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Basic Science

Longitudinal extension of myelomalacia by intramedullary and subdural hemorrhage in a canine model of spinal cord injury

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Abstract

BACKGROUND CONTEXT: In canine intervertebral disc (IVD) extrusion, a spontaneous animal model of spinal cord injury, hemorrhage is a consistent finding. In rodent models, hemorrhage might be involved in secondary tissue destruction by biochemical mechanisms.

PURPOSE: This study aimed to investigate a causal association between the extents of intramedullary, subdural and epidural hemorrhage and the severity of spinal cord damage following IVD extrusion in dogs.

STUDY DESIGN/SETTING: A retrospective study using histologic spinal cord sections from 83 dogs euthanized following IVD extrusion was carried out.

METHODS: The degree of hemorrhage (intramedullary, subdural, epidural), the degree of spinal cord damage in the epicenter (white and gray matter), and the longitudinal extent of myelomalacia were graded. Associations between the extent of hemorrhage and the degree of spinal cord damage were evaluated statistically.

RESULTS: Intramedullary and subdural hemorrhages were significantly associated with the degree of white ($p<.001$/ $p=.004$) and gray (both $p<.001$) matter damage, and with the longitudinal extension of myelomalacia ($p<.001$/$p=.005$). Intriguingly, accumulation of hemorrhagic cord debris inside or dorsal to a distended and ruptured central canal in segments distant to the epicenter of the lesion was observed exhibiting a wave-like pattern on longitudinal assessment. The occurrence of this debris accumulation was associated with high degrees of tissue destruction (all $p<.001$).

CONCLUSIONS: Tissue liquefaction and increased intramedullary pressure associated with hemorrhage are involved in the progression of spinal cord destruction in a canine model of spinal cord injury and ascending or descending myelomalacia. Functional and dynamic studies are needed to investigate this concept further.

Keywords: Ascending; Central canal; Descending; Intervertebral disc extrusion; Intramedullary pressure; Spinal trauma

FDA device/drug status: Not applicable.

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Introduction

Canine intervertebral disc (IVD) extrusion, a spontaneous large animal model for acute spinal cord injury (SCI) [1], leads to damage of the spinal cord ranging from mild changes of gray and white matter to significant structural disruption and softening of the spinal cord, referred to as myelomalacia [2]. The pathophysiology of traumatic myelomalacia involves primary mechanical damage to the cord which is followed by secondary damage caused by decreased vascular perfusion, electrolyte shifts, and release of free radicals, cellular enzymes, and vasoactive substances [3–5]. As in experimental SCI, where the initial lesion expands transversally as well as longitudinally [6,7], in canine IVD extrusion, focal myelomalacia may ascend or descend, involving multiple additional spinal cord segments [8–11] or even the whole spinal cord. The pathophysiology of this phenomenon remains poorly understood.

Hemorrhage is a consistent finding in spontaneous [12,13] and experimental [6] SCI, and its underlying molecular mechanisms have been investigated such as expression of endothelin-1 [14], sulfonylurea receptor 1 [15], and the transient receptor potential cation channel subfamily M member 4 [15,16]. Although hemorrhage is a consequence of SCI, it may also be a contributing factor to further progression of traumatic myelomalacia. Experimental studies suggest that the mechanism of this contribution involves detrimental biochemical effects of blood products on spinal cord tissue [7].

The purpose of the present study was to investigate a causal association between intramedullary, subdural, or extradural hemorrhage and the severity of spinal cord damage in a canine model of thoracolumbar IVD-induced SCI by semiquantitative and qualitative histologic analysis.

Materials and methods

Histopathologic examination of the spinal cord was performed in dogs with thoracolumbar IVD extrusion, which were euthanized between January 1985 and December 2014 at the veterinary teaching hospital of the University of Bern. Inclusion criteria were well-documented records of the neurologic history and availability of histologic sections of the entire myelon.

Clinical data

Data collected from the medical records included breed, age, gender, duration of clinical signs, neurologic grade including clinical signs of ascending and/or descending myelomalacia, and treatment.

The duration of clinical signs was defined as the time from the first neurologic signs until euthanasia, and grouped in line with previous studies as acute (<24 hours before euthanasia), subacute (1–7 days), and chronic (>7 days) [17].

The neurologic status of the animals had been graded according to a standard protocol from grade I (only pain) to grade V (paraplegia without nociception) [2,18].

Histopathologic examination

The spinal cord was removed shortly after euthanasia in all dogs, and fixed in 10% formalin. For gross inspection, the fixed spinal cord was cross-sectioned at multiple levels; initially, segments flanking the IVD extrusion ("epicenter") identified by mechanical deformation and the presence of IVD material or hemorrhage adhering to the dura; afterward, the immediately adjacent segments on either side; subsequently, additional segments of the spinal cord exhibiting macroscopic changes; and finally, more remote segments proximal and distal with grossly intact tissue. Cross-sectioned blocks of these levels were embedded in paraffin wax, following a standard protocol, and sections of 5 μm were cut from all samples and stained with hematoxylin and eosin. The number of transverse sections cut and stained ranged from 10 to 30 and depended on the longitudinal extension of the lesion. For histopathologic grading, the section with the most severe histologic changes directly in the epicenter was used.

All slides were examined and graded independently by two experienced observers (DH, MV). If discordance occurred between the observers, slides were re-examined and consensus was agreed.

Semiquantitative assessment of spinal cord damage and hemorrhage

The severity of white and gray matter changes at the epicenter (site of the IVD extrusion) were graded from 0 to 5 and 0 to 2, respectively, on cross sections as previously described [2] and explained in Table 1.

Table 1
Grading of the spinal cord white and gray matter lesions in the epicenter of the entire cross section

Grade	White matter changes
0	No pathologic abnormalities
1	Small, focal, scattered areas of axonal and myelin sheet swelling; morphologically unremarkable tissue in >75% of the spinal cord cross-sectional area
2	Significant diffuse damage with normal gross architecture; morphologically unremarkable tissue in 50%–75% of the spinal cord cross-sectional area
3	Significant diffuse damage with normal gross architecture; morphologically unremarkable tissue in 25%–50% of the spinal cord cross-sectional area
4	Significant diffuse damage and loss of gross architecture in large areas; morphologically unremarkable tissue in 10%–25% of the spinal cord cross-sectional area
5	Complete dissolution of the spinal cord over the entire cross-sectional area with loss of gross architecture; morphologically unremarkable tissue in <10% of the spinal cord cross-sectional area
Grade	**Gray matter changes**
0	No pathologic abnormalities
1	75%–100% of the gray matter of the spinal cord cross-sectional area intact
2	<75% of the gray matter of the spinal cord cross-sectional area intact