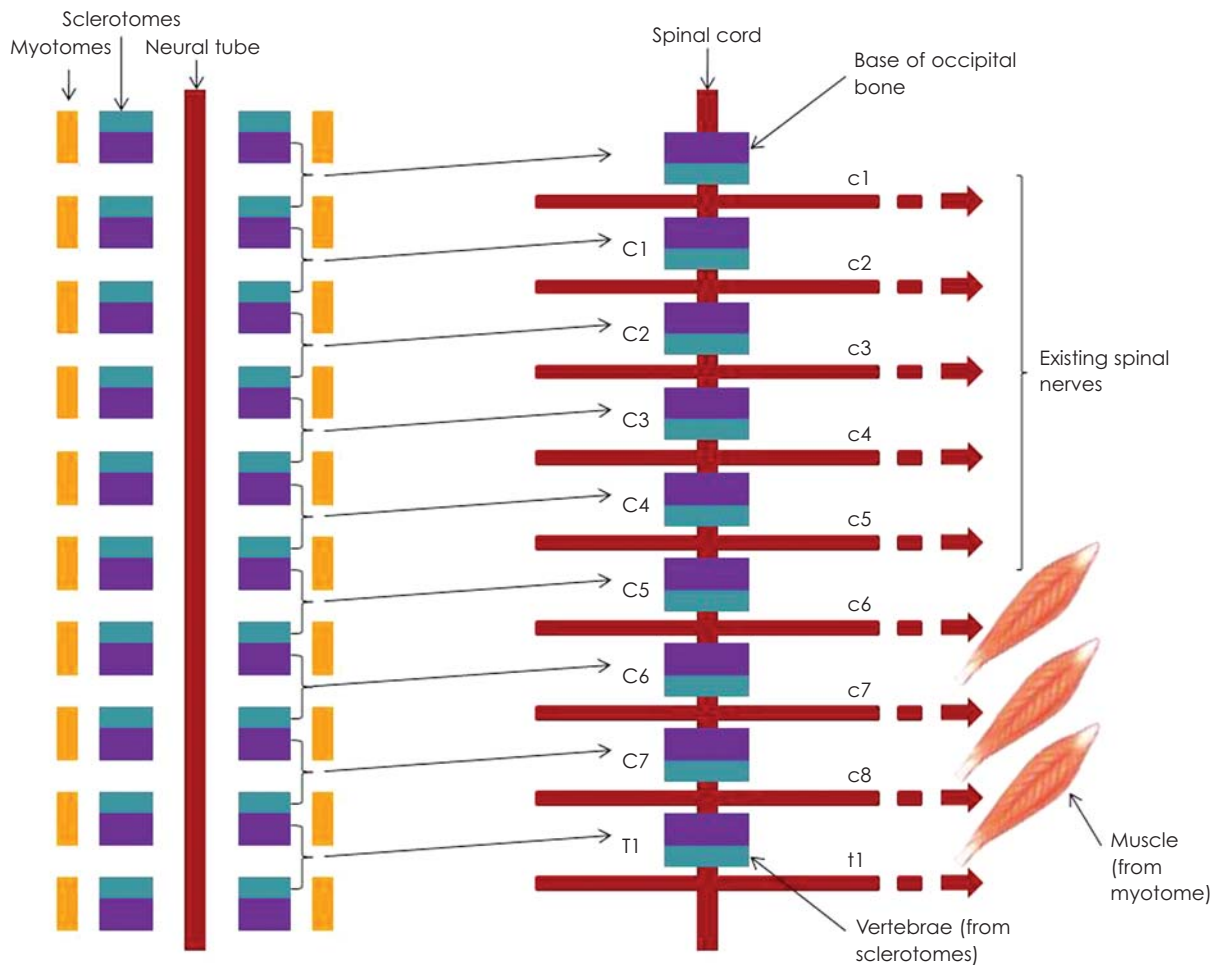


Fig 1: Diagrammatic representation of cervical vertebral embryological development after neurulation and somatogenesis. The more cranial somitomeres that contribute to the tissues of the head are not shown. Each vertebra is formed from 2 sequential sclerotomes (as indicated). Note that whilst there are 7 cervical vertebrae, there are 8 cervical spinal nerves.

nervous system (CNS) differentiation and results in abnormalities of the overlying structures including the vertebral arches, and in particular, the condition, spina bifida (Larsen 2001). In man, spina bifida of the lower lumbar and upper sacral region is quite common (Larsen 2001); spina bifida is also seen in horses (Hong *et al.* 1993; Rivas *et al.* 1996) where in one case it was associated with a cervical meningomyelocele (Rivas *et al.* 1996).

When somites or associated mesenchyme fail to separate, the resulting segmentation defect results in the formation of fused vertebrae, sometimes with loss of the corresponding associated growth plates (Kaplan *et al.* 2005). Such defects in vertebral formation alter growth patterns and may result in hemi- or wedge-shaped vertebrae (Kaplan *et al.* 2005) (**Fig 2**) similar to the Case Report of Crochik *et al.* (2009) in this issue. Various equine cases of malarticulation and subluxation of cervical vertebrae have been described (Crabill 1992; McClanahan *et al.* 1998) including 2 Clydesdale foals with multiple deformities of both cervical and thoracolumbar vertebrae (Boyd 1976). Congenital anomalies of thoracic, lumbar, sacral or coccygeal vertebrae may occur without detectable CNS disease but in, contrast, cervical vertebral

anomalies, such as vertebral duplications and omissions, are frequently associated with spinal ataxia (Mayhew 1999a,b, 2008). Occipitoatlantoaxial malformations (OAAM), although rare in domestic animals (Mayhew *et al.* 1978) are reported in several species (Wilson *et al.* 1985). In particular, several authors have documented equine cases in Arabians (Mayhew *et al.* 1978; Whitwell 1978) and other breeds (Wilson *et al.* 1985) causing variable signs of neck stiffness, neck malpositioning, pain or ataxia.

The case reported by Crochik *et al.* (2009) describes the simultaneous occurrence of a vertebral anomaly and a ventricular septal defect. In man, congenital abnormalities in other body systems that are associated with vertebral deformities are given the acronym VACTERL (Nolting *et al.* 1998; Jaskwich *et al.* 2000) where each letter represents the following defect - vertebral anomalies, imperforate anus or other anal abnormalities, cardiac abnormalities, transoesophageal malformations, renal dysplasia and limb malformations (Nolting *et al.* 1998; Kaplan *et al.* 2005). It remains unclear whether the 2 congenital defects identified in the foal in this issue were merely coincidental or were related.

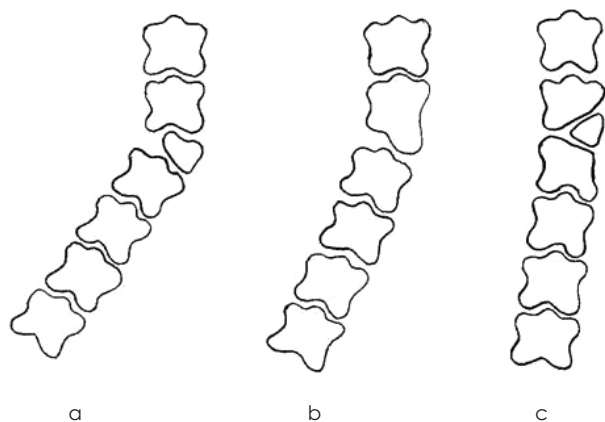


Fig 2: Representations of different vertebral segmentation defects: a) fully segmented hemivertebra; b) nonsegmented vertebrae; c) incarcerated (unlike in a, the cranial and caudal vertebrae are also malformed).

Aetiology

In man, defects of neural tube formation do not have a single genetic or teratogenic cause (Larsen 2001; Kaplan *et al.* 2005). Genetic, environmental, nutritional and toxicogenic causes are postulated (Larsen 2001). Certain drugs, in particular anticonvulsants, may increase risks of neural tube defects in man (Kaplan *et al.* 2005). Several studies have linked neural tube defects in man to folic acid deficiency in pregnant women (Larsen 2001; Kaplan *et al.* 2005), however, although a variety of haematological, renal and dermal congenital defects associated with a postulated *in utero* folate deficiency have been reported in foals, neural tube defects were not seen (Toribio *et al.* 1998).

The breed predilection suggests that OAAM has a genetic cause in Arabian horses (Mayhew *et al.* 1978; Wilson *et al.* 1985; Watson and Mayhew 1986), although to the authors' knowledge a hereditary link has not been proven. This defect, and those involved in the generation of malformed and fused vertebrae may potentially be associated with sporadic or inherited loss or gain of function mutations in Hox genes or other genes involved in somite segmentation and differentiation (see above). Finally, *in utero* and post natal trauma may result in vertebral malformations that are not of genetic origin but that may appear similar (Mayhew 2008).

Conclusions

Congenital vertebral anomalies in horses are rare but when defects are recognised, they help refresh our understanding of the complex but fascinating anatomy and embryology of the mammalian vertebrae and their associated structures. As in the Case Report in this issue (Crochik *et al.* 2009), astute clinical observation, combined with use of several ancillary diagnostic techniques enables an accurate, comprehensive diagnosis.

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