Pain and syringomyelia: a review

D. ROXANNE TODOR, M.D., HARRISON T. M. MU, M.D., AND THOMAS H. MILHORAT, M.D.

Department of Neurosurgery, State University of New York, Health Science Center at Brooklyn, Brooklyn, New York

The pathophysiological basis of chronic pain syndromes remains poorly defined. Central and dysesthetic pain are probably the most disabling of sensory disturbances associated with syringomyelia, and, unfortunately, effective treatment remains elusive. In this paper, the authors review their institutional experience with both clinical and laboratory studies of patients with syringomyelia, and they review the relevant literature. To date, there is no consensus as to the best treatment for central cord pain syndromes, although there are many promising areas of current research involving the use of neurochemicals in the spinal cord.

KEY WORDS  •  syringomyelia  •  substance P  •  spinal cord  •  dysesthetic pain  •  neuropeptide

“Illness is the doctor to whom we pay most heed; to kindness, to knowledge, we make promise only; pain we obey.” Marcel Proust, Remembrance of Things Past, 1922.

“Evil being the root of mystery, pain is the root of knowledge.” Simone Weil, New York Notebook, 1942.

Syringomyelia is a chronic disease characterized by the presence of spinal cord cavitation. It has multiple causes and several classifications but is most commonly seen in association with Chiari I malformation. Pain is a prominent feature in 50 to 90% of adult patients with syringomyelia.10,17,34,36 Patients typically present with complaints of radicular pain (often in a capelike distribution), interscapular pain, and/or central cord pain. In addition to the more common clinical pain syndromes, approximately 40% of patients with syringomyelia experience significant dysesthetic pain,24 which is variously described as a burning sensation, pins and needles, or stretching of the skin (Table 1). Other common characteristics include dermatomal patterns of hypersensitivity, as well as trophic changes such as hyperhidrosis, glossy skin, coldness, and paleness. In patients afflicted with this type of pain, it is often an overwhelming and pervasive symptom that overshadows other complaints. A similar type of pain has also been reported in other spinal cord pathological conditions such as traumatic injury,6 intramedullary tumors,8,23 and multiple sclerosis.5

In animal models and clinical studies of spinal cord pain, the investigators have focused on traumatic SCI. There are few papers in which the authors specifically discuss syringomyelia and its relationship to the various pain syndromes. There have been, however, numerous anatomical studies of the normal spinal cord pain pathways in both human and animal models. Yezierski37 has comprehensively reviewed the ischemic, mechanical, and excitotoxic models of SCI, as well as three mechanisms of post-SCI pain. In patients with syringomyelia, the distribution of symptoms imperfectly correlates with the anatomical location of the spinal cavitation. In our experience syrinx cavities that extend paracentrally have rarely been found.

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td>Incidence of pain in 137 syringomyelia patients</td>
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</table>

<table>
<thead>
<tr>
<th>Pain Type</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>no pain</td>
<td>29</td>
</tr>
<tr>
<td>radicular pain</td>
<td>36</td>
</tr>
<tr>
<td>headache</td>
<td>25</td>
</tr>
<tr>
<td>suboccipital or neck pain</td>
<td>67</td>
</tr>
<tr>
<td>back pain</td>
<td>17</td>
</tr>
<tr>
<td>trigeminal pain</td>
<td>9</td>
</tr>
<tr>
<td>dysesthesias</td>
<td>51</td>
</tr>
<tr>
<td>burning pain</td>
<td>43</td>
</tr>
<tr>
<td>hyperesthesia</td>
<td>41</td>
</tr>
<tr>
<td>pins &amp; needles</td>
<td>37</td>
</tr>
<tr>
<td>stretching or pressure of skin</td>
<td>17</td>
</tr>
<tr>
<td>trophic changes</td>
<td>15</td>
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</tbody>
</table>

Abbreviations used in this paper: DH = dorsal horn; MR = magnetic resonance; NK = neurokinin; SCI = spinal cord injury.
to be asymptomatic, and most have been characterized by segmental signs that could be related to the level and side of the paracentral extension.25,26

Current research efforts are now predominantly focused on the role of neurochemicals and their receptor molecules. There is an extensive list of compounds being evaluated for their putative nociceptive function. The most widely investigated pain-related compound is substance P, which has been studied by our group in autopsy specimens. In this paper, we summarize our findings with regard to pain and syringomyelia as well as review the current literature.

SUBSTANCE P AND SYRINGOMYELIA

Substance P is an undecapeptide included in the tachykinin family of peptides, which also includes NK A and NK B.19 The tachykinins act preferentially on the three major neurokinin receptors of NK1, NK2 and NK3. Substance P has been thoroughly localized in the human brain and spinal cord.4,18,30 The distribution, physiological effects, and alterations in pain states have led to its putative nociceptive modulatory role.

In the normal spinal cord, animal and human studies have localized this neuropeptide to the sensory DH (Rexed laminae 1, 2, 3, and 5), central canal region, and the intermediolateral gray zone.3,7,11,16,22,33 It has also been found in the unmyelinated afferent C-fibers, which are thought to be responsible for slow pain transmission. Three sources have been proposed for spinal substance P: 1) synthesis has been demonstrated in dorsal root ganglion neurons that then project fibers to the sensory spinal gray regions; 2) dorsal horn neurons have also been shown to have substance P immunoreactivity, which suggests local synthesis; and 3) substance P–positive raphe nuclei have been shown to project to the spinal DH region, particularly Rexed laminae 1 and 2. These three sources all have implications in the proposed mechanisms of spinal pain.20

Electrical stimulation has been shown to cause DH neurons to release this tachykinin.80 Iontophoretic application of substance P has been found to cause excitation of neurons that are known to respond to noxious stimuli.15 Substance P was also shown to potentiate the response of nociceptive neurons to painful cutaneous stimuli. This effect, in part, may be related to upregulation of the NK1 receptor.9 Results obtained after intrathecal injections in animal models have been interpreted as indicating either a decrease in pain threshold or increase in pain perception.16

The results of neuroanatomical studies in pathological states have also supported the role of substance P in pain modulation. In the cat spinal cord transection model, immunohistochemical analysis has demonstrated an accumulation of substance P below the level of the lesion, consistent with an afferent rostral flow.29 Quantitative autoradiography performed in the rat transection model revealed that substance P receptors were significantly increased below the level of the lesion, a finding consistent with upregulation of these receptors.35

Substance P has been found to be quite stable through tissue processing and postmortem intervals.2,13,14,29 Several human autopsy studies have demonstrated changes in the distribution of substance P with various spinal cord lesions. Pearson et al.31 have studied five patients with Riley–Day syndrome, a familial dysautonomia characterized by decreased pain sensation. Using immunohistochemical staining, they found a significant decrease in primary substance P axons terminating in the substantia gelatinosa. Interestingly, in patients with amyotrophic lateral sclerosis, a condition without altered sensory findings, Gillberg, et al.12 found no change in substance P–like immunoreactivity in the spinal cord.

In our laboratory, the spinal cords of 10 patients with syringomyelia and of 10 age-matched controls were studied for the distribution of substance P.27 Paraffin blocks obtained from seven levels were studied: medulla oblongata, C-2, C-5, T-2, T-5, T-8, and the conus medullaris region. The Sternberger peroxidase–antiperoxidase immunohistochemical staining technique was used.

Above the level of the syrinx, a marked reduction in the substance P staining was observed (Fig.1). At the level of the lesion, a marked reduction or absence of immunoreactivity was noted. In cases in which the syrinx exhibited a
lateral eccentric extension, this finding was only seen ipsilateral to and at the level of the cavity. Contralateral to the extension, normal staining patterns were demonstrated (Fig. 2). Substance P staining was markedly increased below the level of the lesion (Fig. 3). There was only one patient with an incidental syrinx in whom a staining pattern similar to that in the control spinal cords was demonstrated. This syrinx cavity was noted to occupy only 25 to 30% of the transverse diameter of the spinal cord. Our findings are similar to those demonstrated in the animal spinal cord transection models.28,35 Unfortunately, relevant clinical data were not available for these patients, and we were unable to correlate the degree of staining with antecedent pain symptoms.

SYMPATHETIC SYSTEM AND DYSESTHETIC PAIN

Dysesthetic pain is found in slightly less than half of the
patients with syringomyelia. Similar pain syndromes have been described in patients with SCI. It is a serious phenomenon that can disable these patients, and, furthermore, it responds unpredictably and often poorly to currently available treatments.

Our group has studied 137 patients with syringomyelia of various causes and found 51 patients who experienced segmental dysesthesias. Operative treatment for the syrinx was performed in 37 patients, and MR imaging demonstrated collapse or disappearance of the spinal cavity in 32 patients and a slight reduction in five patients over a follow-up period of up to 74 months. Relief or resolution of dysesthetic pain was accomplished in 22 of the 37 patients. However, in the remaining 15 patients, the dysesthesias either persisted or were intensified. No correlation was found among the causative factors, operative factors, or rapidity of syrinx collapse. Medical therapy in which conventional analgesics and neuropathic pain medications were used (Neurontin, Dilantin, Tegretol, Benda- dryl, Valium, Nembutal, Seconal, Motrin, Naprosyn, Clin- oril, and baclofen) provided marginal or no relief. In most patients spontaneous gradual improvement occurred by 1-year follow up, but all continued to complain of unpleasant sensations typical of the initial dysesthetic pain.

Careful review of the signs and symptoms revealed a close resemblance to the classic description of causalgia, which is often associated with peripheral nerve injuries, characterized by exquisite sensitivity to touch, burning and paresthetic qualities, and autonomic and trophic changes. These were often the signs and symptoms described by patients with syringomyelia who suffered dysesthetic pain. Sympathetic blocks have been quite effective in treating causalgia-like pain. Five of our patients underwent sympatholytic treatment (Table 2), and in three significant relief from their dysesthetic pain was obtained. Figure 4 displays MR images of the spinal cord obtained in a 43-year-old woman with posttraumatic syringomyelia and dysesthetic pain. Preoperatively, she experienced weakness of the left arm and leg. Postoperatively her neurological deficit improved, and follow-up MR imaging revealed a well-decompressed syrinx cavity. Postoperatively, the patient experienced a significant worsening of her dysesthetic pain, which was then successfully treated with a stellate ganglion block. Subsequently, she underwent a permanent operative sympathectomy that has resulted in long-term relief of her symptoms. At a five-year follow up, she continues to be pain free.

The similarity of syringomyelia-related dysesthetic pain with causalgia, in addition to the preliminary results obtained using sympatholytic treatment, raises the possibility of sympathetically mediated pain. It is of interest to note that substance P has not only been localized to the intermediolateral cell columns in the spinal cord, but Koni-ishi, et al., have demonstrated substance P-mediated transmission in the sympathetic ganglia.

### SUMMARY

Pain is a disabling and pervasive problem for patients with syringomyelia. It is present in various forms, and often times medical or operative therapies are ineffective. An understanding of the causes requires thorough knowledge of the anatomical, physiological, and neurochemical factors.

Yezierski has comprehensively reviewed the physiological basis of pain in patients with SCI. There are three main groups of theories that support the existence of centrally mediated pain. The first is the loss of a sensory balance. Beric, et al., have suggested that post-SCI dysesthetic pain may be secondary to a disjunction between the anterolateral pain pathways and the dorsal column sensory pathways. The second and third theories relate to loss of spinal cord inhibitions and the release of spinal cord nociceptive neuronal firing.

In addition to these physiological theories, neurochemicals are also thought to be involved in spinal cord pain pathways. Furst has recently reviewed the current literature. Our group has found the presence of substance P changes in patients with syringomyelia. It is likely that the

### TABLE 2

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Cause of Syringomyelia</th>
<th>Sympathetic Block</th>
<th>Pain-Related Outcome</th>
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<tbody>
<tr>
<td>1</td>
<td>43, F</td>
<td>posttraumatic</td>
<td>stellate</td>
<td>significant relief</td>
</tr>
<tr>
<td>2</td>
<td>38, M</td>
<td>posttraumatic</td>
<td>stellate</td>
<td>significant relief</td>
</tr>
<tr>
<td>3</td>
<td>38, M</td>
<td>arachnoiditis</td>
<td>lumbar</td>
<td>significant relief</td>
</tr>
<tr>
<td>4</td>
<td>50, M</td>
<td>Chiari I malformation</td>
<td>stellate</td>
<td>mild relief</td>
</tr>
<tr>
<td>5</td>
<td>38, M</td>
<td>posttraumatic</td>
<td>stellate</td>
<td>significant relief</td>
</tr>
<tr>
<td>6</td>
<td>62, M</td>
<td>posttraumatic</td>
<td>stellate</td>
<td>no relief</td>
</tr>
</tbody>
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D. R. Todor, H. T. M. Mu, and T. H. Milhorat

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**Fig. 4.** Magnetic resonance images of the spinal cord obtained in a 43-year-old woman with posttraumatic syringomyelia and dysesthetic pain. **Upper Left** and **Right:** Preoperative images demonstrating an eccentric cavity that occupies the left dorsolateral quadrant of the spinal cord from C4 to C7. **Lower Left** and **Right:** Postoperative images obtained at 16 months revealing a well-positioned syringocisternostomy shunt and no evidence of a syrinx. Postoperatively the patient complained of dysesthetic pain that was greatly intensified after surgery despite resolution of neurological deficits.
Pain syndromes in syringomyelia are highly varied. Not surprisingly, neurochemical-related investigation in patients with syringomyelia has been sparse. Many of the current studies have focused on measuring the various neurotransmitter concentrations in the cerebrospinal fluid. In animal models, this work has also been lacking. Substance P is only one of many putative pain modulators known to exist in the spinal cord. To understand pain in syringomyelia fully, additional study of the effects on these substances needs to be conducted. Because of the discrete localization of the cavitary lesions, studies of the neurochemical changes in syringomyelia may provide more accurate neuroanatomical correlation and further insight into central spinal pain. Ultimately, we plan on developing standard treatment paradigms for those patients with persistent pain syndromes. Until we have completed the review of our patient follow-up data, it would be premature to advocate sympathectomy as a first-line treatment. Future research clarifying the mechanism of pain in relation to the present classification of syringomyelia will allow us to explore new avenues of pain management.

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*Address reprint requests to:* D. Roxanne Todor, M.D., Department of Neurosurgery, 450 Clarkson Avenue-Box 1189, Brooklyn, New York 11203. email: todorr@pol.net.