Denervation hyperpathia: a convulsive syndrome of the spinal cord responsive to carbamazepine therapy

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Two cases of denervation hyperpathia that responded well to treatment with carbamazepine are presented. A theoretical relation of this disorder to trigeminal neuralgia and focal seizures is emphasized in the light of experimental data and clinical characteristics.

KEY WORDS - denervation hyperpathia - epilepsy, focal - carbamazepine (Tegretol) - spinal cord seizures

The lancinating pain and burning discomfort commonly associated with regional or generalized muscle spasm following intraspinal injury to the nerve roots or spinal cord is a problem particularly resistant to medical and surgical management. Approximately 10% of all cauda equina and spinal cord injuries suffer from this intractable phenomenon. Its etiology has been variously ascribed to the direct effects of the resultant cicatrix or indirect effects of "bypassing" the lesion through the sympathetic system. More recently this pain has been described as due to a relative increase in afferent C fiber influence on the substantia gelatinosa. Is the pain sensation spontaneously generated by centrally located neurons cut off from their usual afferent input by the destructive lesion? If so, a spontaneous, pain-generating, neuronal seizure state could exist.

In our laboratory, physiological studies of induced epileptic foci in the cerebral cortex show, in single cells, evidence of periodic abnormal burst firing which can rarely be evoked by afferent input. These pathological cells are found in cortex with histological evidence of small fiber and terminal axon degeneration surrounding neurons which, on Golgi impregnation, show irregularities of the dendritic membrane and absence of synaptic spines. Recent studies on the effects of afferent denervation of the dorsal horn gray of the spinal cord and its extension into the brain stem show similar pathological cells; preliminary morphological studies confirm the presence of degeneration and membrane alterations in the resident cells. This led Loeser, et al., to sample the single unit activity in the chronic denervated conus medullaris of a paraplegic patient with intractable pain prior to carrying out a cordectomy for the management of his discomfort. Similar cells with periodic burst firing recorded from this patient are illustrated in Fig. 1.

These data encouraged us to use anticonvulsant therapy in two subsequent cases of hyperpathia following spinal cord trauma. These patients were placed on carbamazepine with satisfying results.

* In the form of Tegretol, Geigy Pharmaceuticals, Ardsley, New York.
Fig. 1. Tracings showing spontaneous hyperactivity in the deafferented dorsal horn of man. The time marks are equal to 5 msec. A is taken from a unit at T-11, B from a unit at T-12, and C from a unit at L-1. The patient had an L-1 motor and sensory level. These recordings are similar to those seen in the chronically deafferented spinal cord of cats. Although normal human neurons were not available, Loeser and Ward (1967) found that in cats spontaneous activity in the normal dorsal horn was minimal. Typical units fired at rates of 0.5 to 20 per sec. Following dorsal rhizotomy, many units fired at frequencies as high as 1400 per sec. (This illustration is reprinted from Chronic deafferentation of human spinal cord neurons. John D. Loeser, Arthur A. Ward Jr., and Lowell E. White, Jr., Journal of Neurosurgery, 1968, 29:48-50.)

Case Reports

Case 1

This 34-year-old paraplegic man complained of intractable pain in the left leg. He was injured in 1962 at the age of 27 years. He suffered an L2-3 fracture dislocation with immediate motor and sensory loss distal to the L-2 segment. Decompressive laminectomy and fusion 1 month after the injury afforded no neurological recovery. His neurological picture stabilized with some psoas function at the hips but otherwise complete loss of motor function in the legs. Cutaneous sensory loss was present distal to L-2, and, although some bladder sensation of fullness was present, voiding could only be accomplished with the Credé maneuver.

Three months after the injury, pain developed in the left leg starting in the hip and radiating down the posterior thigh to the calf, heel, medial malleolus and into the toes. He described the sensation as aching and burning in character. Activity increased the discomfort and bed rest afforded some relief. The discomfort would occasionally spread to the right leg but never so sharply as in the left. This pain syndrome became steadily worse over the next 5 years, requiring persistent analgesic medication.

In 1967 a lumbar myelogram demonstrated a complete block to Pantopaque at the L-2 level. A decompressive laminectomy was carried out and revealed severe focal arachnoiditis with constriction of the cauda equina in the anteroposterior diameter. A partial neurolysis was done and 40 mg of Depomedrol instilled into the operative site. The dura was left open on closure of the wound. The patient reported an immediate 50% decrease in his pain. Six months later the pain returned with increased intensity and some minor increase in volitional motor power about the right hip. He described the
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pain as severe, burning and deep in the bones of the left leg. It was pulsatile and tingling in quality often associated with tightening of the muscles about the hip region which he found particularly unpleasant.

In May, 1968, he was started on carbamazepine 200 mg four times a day. This was subsequently reduced to 700 mg per day because of gastrointestinal disturbance. He noted rapid relief of his discomfort, particularly those sensations he described as pulsatile and tingling as well as the associated muscle contractions. Approximately 3 to 4 months after instituting the medication the patient intentionally stopped it and noted the immediate return of his discomfort. Reinsti- tution of the drug again afforded relief which has persisted. Some deep ache still remains but is tolerable and has not interfered with his rehabilitation.

Case 2

This 37-year-old paraplegic man complained of intractable pain and associated muscle spasms. He had been completely paraplegic since a gunshot wound of the thoracic spine at the age of 2 years, with a complete motor and sensory loss below the T-8 level. He had a relaxed anal sphincter and flaccid bladder without sensation. Infected decubiti led to bilateral mid-thigh amputations in the early 1940's.

Beginning in 1961 the patient had increasing spasms of both stumps associated with severe, sharp, lancinating pain at the level of injury with extension into the remainder of his lower torso but no phantom limb pain.

During the year prior to our evaluation he received numerous subarachnoid alcohol blocks without persistent relief of spasm or pain. It is reported that spinal anesthesia afforded relief when the level of the block reached T-6. However, resolution of the block led to an increased intensity of the pain.

A trial of Dilantin and Valium for 1 week afforded no relief and in May, 1968, the patient was started on carbamazepine 600 mg a day. The patient noted a marked relief of pain and spasms, but the dosage was reduced to 500 mg a day because of occasional nausea. The relief has persisted with only occasional burning sensations. After 8 months on medication the patient commented during a clinic visit: "This medicine is the greatest thing that has ever happened to me."

Discussion

The two cases reported in detail are characteristic of our clinical observations to date and lend themselves well to empirical clinical evaluation because of their prolonged relief of pain. Several similar cases with lancinating pain complaints have been observed associated with various anatomical lesions involving direct central and peripheral nervous system trauma. These cases have responded to carbamazepine, but are not included because of the length of follow up. Likewise, we have confirmed the findings of Albert in selected cases of multiple sclerosis associated with similar pain complaints.

The similarity in the pain complaint appears to be the crucial clinical sign in these patients. First there is evidence of nerve destruction usually associated with weeks to months of delay before the onset of the characteristic discomfort. The patient notes a deep, burning dysesthesia associated with superimposed lancinating attacks of sharp pain. The latter are commonly associated with muscle cramping or spasm. Although these patients often respond well to nerve blocks they do not respond well to operative denervation. On many occasions we have noted a distinct worsening of complaints following nerve blocks and, after some delay, similar results from operative denervation.

In many ways the lancinating complaint is similar to that seen in classical trigeminal neuralgia. A central mechanism for this disorder has been suggested over the years and recently studied by Kerr, King and others in the experimental animal. King suggests an epileptic nature for the behaviors suggesting pain in his animals. Recent studies in similarly prepared animals by Anderson and Black in our laboratory confirm the finding of abnormal neuronal activity in the spinal trigeminal complex similar to that found in the induced epileptic focus in the cortex of animals.

Morphologic studies of cortical epileptic foci demonstrate axonal degeneration and synaptic alternations in the experimental animal associated with pathophysiologic cells
firing in a periodic burst pattern.\textsuperscript{5,22} Likewise, recordings from human epileptic foci\textsuperscript{23} and segments of denervated human spinal cord confirm a similar pathophysiological pattern\textsuperscript{17} in man (Fig. 1).

The anticonvulsant properties of carbamazepine are well documented as well as its pharmacological action on trigeminal neurons. Since the work of Cannon\textsuperscript{8} it has been recognized that cells become spontaneously hyperactive after prolonged denervation. Drake and Stavraky\textsuperscript{7} demonstrated the extension of Cannon’s concept of denervation hyperactivity to the deafferented spinal cord. Ward\textsuperscript{21} postulated that deafferentation is one of the etiological factors in the development of focal cortical epilepsy, and Loeser and Ward\textsuperscript{16} and others\textsuperscript{15} have demonstrated evidence of a similar phenomenon in the spinal cord. The clinical response to carbamazepine lends confirmatory evidence to the hypothesis that the complaint of lancinating pain associated with muscle spasm following afferent denervation of spinal cord segments is central in origin, the perceptive abnormality being generated by afferent cell groups which have developed hyperactive characteristics secondary to the denervation.

Summary

Two cases of intractable pain following spinal cord trauma have been presented. Both patients had significant pain relief during treatment with carbamazepine. This observation substantiates earlier evidence suggesting a central origin of severe atypical pain following afferent denervation of the spinal cord.

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