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Topical review

Venipuncture-induced neuropathic pain: the clinical syndrome, with comparisons to experimental nerve injury models

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1. Introduction

Venipuncture, the most frequently performed invasive medical procedure (Horowitz, 1994), is usually benign, producing only transitory mild discomfort. However, several case series (Berry and Wallis, 1977; Newman and Waxman, 1996; Horowitz, 1994, 2000; Newman, 2001) and individual patient reports (see Horowitz, 1994) document nerve injuries consequent to the procedure. While such injuries are reportedly rare, 1:21 000–26 700 (Berry and Wallis, 1977; Newman and Waxman, 1996) or 1:6250–6928 (Newman, 2001), some can be severe with permanent residua, the most disturbing being chronic neuropathic pain – the Complex Regional Pain Syndrome Type 2 (CRPS-II), or causalgia. It is defined (Merskey and Bogduk, 1994), as a persistent shooting, electrical, burning pain in the distribution of the affected nerve with frequent spread to adjoining areas, often in association with autonomic and motor dysfunctions.

Recent articles in this journal (Eliav et al., 1999; Pitcher et al., 1999; Li et al., 2000; Eschenfelder et al., 2000; Decosterd and Woolf, 2000; Han et al., 2000; Liu et al., 2000a,b,c; Habler et al., 2000; Lindenlaub and Sommer, 2000), employing various peripheral nerve injury models and methodologies in the rat, have studied the pathophysiology of injury-induced neuropathic pain and associated phenomena (mechanosensitivity, allodynia, hyperalgesia). While sites and types of experimental injury differ, each study links the pain to ectopic discharges in primary afferent neurons and 'central sensitization', i.e. increased excitability of spinal cord dorsal horn neurons – changes in receptive field properties, decreased thresholds and increased responsiveness to peripheral input (Woolf, 1996). Two sources of discharges are currently favored (Gold, 2000): (1) injured afferent fibers at the lesion site and/or their dorsal root ganglia (DRG) soma (Devor and Seltzer, 1999; Han et al., 2000; Liu et al., 2000a,c); or (2) uninjured afferent fibers consequent to peripheral interactions with injured afferents undergoing Wallerian degeneration (Li et al., 2000; Eschenfelder et al., 2000). In either case, post-injury, spontaneous pain appears due to spontaneous electrogenesis, and pain with movement or palpation secondary to mechanosensitivity at these sites. Innocuous or noxious stimulation in the dermatomal distribution of surviving uninjured Aβ low threshold afferent mechanoreceptors trigger heightened sensitivity (allodynia or hyperalgesia, respectively) (Woolf, 1996), due to spinal amplification. This central sensitization may be initiated and maintained by peripheral impulse generation ('ectopia') from injured fibers (Devor and Seltzer, 1999; Tal et al, 1999; Liu et al., 2000b), or, conversely, a loss of input to the dorsal horn (deafferentation hypersensitivity) (Eschenfelder et al., 2000).

Venipuncture-induced CRPS-II/causalgia is, perhaps, the most paradigmatic human neuropathic pain that can follow acute nerve trauma. It has many similarities to the experimental situation: the procedure – venipuncture – and instrument involved – hypodermic needle – are always identical; the exact timing of injury is known; and the same cutaneous sensory nerves are always involved, i.e. medial or lateral antebrachial cutaneous nerves in the antecubital fossa, superficial radial nerve at the wrist, or dorsal sensory nerves of the hand. As our current concepts of the pathophysiology and treatment of human neuropathic pain are inadequate, it is useful to relate the hypotheses discussed to the clinical venipuncture syndrome, specifically the onset and duration of symptoms and signs, type of nerve fibers affected, and sympathetic nervous system effects.

2. Clinical observations

In this series, accrued over 20 years (Horowitz, 1994, 2000), 30 patients, 23 female (77%) and seven male

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(23%), ages 23–71 years, underwent neurologic examinations by the author 9 months to 7 years after venipuncture injury to one of the aforementioned upper extremity cutaneous nerves. Seven (23%) were over 50 years old at onset. By description, a 'burning', 'lancinating', 'shooting', 'electrical' pain began with movement of the venipuncture needle in situ in 27 patients (90%), or developed within 18 h in three (10%). Twenty-four patients (80%) described traumatic venipunctures with multiple attempts and/or subsequent hematoma formation (18 patients, 60%). The immediacy of pain with needle movement implicates direct needle-induced nerve trauma, rather than neurotoxic effects of blood products or inflammatory mediators. Each patient sought medical attention within a few days and medical records, neurologic consultations, diagnostic work-ups and therapeutic responses support the diagnosis of CRPS-II/causalgia.

All patients described the pain as changing over time. Initially spontaneous, constant and intense, the 'burning' 'electrical' qualities gradually metamorphosed into 'dull', 'boring', 'aching' or 'tingling' chronicity. Thereafter, the former characteristics recurred intermittently, superimposed on the background chronic pain, sometimes spontaneously but more often after mechanical stimulation such as inadvertent touching or movement of the limb. In severe cases this transformation began after 3–6 months; in milder cases it started after several weeks. Immobilizing the extremity close to the torso with shoulder adduction and flexion at the elbow, wrist and fingers was the typical posture adopted to limit the frequency, intensity and duration of exacerbations, and for protection.

Stimulus-evoked discomfort, allodynia and hyperalgesia, occurred in 25 patients (83%); most often concurrent with the pain. For example, a woman who experienced a 'burning' 'electrical' pain during attempts at catheter insertion in her right antecubital fossa for intravenous sedation during a dental procedure, could not be touched in the entire right upper extremity when assisted from the dental chair a few minutes later. Allodynia or hyperalgesia never occurred in five patients (17%), despite persistent pain and sensory deficits to pin and touch.

During 1.5–13 year follow-up periods, pain, allodynia and hyperalgesia resolved in three patients (10%) within weeks. In two others, one without allodynia and hyperalgesia, pain ceased in six (with celecoxib) and 18 months (with gabapentin and nine stellate ganglion blocks). All five continued to exhibit subtle sensory deficits in affected nerve distributions. In the patient seen at 9 months, burning pain and aching, without allodynia and hyperalgesia, occurred only with physical activity and in certain positions. In 24 patients (80%), pain (with allodynia and hyperalgesia in 21) persisted for years; in eight confined to injured nerve distributions without motor or autonomic changes.

In 16 patients (53%) pain and sensory phenomena worsened over time and spread to contiguous anatomic areas. Involvement of non-contiguous areas, e.g. another extremity, occurred in seven (23%). Sometimes (six patients) new regions became more severely affected than primary areas. For instance, the aforementioned patient suffered injury to the right lateral antebrachial cutaneous nerve, but demonstrated more prominent sensory symptoms and signs in the medial antebrachial cutaneous and ulnar nerve distributions. In 12 patients (40% of total) autonomic changes, e.g. sweating abnormalities, loss of skin turgor, skin pallor, hair loss, vasomotor instability, and/or temperature alterations occurred in affected limbs. Motor abnormalities occurred in all 16 patients whose condition worsened. Most frequent were limb contractures associated with disuse and protection. Five (17%) demonstrated dystonic posturing in the affected limb and two (7%) elsewhere.

Therapies included analgesic, antinflammatory, tricyclic antidepressant, and anticonvulsant medications, and transcutaneous electrical nerve stimulation, nerve blocks, stellate ganglion blockades (at least 30 in several patients), and sympathectomy. Excluding the five patients in whom the pain resolved completely, only transitory or modest benefits occurred in the 25 others. Stellate ganglion blockade was not accompanied by sustained improvement in 13 of 14 patients (93%), nor was sympathectomy in three.

Three other series (Berry and Wallis, 1977; Newman and Waxman, 1996; Newman, 2001) reported venipuncture-induced nerve injuries qualitatively different than those described herein; the nerve injuries resolved with no or minimal deficits. Only one patient developed the permanent pain and dysfunction seen in these 24 most severely affected patients. It is presumed that there was selection bias; all patients were referred to me because of my interests in nerve injuries.

These patients raise many unanswerable questions regarding incidence, predisposition and causation of disabling nerve injuries, including why so few cases are reported. Without a denominator it is impossible to determine incidence with respect to these 30 patients; the one estimate available indicates one severe injury in 1.5 million blood donations (Newman, 2001). Nerve injuries occur more commonly in females – 77% in this series and 65 and 82% in Newman's two reports (Newman and Waxman, 1996; Newman, 2001). Younger patients predominate here and in Newman and Waxman's series (1996). As venipuncture is so common and the anatomy of upper extremity cutaneous nerves and superficial veins appears to favor needle-nerve contact far more frequently than nerve injuries are reported (Horowitz, 2000), additional factors must be relevant.

3. Comparisons between the clinical syndrome and experimental models

For ectopic afferent discharges to be the credible pathophysiologic substrate for the venipuncture pain syndrome their characteristics must relate to the particular clinical

features of this pain: its immediate onset, endurance as a stimulus-independent symptom, continuation as stimulus-evoked pain and discomfort (allodynia and hyperalgesia) for years, even after spontaneous pain has mitigated, frequent spread to unaffected areas, and refractoriness to therapy – including sympathetic blockade and sympathectomy.

However, extrapolations from animals to humans are limited by differences between experimental and clinical nerve injuries. These include: (1) use of general anesthesia in animals; (2) the type of nerve damage that occurs during venipuncture is unknown; (3) neuromas commonly develop after experimental nerve transection; their formation following needle injury is unknown; (4) animals exhibit behavior that is interpreted as indicating pain, but aversive and protective movements representing allodynia and hyperalgesia are not evidence of pain per se; (5) 'neuropathic pain' is a constellation of symptoms and signs, reflecting multiple pathophysiologic mechanisms. Clinically, different types of hyperalgesia can coexist simultaneously and single sensory abnormalities may not be associated with multimodal sensory disturbances (Koltzenburg et al., 1994). Therefore, equating animal behavioral responses and specific neurophysiologic phenomena to the human syndrome may be simplistic. Given these caveats, the findings in experimental studies that may be pertinent to venipuncture-induced neuropathic pain can be examined.

There are several possible mechanisms for the immediate onset of pain:

1. Long lasting ectopic discharges may develop immediately post-axotomy. While Wall et al. (1974); Devor and Bernstein (1982), and Devor (1995) assumed that, apart from short-lived injury discharges, axons are otherwise silent, and Tal et al. (1999); Liu et al. (2000c), and Liu et al. (2000a) found little spontaneous activity in the early hours after surgery, other studies reported discharges immediately upon sensory nerve sectioning, some discharges continuing for 1–2 days (Baik-Han et al., 1990; Chung et al., 1992; Blenk et al., 1996). Li et al. (2000) hypothesized that hyperalgesia may consist of two parts: an early stage resulting from an injury barrage, and a later stage associated with peripheral nerve Wallerian degeneration. Wall et al. (1974) sought to explain Adrian's (1930) findings of prolonged injury discharges following nerve injury; they speculated that in his nerve preparations "the small side branches of the damaged nerves were left intact. The normal endings of these side branches would respond normally to the damage and blood seepage from the site of nerve section" (p. 587). Such may be the case in venipuncture-nerve injuries. Central sensitization could be initiated and maintained by ectopic discharges.
2. Dorsal horn deafferentation hypersensitivity may result from loss of normal low threshold mechanoreceptor input (Eschenfelder et al., 2000). Sudden deprivation of inhibitory peripheral activity could induce central sensitization and be instantaneously perceived as pain and/or allodynia during tactile stimulation of affected segments (also Li et al., 2000). This proposed loss of input to the dorsal horn is opposite to the peripheral ectopia of the injured afferent hypothesis.
3. A biochemical signal arising from the nerve stump in the initial hours post-injury may trigger abnormal behavior in animals (Liu et al., 2000c; Eschenfelder et al., 2000). This signal would interact with normal DRG signals to the dorsal horn in an undetermined manner.
4. Pain-producing mechanisms may vary over time; Lindenlaub and Sommer (2000) and others, assume at least two different mechanisms for neuropathic pain: an immediate post-injury discharge which induces central sensitization, and later neuroma development with persistent ectopia and hypersensitivity. Also, there may be different mechanisms for spontaneous pain versus allodynia and hyperalgesia, witnessed by the five patients with pain but no allodynia or hyperalgesia.

The spread of pain, allodynia and hyperalgesia to non-traumatized limbs in severely affected patients is supported by Pitcher et al.'s (1999) findings in rats that unilateral sciatic nerve cuff constriction produced bilateral hind paw decreases in withdrawal thresholds as did sham surgery without nerve constriction, albeit to a lesser degree. They proposed persistent peripheral nociceptor input and altered central mechanisms, and note that even minimal nerve contact may be sufficient to induce hind limb tactile allodynia. Thus, these findings indicate that nerve injury could occur during a procedure as common and as usually innocuous as venipuncture. Han et al. (2000); Liu et al. (2000c), and Liu et al. (2000a) found the greatest amount of spontaneous activity in the first week post-injury with gradual decay thereafter. This is at variance with the protracted symptomatology seen in 80% of the venipuncture patients. However, Pitcher et al. (1999) found evidence of tactile allodynia in rats as long as 145 days post-injury.

Han et al. (2000); Liu et al. (2000c), and Liu et al. (2000a), recording from A- and C-neurons, found only A-neurons exhibiting spontaneous ectopic discharges. Tal et al. (1999); Michaelis et al. (2000) found ectopia almost completely confined to Aβ muscle afferents, not cutaneous afferents. Relating these experimental results to the clinical venipuncture syndrome is problematic as no muscle afferents exist in cutaneous nerves, yet spontaneous pain is its cardinal feature. Also, in normal human volunteers and patients with traumatic nerve injuries and chronic neuropathic pain (Koltzenburg et al., 1994) differential nerve blocks indicate burning pain is conducted via C-fibers and brush-evoked pain (allodynia and hyperalgesia) via Aβ-fibers. The lack of demonstrable ectopic activity in C-fibers in these animal studies questions their role in neuropathic pain, allodynia, and hyperalgesia.

Han et al. (2000); Liu et al. (2000c) and Habler et al.

(2000) studied sympathetic effects on nerve injury. Han et al. (2000) demonstrated sympathetically-dependent and -independent components to pain responses and ectopia. Liu et al. (2000c) found no amelioration of ectopia following sympathectomy. Habler et al. (2000) did not find that axotomized afferents exhibiting ectopic activity could be activated by exogenous norepinephrine and/or electrical stimulation of sympathetic axons. These studies suggest that ectopia and neuropathic pain behavior are little affected by alterations in sympathetic activity. This is compatible with the failure of sympatholysis to affect the clinical course in all but one of the venipuncture patients so treated.

4. Conclusions

Venipuncture-induced neuropathic pain, albeit rare and with some limitations, is a useful clinical model with which to assess current hypotheses of neuropathic pain pathophysiology. Pertinent symptoms in severely affected patients are: immediate onset of pain, spontaneous pain and stimulus-induced discomfort persisting for years, and limited responses to current therapies. These patients may be exceptional due to selection bias and because others with venipuncture injuries are not as incapacitated (Berry and Wallis, 1977; Newman and Waxman, 1996; Newman, 2001); but their situations indicate that venipuncture is capable of inflicting great harm. Therefore, elucidating the mechanisms underlying this pain is important in regards to future treatments, for these patients and for those with other neuropathic pain disorders.

The animal studies, upon which these hypotheses are based, offer attractive insights into the human condition but important issues remain. Foremost is the immediacy of the pain. Long-lasting injury discharges beginning with nerve injury, deafferentation hypersensitivity of the dorsal horn, or biochemical signals emanating from nerve stumps are viable pain mechanisms, but lack unequivocal experimental support. Neuroma hypersensitivity cannot explain this human pain, as neuroma development is delayed (Devor and Seltzer, 1999). Also, while the character of pain often changes, many patients suffer continuously for years. In most animal experiments, spontaneous and/or stimulus-evoked ectopia diminish with time. Further, the type of neuron responsible for human pain is uncertain. Slowly adapting low threshold muscle afferents, which demonstrate spontaneous activity in animals, are not present in human cutaneous nerves. C-fiber activity is thought to be responsible for burning pain in patients with similar neuropathic pain syndromes (Koltzenburg et al., 1994), but spontaneous C-fiber activity has not been confirmed experimentally.

Of interest to human/animal comparisons are five patients without allodynia or hyperalgesia, but with otherwise identical pain. The studies reporting behavioral responses in animals cannot address this situation. Whether these patients harbor spontaneous or stimulus-induced ectopic discharges is unknown; microelectrode studies would be helpful in this regard.

Pitcher et al.'s (1999) findings of minimal physical contact sufficient to induce symptoms, prolonged allodynia, and spread to non-traumatized limbs in rats most resemble the clinical picture, and support clinical evidence that significant nerve damage can occur during procedures as common and as usually innocuous as properly performed venipunctures. That immediate pain is so prominent a feature of this clinical state challenges current experimental hypotheses and raises the possibility of 'non-electrical' sources of central sensitization. Future studies should consider such alternatives.

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