This proposal evaluated key factors responsible for the development of central canal (CC) enlargement related to post-traumatic spinal cord injury (SCI). Our central hypothesis was that alterations in CSF flow, changes in the permeability of the CC wall, and rebalancing of compensatory mechanisms contribute to the developing of intracanalicular syringomyelia (SM).

Alterations in cervical CSF flow are reported to be associated with development of SM. Expansion of the central canal (CC) in SM following alterations in CSF flow are caused by a hydrostatic pressure differential between the subarachnoid space (SAS) and CC. Increased porosity of the ependymal lining of the CC permits an increase in the transependymal water transport and compartmentalization of the CC in which reabsorption of CSF from the CC into spinal cord tissue is impaired. In this study, CSF flow in the cervical SAS and CC was blocked by kaolin-induced inflammation, producing an increase in the size of the CC. Focal occlusion of the SAS (arachnoiditis) at C5 caused a 0-3X expansion of the CC cephalad to C5. Occlusion of the CC at a single site caused enlargement of the CC (> 5X normal), however, multifocal segmental occlusion of the CC caused SM (>10X normal). SM developed between sites of multifocal CC occlusion. Twelve weeks after multifocal segmental occlusion of the CC caused a 5X expansion in 87.5% of the animals, and in 62.5% of that number the CC were >10X normal. The largest syrinx was >50X that of normal controls.

Under normal physiological conditions the CC extends throughout the entire spinal cord. We suggest that the CC serves as a conduit allowing intracanalicular fluid accumulation to rebalance, thereby preventing an increase in CC pressure. If the water balancing mechanisms within an isolated segment of the CC is disturbed, SM may occur. Furthermore, concomitant with an expansion of the CC, upregulation in the water channel protein aquaporin4 (AQP4) in the region of the ependymal lining of the CC was noted. In the multifocal segmental CC...
occlusion group, AQP4 expression of the CC lining was significantly higher than following saline control injections at weeks 2, 4, 8 and 12. Upregulation of AQP4 correlated better with CC expansion than with the degree of kaolin-induced inflammation following SAS or CC occlusion. AQP4 expression was significantly higher in the expanded segment of the CC than of the non-expanded segment in an adjacent area. No alteration of AQP4 was noted in the CC lining following experimental arachnoiditis alone. AQP4 is not involved in water transmembrane (extracellular/intracellular) transportation alone, but this study suggests that AQP4 influences water movement across the lining of the CC. AQP4 upregulation and alteration of the water permeability in the CC facilitates a rapid expansion of the CC. Knowledge of the mechanics of CSF blockade and associated water channel modulation will assist our understanding of the pathogenesis of SM and lead to development of therapeutic strategies.

**SIGNIFICANCE:**
This study identified that the pathogenesis of intracanalicular SM is associated with certain patterns of CSF occlusion that suppressed compensational mechanisms of CSF rebalancing by the long intact CC. An isolated segment CC between two points of CC occlusion after SCI may be a mechanism causing PSM.

This study has also identified involvement of the water channel protein aquaporin4 (AQP4) in the formation of SM. This is the first report that AQP4 influences water accumulation in the CC. This indicates that water channels not only involve water transmembrane transport between extracellular and intracellular space, but also involve water transport among the different compartment within the spinal cord.

Understanding mechanism of development of SM may provide effective therapies to prevent the development of post-traumatic SM.

**SUMMARY:**
We have completed most of the initial proposal within the first year with a one year extension.

**PRESENTATION AND PUBLICATIONS:**
Publication ready for submission to Annals of Neurology

Pathogenesis of Central Canal Enlargement and AQP4 Expression following Experimentally Induced Cervical CSF Occlusion in Noncommunicating Intracanalicular Syringomyelia

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Poster at the 2006 Neuroscience Meeting (Atlanta, GA)

Poster in the 2007 Neuroscience Day (Louisville, KY). Awarded the first place prize.