Editorial

Posttraumatic syringomyelia

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Spinal cord injury (SCI) results in profound functional and sensory deficits, which negatively affect patient quality of life and increase the burden on the health care system. Unexpected patient deterioration associated with the development of a fluid-filled syrinx (or multiple separate syrinx cavities) can occur in up to 30% of cases from weeks to years after injury.2,12,21 This condition is known as posttraumatic syringomyelia (PTS) and is characterized by the gradual onset of neuropathic pain, weakness, sensory loss, autonomic dysfunction, and spasticity in cases otherwise thought to be stable. Although PTS will develop in a large population of patients with SCI (up to 30%), not all cases are immediately symptomatic, most likely as a result of smaller syringes.5,12,13,17,20 However, syrinx enlargement over time is common.4,16 Evidence suggests that PTS is increasingly recognized with the greater use of MR imaging in recent years.19 Clinical observations and animal models suggest that the development of PTS is associated with the formation of an initial lesion due to secondary pathological SCI mechanisms (excitotoxic cell death and apoptosis) as well as subarachnoid scarring and alteration of CSF fluid flow and pressure dynamics causing increased CSF flow into the spinal cord (Fig. 1).5,7,10,14

Posttraumatic syringomyelia is poorly understood, and treatment options are limited to detethering subarachnoid adhesions, shunting larger cysts, and releasing areas of compressive pathology. Unfortunately, even in the best hands, many patients fail to improve with surgical treatment and cysts can recur.3 Retrospective studies have determined that surgical procedures for managing once-established PTS are prone to failure on long-term follow-up with resulting recurrence of symptoms.10 A joint retrospective study from California and Germany showed that recurrence rates after shunting procedures were 92% and 100% in cases in which there was focal or extensive arachnoid scarring, respectively.10 Additionally, cases treated with surgical decompression and dissection of the scar were 83% and 17% effective for focal or extensive arachnoid scarring, respectively. Other studies have reported higher success rates for shunting (80%) but have failed to describe the extent of arachnoid scarring.8 Since PTS can take a long time to develop, it is probable that follow-up times of postsurgical intervention for PTS in retrospective analyses (within 2–5 years) may not accurately capture the extent of recurrence. Although it is admittedly difficult to follow up patients for decades postsurgery, studies that do so may be warranted to accurately assess current treatment efficacy.

The most promising avenues for developing treatment strategies for PTS involve preventing cyst recurrence following surgical intervention and limiting the development of syringes in the first place. Reducing the recurrence of syringes postsurgery may involve the application of therapeutics to prevent arachnoid adhesions and scar tissue from reforming. Preventing the initial development of syringes is a more difficult task given the fact that syrinx development generally occurs prior to the onset of symptoms and subsequent diagnosis. The identification of a “presyrinx state” that can be detected with MR imaging prior to syrinx formation is a promising discovery.9 It has been shown that complete injuries are more prone to the development of PTS,1,8,11,22 suggesting that patients with these injuries could be more closely monitored to identify any visible changes associated with a presyrinx state. Therapeutic intervention could then be started before or in the early stages of asymptomatic syrinx development. Alternatively, perhaps altering the subacute postinjury parenchymal environment with therapeutics or stem cells might prevent the formation of syringes regardless of the presence of arachnoid scarring.

Of the many avenues of therapy for SCI and PTS, harnessing endogenous precursor cells to alter injury progression and promote regeneration is an attractive approach. It is well established that NG2+ (a chondroitin sulfate proteoglycan expressed on the cell surface of progenitor cells following injury) precursors are the major proliferating progenitor cells following SCI and that temporal and spatial cues can alter their differentiation.15 As the pathophysiology of PTS differs from that of SCI, the characterization of endogenous precursors in animal models of PTS is essential.

In the following article, Tu et al.18 characterize the proliferation, distribution, and differentiation of endogenous progenitor cells in a rat model of PTS involving the intraparenchymal injection of the excitotoxin quisqualic acid and the subarachnoid injection of kaolin to induce scarring. They report that Ki 67+ (a protein present in all...
active phases of the cell cycle) proliferating cells were present in large numbers within 2 weeks following injury and remained for up to 8 weeks, mostly in the gray matter along the border of the cysts. Furthermore, they indicate that a proportion of Ki 67+ cells expressed NG2, nestin (stem cell intermediate filament protein), glial fibrillary acidic protein (GFAP, an astrocytes marker), or ED1 (a marker of macrophages/microglia). None of the Ki 67+ cells colocalized with neuronal or oligodendroglial markers of macrophages/microglia. None of the Ki 67+ cells expressed NG2, nestin and remained for up to 8 weeks, mostly in the gray matter present in large numbers within 2 weeks following injury.

Furthermore, they indicate that a proportion of Ki 67+ cells expressed NG2, nestin (stem cell intermediate filament protein), glial fibrillary acidic protein ([GFAP], an astrocytes marker), or ED1 (a marker of macrophages/microglia). None of the Ki 67+ cells colocalized with neuronal or oligodendroglial markers. While there is some confusion as to which population of Ki 67+ cells are actual progenitors and which are adult cells that undergo proliferation because of postinjury cues (as is most likely the case for GFAP+ astrocytes and ED1+ microglia), they have taken a promising initial step in the characterization of endogenous progenitors for a typical complication of SCI.

Elucidating the pathophysiology of PTS is essential in the development of more effective therapies. Posttraumatic syringomyelia is a common complication that is becoming more prevalent, which certainly warrants more attention from the research community. Manipulating endogenous precursor cells to aid in repair and regeneration in models of PTS is a promising preclinical approach. Before it is realized, however, initial steps need to be taken to characterize the endogenous precursor cell population both spatially and temporally following injury. We commend Tu and colleagues for their initial foray into characterizing the progenitor cell population in the development of therapies that harness the regenerative capability of endogenous precursors. Future studies might focus on the local environment or chemical cues that determine the fate or function of these cells.

References


Fig. 1. Illustrations depicting mechanisms underlying the development of PTS. Left: Normal CSF flow in the subarachnoid space (SAS). In the normal spinal cord, CSF flows unobstructed in the SAS and is thought to flow in and out of the spinal cord parenchyma to the central canal and back to the SAS in a balanced fashion. Right: Altered CSF flow due to subarachnoid scarring contributes to the development of syrinxes. Subarachnoid scarring alters fluid flow and pressure dynamics, resulting in obstruction of CSF flow in the SAS and increased CSF inflow to the spinal cord. The presence of an initial cyst or cavity might be a prerequisite for syrinx formation. PVS = perivascular space.
The editorial by Fehlings and Austin highlights the unresolved clinical problem of PTS. This poorly understood condition has limited therapeutic options, none of which has been shown to be effective over the long term. Improvements in treatment are unlikely unless we develop a better understanding of the mechanisms underlying PTS. I agree that there are probably separate mechanisms for initial cyst formation and subsequent syrinx development. Initial traumatic cyst formation is likely to result from direct injury effects including hemorrhage, excitotoxic injury, and ischemia, which may point to avenues for PTS prevention. For example, even if acute therapies aimed at limiting the effects of SCI do not prevent early neurological deficits, they could be beneficial in the long term if they minimize early cyst formation and prevent PTS.

After an initial cyst is formed, hydrodynamic factors, as indicated by Fehlings and Austin, are likely to play a role in PTS development. However, additional factors in the surrounding tissue may play a role. For example, once a cyst starts to expand in the cord parenchyma, it can damage the surrounding blood-spinal barrier and allow additional fluid from the vasculature to enter the cyst. Such tissue damage can also alter fluid clearance mechanisms, including aquaporin expression and function. In addition to fluid inflow and outflow, tissue properties are also likely to be important in PTS development. The glial response around PTS cavities may be beneficial in restricting cyst expansion or harmful in causing further damage to neurons and white matter tracts.

Fehlings and Austin have emphasized the need for basic science research into the problem of PTS. There are many questions that basic science research can address. What are the fluid inflow and outflow pathways and forces driving flow? Is the glial reaction beneficial or harmful? Is demyelination a dominant process that would be amenable to oligodendrocyte therapy? Would repair of the blood-spinal barrier limit syrinx expansion? Would altering aquaporin function reduce syrinx formation?

A critical aspect of such research is the selection of an appropriate animal model; it should be recognized that what is being studied is the pathophysiology of an expanding spinal cord cyst rather than the effects of spinal cord injury per se. The ideal model would produce minimal initial cord damage, with the expanding cyst producing the majority of cord damage. My group has used the excitotoxic/arachnoiditis model because of its reliability in producing expanding cystic lesions, although we recognize that there may be differences between this model and the human condition. We are currently working on an impact model (with arachnoiditis) in an effort to more closely reproduce the human condition, although a high rate of syrinx formation will be necessary if it is to be of practical use. In addition, large animal models may be necessary to study fluid outflow, pressure changes, and the effects of treatments.

Fehlings and Austin's recognition of our initial work on cellular reactions around PTS cavities is appreciated. Basic science research in this and other areas of PTS pathophysiology may lead to improved cellular, biochemical, and hydrodynamic therapies to prevent or treat this seemingly simple but enigmatic condition. The editorial by Fehlings and Austin will, we hope, spur on such research.

References

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Please include this information when citing this paper: published online February 25, 2011; DOI: 10.3171/2010.4.SPINE1047.