RIGEMINAL neuralgia (tic douloureux) is a chronic pain syndrome characterized by brief, but excruciatingly intense stabbing or electrical shocklike pain paroxysms experienced in one or more divisions of the trigeminal distribution, either spontaneously or in response to gentle tactile stimulation of a trigger point on the face or in the oral cavity. Dandy16 and Gardner 29 proposed a causal relation between the pain paroxysms and compression of the trigeminal root by adjacent arterial loops or, occasionally, by tumors, arteriovenous malformations, or aneurysms. The hypothesis of microvascular compression was strongly supported by Jannetta37,38 and others, who documented not only that vascular contact occurs in a high proportion of patients with TN, but also that prolonged pain relief can often be obtained surgically by MVD.30 These observations, as well as others, have led to the widely held opinion that the primary pathological factor in TN is demyelination of sensory axons due to sustained (static) or pulsatile microvascular compression of the trigeminal root.27,44 This idea also complements the fact that there is an increased incidence of TN in patients with multiple sclerosis28,65 and leads to the question, what is the link between demyelination and pain paroxysms? Demyelination per se is expected to block impulse propagation, yielding numbness and not pain. In addition, activity in myelinated afferents is generally associated with innocuous touch and vibration sense.67 Ephaptic contact between adjacent denuded axons has long been cited as a pain mechanism in TN,22 although little specific evidence of such coupling is actually available.41 Moreover, ephaptic contact should yield hyperesthesia by a one-to-one duplication (amplification) of afferent signals evoked by application of stimuli. It is not obvious how ephaptic contact could trigger pain paroxysms that outlast the trigger stimulus, or why the intensity of pain that is experienced is not proportional to the strength of the stimulus.46 The aim of the present study was to bridge this explanatory gap by considering the lesion caused by microvascular compression in light of new information on the electrogenic properties of injured afferent axons.61

Mechanism of trigeminal neuralgia: an ultrastructural analysis of trigeminal root specimens obtained during microvascular decompression surgery

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Object. Recent progress in the understanding of abnormal electrical behavior in injured sensory neurons motivated an examination, at the ultrastructural level, of trigeminal roots of patients with trigeminal neuralgia (TN).

Methods. In 12 patients biopsy specimens of trigeminal root were obtained during surgery for microvascular decompression. Pathological changes in tissue included axonopathy and axonal loss, demyelination, a range of less severe myelin abnormalities (dysmyelination), residual myelin debris, and the presence of excess collagen, including condensed collagen masses in two cases. Within zones of demyelination, groups of axons were often closely apposed without an intervening glial process. Pathological characteristics of nerve fibers were clearly graded with the degrees of root compression noted at operation. Pain also occurred, however, in some patients who did not appear to have a severe compressive injury.

Conclusions. Findings were consistent with the ignition hypothesis of TN. This model can be used to explain the major positive and negative symptoms of TN by axonopathy-induced changes in the electrical excitability of afferent axons in the trigeminal root and of neuronal somata in the trigeminal ganglion. The key pathophysiological changes include ectopic impulse discharge, spontaneous and triggered afterdischarge, and crossexcitation among neighboring afferents.

Key Words • cranial nerve neuralgia • tic douloureux • trigeminal neuralgia • nerve pathophysiology • microvascular decompression

TRIGEMINAL neuralgia (tic douloureux) is a chronic pain syndrome characterized by brief, but excruciatingly intense stabbing or electrical shocklike pain paroxysms experienced in one or more divisions of the trigeminal distribution, either spontaneously or in response to gentle tactile stimulation of a trigger point on the face or in the oral cavity. Dandy16 and Gardner 29 proposed a causal relation between the pain paroxysms and compression of the trigeminal root by adjacent arterial loops or, occasionally, by tumors, arteriovenous malformations, or aneurysms. The hypothesis of microvascular compression was strongly supported by Jannetta37,38 and others, who documented not only that vascular contact occurs in a high proportion of patients with TN, but also that prolonged pain relief can often be obtained surgically by MVD.30 These observations, as well as others, have led to the widely held opinion that the primary pathological factor in TN is demyelination of sensory axons due to sustained (static) or pulsatile microvascular compression of the trigeminal root.27,44 This idea also complements the fact that there is an increased incidence of TN in patients with multiple sclerosis28,65 and leads to the question, what is the link between demyelination and pain paroxysms? Demyelination per se is expected to block impulse propagation, yielding numbness and not pain. In addition, activity in myelinated afferents is generally associated with innocuous touch and vibration sense.67 Ephaptic contact between adjacent denuded axons has long been cited as a pain mechanism in TN,22 although little specific evidence of such coupling is actually available.41 Moreover, ephaptic contact should yield hyperesthesia by a one-to-one duplication (amplification) of afferent signals evoked by application of stimuli. It is not obvious how ephaptic contact could trigger pain paroxysms that outlast the trigger stimulus, or why the intensity of pain that is experienced is not proportional to the strength of the stimulus.46 The aim of the present study was to bridge this explanatory gap by considering the lesion caused by microvascular compression in light of new information on the electrogenic properties of injured afferent axons.61 A preliminary account was published previously.61

Clinical Material and Methods

Patient Population

Trigeminal root biopsy specimens were excised from 12 consecutive patients scheduled to undergo posterior fossa craniotomy and root exploration. The intention was to perform MVD and insertion of a shredded Teflon sponge.
Trigeminal neuralgia

wedge to maintain separation between the root and the compressing arterial or venous loop. The default procedure, to be performed if no compressing vessel was found, was a partial rhizotomy involving no more than one third of the root cross section. The rationale and predicted outcome of surgery was explained to the patients, including the intention to remove a small biopsy sample for investigational purposes. The patients were additionally informed that biopsy was unlikely to have significant positive or negative functional consequences beyond those of the surgery itself. Informed consent was obtained from all patients. These procedures were approved by the Helsinki Committees on Human Experimentation of the Rabin Medical Center and the Israel Ministry of Health.

Surgical Procedure

Clinical indications for surgery included typical idiopathic TN intractable to medical therapy. Surgery was offered to patients younger than 70 years of age without significant medical risks; others were encouraged to undergo a percutaneous rhizolytic procedure. All patients who underwent biopsy had undergone a regimen of anticonvulsant therapy including carbamazepine, phenytoin, and/or baclofen, with eventual recurrence of symptoms. One patient (Case 12) had previously undergone a neurolytic procedure involving retrogradient injection of glycerol, and an additional three patients (Cases 7, 9, and 11) had undergone ablative surgery on peripheral branches of the trigeminal nerve. Individual patient parameters are summarized in Table 1.

After induction of general anesthesia, patients underwent surgery in the supine position with the head turned to the side opposite the site of pain. A linear retromastoid incision was followed by a 25-mm-wide craniectomy. At the junction of the transverse and sigmoid sinuses the dura mater was opened parallel to the sinuses. The superolateral aspect of the cerebellum was mobilized. An operating microscope was used for the intradural portion of the procedure. The arachnoid was opened over the trigeminal root, which was then inspected. Brain retraction was used sparingly until egress of cerebrospinal fluid allowed its discontinuation.

A convincing area of arterial compression was seen in seven of the 12 patients (Table 1). In three of these seven patients (Cases 1–3) there were grooves in and a grayish discoloration of the root at the site of contact, and in four of the patients (Cases 4–7) there were grooves in the rootlets or they were deformed by the vessel, but there was no obvious discoloration. In an eighth patient (Case 8), arterial contact was seen and minor compression was considered a possibility, although specific signs of this were absent. In these eight cases a biopsy sample was taken at the apparent site of injury (see later), and one or more shredded Teflon sponges were inserted between the trigeminal root and the offending vessel.

In four (Cases 9–12) of the 12 patients no arterial compression was detected, despite careful searching and, thus, partial rhizotomy was performed in the area of the root somatotopically appropriate to the symptomatology, to a depth of no more than one third of the root diameter. A biopsy sample was taken from the cut portion of the root. In two patients (Cases 9 and 10) prominent veins either coursed on the surface of the root or penetrated it, and in one patient (Case 10) there was also possible arterial involvement. The veins were separated from the root, coagulated, and cut. In Case 12 we believed that there might have been an arterial conflict that resolved when the arachnoid was opened. In all three of these patients (Cases 9, 10, and 12) a Teflon sponge was inserted into the site. Finally, in Case 11 treatment was limited to partial rhizotomy because there was no hint of microvascular abnormality.

Biopsies, Control Tissue, and Histological Studies

The biopsy samples were 1 mm or less in diameter and approximately 4 mm in length. Using a diamond knife, a small incision was made into the trigeminal root sheath approximately 2 to 4 mm from the junction of the root and pons. A strand of nerve fibers was grasped with the aid of a microforceps and teased from the body of the root in the central-to-peripheral direction until a 3- to 4-mm strand was separated from the root. The peripheral end of the strand was then cut with microscissors. The resulting root biopsy sample was immediately removed and placed on a small sheet of dental impression wax. Ends were pinned to the wax under slight tension by using stainless steel minuten pins, and the wax sheet was immersed in a vial containing 1.5% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M cacodylate buffer (or occasionally PO 4 buffer), pH 7.4, at 20°C. The vial was then cooled to 4°C. The surgical procedure was completed in a routine manner.

During the course of this study we had the opportunity to examine a biopsy specimen from a patient with the diagnosis of glossopharyngeal neuralgia. Results are presented in a companion article. Additional comparison tissue was taken from animal and human sources to aid in the evaluation of possible artifacts. First, trigeminal root fragments were dissected from two rats (in which anesthesia had been induced by an intraperitoneal injection of 50 mg/kg pentobarbital) by using the same exposure, dissection, and fixation procedures used to obtain and prepare the human biopsy samples. Second, trimmed blocks of spinocranial root tissue and small fragments, teased similarly to the biopsy samples, were taken from three aldehyde-fixed human trigeminal roots obtained from cadavers (without known root disorders), and from the dorsal root end of two cervical and five lumbosacral dorsal root ganglia excised from live patients in the course of ganglionectomy for headache or for back and leg pain due to ruptured intervertebral disc, respectively. Additional trigeminal tissue was excised from a perfusion-fixed rat.

The fixed tissue samples were rinsed, immersed in 0.1 M cacodylate buffer containing 1.25% OsO 4 and 1.5% sodium ferricyanide (1–2 hours), dehydrated in ascending grades of ethanol, and embedded in resin. Semithin (1–2 μm) transverse or longitudinal sections stained with toluidine blue were used for orientation. Thin sections were cut from the middle of these blocks, laid on 300-mesh copper grids, stained with uranyl acetate and lead citrate, and examined with the aid of an electron microscope (JEOL 100CX; Japan Electron Optics Ltd., Akishima, Japan). Individual grid squares were located in relation to the whole specimen by matching the external boundary of the section and internal landmarks to the semithin sections. In two cases semithin sections were etched with saturated NaOH in ethanol, rinsed in ethanol, and air dried. They were then stained for

Table 1.
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Diagnosis</th>
<th>Pain Dura-</th>
<th>Prior Treatment &amp; Response</th>
<th>Surgical Findings</th>
<th>Lesion Severity†</th>
<th>Surgery</th>
<th>Pain Relief (follow up in mos)</th>
<th>Intact Axons at Specimen Edge</th>
<th>Scattered Intact Axons</th>
<th>Pathological Findings†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57, M</td>
<td>lt V2 &amp; 3 neuralgia</td>
<td>5</td>
<td>inadequate relief from CBZ</td>
<td>SCA loop compressing root anterosuperiorly at pons w/ gray discoloration</td>
<td>+++</td>
<td>MVD</td>
<td>excellent (40)</td>
<td>yes</td>
<td>few</td>
<td>+++</td>
</tr>
<tr>
<td>2</td>
<td>60, M</td>
<td>rt V2 neuralgia</td>
<td>3</td>
<td>recently only partial response to CBZ</td>
<td>SCA loop made groove in inferior surface of root w/ discoloration, 4 mm from pons</td>
<td>+++</td>
<td>MVD</td>
<td>excellent (44)</td>
<td>no</td>
<td>yes</td>
<td>+++</td>
</tr>
<tr>
<td>3</td>
<td>59, F</td>
<td>lt V3 neuralgia</td>
<td>6</td>
<td>only partial response to 1000 mg CBZ</td>
<td>AICA loop compressing entire course of root w/ gray discoloration at contact site</td>
<td>+++</td>
<td>MVD</td>
<td>excellent (29)</td>
<td>no</td>
<td>yes</td>
<td>+++</td>
</tr>
<tr>
<td>4</td>
<td>50, M</td>
<td>rt V2 neuralgia</td>
<td>5</td>
<td>lately receiving 2400 mg CBZ w/out benefit</td>
<td>2 branches of AICA made groove in inferior root surface 2–5 mm from pons</td>
<td>+++</td>
<td>MVD</td>
<td>excellent (49)</td>
<td>yes</td>
<td>yes</td>
<td>+++</td>
</tr>
<tr>
<td>5</td>
<td>57, M</td>
<td>lt V2 &amp; 3 neuralgia</td>
<td>2</td>
<td>no longer responds to drug therapy</td>
<td>root flattened between inferior &amp; superior arterial loops</td>
<td>+++</td>
<td>MVD (both loops)</td>
<td>significant pain relief, small cerebellar infarct w/ unsteady gait (41)</td>
<td>no</td>
<td>yes</td>
<td>+++</td>
</tr>
<tr>
<td>6</td>
<td>61, M</td>
<td>rt V2 neuralgia</td>
<td>4</td>
<td>brief response to CBZ</td>
<td>large artery compressing anteroinferior aspect of root 2 mm from pons</td>
<td>+</td>
<td>MVD</td>
<td>excellent (50)</td>
<td>yes</td>
<td>yes</td>
<td>+++</td>
</tr>
<tr>
<td>7</td>
<td>66, F</td>
<td>lt V1 &amp; 2 neuralgia</td>
<td>15</td>
<td>trigger-point alcohol injection, only partial response to CBZ</td>
<td>AICA loop compressing anterior root surface 2–4 mm from pons</td>
<td>+</td>
<td>MVD</td>
<td>excellent (34)</td>
<td>many†</td>
<td>many‡</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>38, F</td>
<td>rt V2 &amp; 3 neuralgia</td>
<td>3</td>
<td>only partial response to CBZ</td>
<td>2 small arteries contacting superficial of root near pons, w/ clear compression ve nous contact</td>
<td>+</td>
<td>MVD</td>
<td>excellent for 35 mos, then pain recurrence, partial rhizot 56 mos after MVD yielded partial relief (59)</td>
<td>no</td>
<td>no</td>
<td>+++</td>
</tr>
<tr>
<td>9</td>
<td>51, M</td>
<td>lt V1–3 neuralgia</td>
<td>6</td>
<td>stopped responding to multiple drugs, ION neurectomy 2 yrs preop</td>
<td>venous contact</td>
<td>+</td>
<td>excised veins, partial rhizot</td>
<td>no</td>
<td>yes</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>45, M</td>
<td>rt V1–3 neuralgia</td>
<td>6</td>
<td>only partial response to CBZ</td>
<td>vein contacting root inferior surface, possible AICA contact on anterior surface</td>
<td>+</td>
<td>MVD of AICA, vein excited, partial rhizot posteriorly</td>
<td>excellent, partial numbness (27)</td>
<td>yes</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>38, F</td>
<td>lt V3 neuralgia</td>
<td>5</td>
<td>poor response to drugs, ION neurectomy 4 yrs preop</td>
<td>no vascular compression or root contact seen</td>
<td>0</td>
<td>MVD</td>
<td>significant pain relief but dysesthesias &amp; numbness, receiving elatrol (69)</td>
<td>yes</td>
<td>yes</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>49, F</td>
<td>rt V2 &amp; 3 neuralgia</td>
<td>5</td>
<td>glycerol rhizogangliolysis</td>
<td>possible AICA contact w/ inferior surface of root</td>
<td>+</td>
<td>MVD &amp; partial rhizot</td>
<td>recurrent V2 pain at 54 mos postop, RF rhizolysis after 80 mos gave complete pain relief (12)</td>
<td>no</td>
<td>none</td>
<td>NA</td>
</tr>
</tbody>
</table>

* AICA = anterior inferior cerebellar artery; CBZ = carbamazepine; demyel = demyelination; dysmyel = dysmyelination; ION = infraorbital nerve; RF = radiofrequency; rhizot = rhizotomy; SCA = superior cerebellar artery.
† The symbols --, +, ++, and +++ indicate degrees of damage from none to severe.
‡ The site of biopsy was away from the site of compression.
collagen by using 0.5% aniline blue dye in saturated picric acid. Histological data were evaluated by colleagues having no knowledge of the clinical status of the patient or whether the surgeon had identified any visible compression. All clinicopathological correlations were made post hoc.

Results

Orientation and Summary of Observations

Approximately one third to one half of the perimeter of each specimen was ragged, with unmistakable signs of having been torn from the subjacent root. The remainder had a natural root boundary (Fig. 1, arrows). This permitted orientation of the biopsy samples as they would have rested in situ and identification of the surface that contacted the compressing blood vessel, if any. Larger specimens included a central region of severe injury and one or more edges that were relatively spared; smaller specimens showed axonal disruption throughout (Figs. 1 and 2). The principal observation was massive disruption of tissue ultrastructure in the presence of microvascular root compression, with less damage in cases in which there was root contact without compression. There was a clear correspondence between the macroscopic appearance of the root during surgery and the microscopic observation of injury (Table 1). In areas of the most severe damage, few axons remained and nearly all that did were demyelinated. Adjacent areas contained more surviving axons, including a significant proportion having a residual myelin sheath, albeit disrupted. We refer to these areas as zones of “demyelination” and “dysmyelination,” respectively. Histopathological findings always extended to at least one edge of the sample, and encompassed much of its cross section, implying that damage extended deeper into the trigeminal root.
beyond the biopsy site itself. The most severe injury was not usually observed in a single contiguous region, but rather interdigitated with areas of less severe damage. Interestingly, the portion of sample perimeter directly apposed to the compressive blood vessel tended to be relatively spared (dysmyelinated; Fig. 1). There were no obvious signs of inflammatory infiltrates.

A peculiarity of many biopsy samples was a striking overproduction of collagen in the extracellular matrix (Table 1). Usually collagen fibrils filled the space between surviving axons diffusely. In two cases, however, there were massive clumps of nearly pure condensed collagen centered on a zone of severe demyelination and axon loss (Fig. 3). The makeup of the clumps was established using collagen-specific staining and light microscopy, and was confirmed ultrastructurally by visualizing the characteristic periodic striations of collagen fibrils (Fig. 3E–G). The severe damage surrounding the clumps may indicate that they, in fact, contributed to the damage. Fibroblasts were present, but not in unusual density. An excess of collagen is a recognized sequel of compressive injury to spinal roots.28

Areas of Axonal Loss and Demyelination

These regions were dominated by the following: 1) astrocytic processes; 2) a froth of single and multilamellar liposomes (0.2–1 μm), residue of shattered myelin sheaths; and 3) large- and small-diameter axons mostly denuded of...
myelin, with their axolemma directly exposed to the extracellular medium (Fig. 2). Axons were identified as demyelinated by virtue of a cross-sectional diameter in the range of 1 to 4 μm. Small-diameter (< 1 μm) nonmyelinated axons were also present, although they were not bundled by glial processes. Astrocytic and axonal profiles in human trigeminal roots were distinguishable on the basis of cytoplasmic structure, as demonstrated by electron microscopy immunolabeling for glial fibrillary acidic protein.35

Denuded axons, in isolation and also in bundles, occurred in direct apposition to one another without an intervening sheet of glial cytoplasm (Fig. 2A and C). The axoplasm looked viable, and these axons did not appear to be degenerating. The density of axons was often much lower than that observed in contiguous dysmyelinated regions and, sometimes, there were no axons at all, evidence of massive axonal loss. Conspicuous by their absence were phagocytosing macrophages, cells that are highly prominent in comparable regions of injured peripheral nerves.25,26,54,55 We do not know if this is a peculiarity of the trigeminal root or if phagocytes were present early and then withdrew. Be that as it may, considerable amounts of residual myelin debris remained (Figs. 1 and 2).

Areas of Dysmyelination

There were four main types of fiber injuries short of frank demyelination and axonal loss. The most striking dysmyelinated fibers had large (up to 40 μm) round profiles, with a myelin sheath that was thin in proportion to the fiber diameter (Figs. 1 and 2A), apparently the result of swelling. The axonal cytoskeleton was fragmented within a watery matrix. A second form featured bulges and crenulated invaginations of compact myelin, with swelling of the glial cytoplasm present within the innermost loop(s) of myelin (the inner mesaxon), or within the compact myelin itself (presumably at Schmidt–Lanterman incisures). These changes were at the expense of a reduced axonal cross

Fig. 3.  A–C: Case 6. Photomicrographs of serial semithin sections from a trigeminal root biopsy sample in which a collagen mass was present (arrow) and surrounded by a zone of demyelination. D: Schematic reconstruction of the sample as it would appear in situ. Letters A–C indicate the approximate locations of the areas shown in the three corresponding photomicrographs. E-G: Electron micrographs (E and F) and photomicrograph (G) documenting that the mass consisted of nearly pure collagen. A longitudinal view of a collagen fibril within the mass, showing characteristic collagen striations (E); collagen fibrils in cross section (F); and a semithin tissue section stained for collagen (G). Bars: A–C and G, 200 μm; E and F, 0.5 μm.
A third form involved atrophy and loss of the ensheathed axon. The myelin lamellae loosened, interlamellar spaces opened (myelin delamination), and unravelled myelin lamellae came to fill the entire cross section of the nerve fiber (Figs. 1 and 2C). In the past, this type of change has been interpreted as “hypermyelination” or “myelin proliferation.” Finally, a few fibers contained numerous (sometimes tens of) individual small and large axonal profiles, apparently regenerating sprouts, within an original, surviving myelin sheath. Neighboring profiles within a cluster were in close apposition (Fig. 2B). Sprouts presumably originated at the cut end of the parent axon, somewhere between the TG and the point of observation, although some may have been sprouts of adjacent axons that entered the myelin tube upstream.

**Relatively Preserved Axons**

Zones of dysmyelination often transitioned into areas where an increasing proportion of fibers were relatively well preserved (Figs. 1, 3, and 4A). Here we also began to find bundles of unmyelinated afferents with a normal appearance (Remak bundles); however, there were always some dysmyelinated axons, particularly those of the crenulated type of myelin, representing 5 to 20% of the fibers present. Most specimens contained adjacent patches of fibers bearing both PNS and CNS types of myelin. This is consistent with the fact that samples had been taken from a site within a few millimeters of the point of root entry into the brainstem. Both types of myelin showed demyelinating and dysmyelinating injuries.

Although relatively preserved, axons in these areas had a higher proportion of myelin anomalies than axons taken from healthy young animals (Fig. 4B). Nevertheless, they were similar to our other control samples (see data given later) and to control samples studied by others. It is likely, therefore, that much of the residual abnormality in areas of relatively preserved tissue represents normal changes associated with aging, or artifacts of tissue preservation, rather than a pathological change associated with microvascular compression (see Discussion). The PNS type of myelin was better preserved than the CNS type in...
Trigeminal neuralgia

both biopsy and control samples. This may reflect differential susceptibility to microvascular compression.

Correlation with Observations at Surgery

Tissue was coded for the degree and type of microscopic injury, and only later was compared with macroscopic observations made at the time of surgery. Overall, the correlation was what might have been expected (Table 1). Cases in which root compression, flattening, or grooving were noted by the surgeon showed extensive dysmyelination, demyelination, and axon loss, with particularly severe damage found in cases in which discoloration was noted (especially in Case 1). Cases in which vessel contact alone was noted had less damage, mostly dysmyelination rather than demyelination, and more preserved axons. Damage was similar whether microvascular compression affected the superior or the inferior surface of the root. In the one case in which there was no hint of microvascular abnormality (Case 11), there was no evidence of demyelination, only modest dysmyelination, and many axons that appeared intact. Hilton et al., 35 likewise reported minimal pathological findings in five TN biopsy samples in which no microvascular compression could be documented at the time of surgery.

In the patient in whom the most severe tissue necrosis was found (no surviving axons evident, Case 12), microvascular compression was minor at best. On decoding, however, we found that this patient had undergone glycerol rhizogangliolysis 5 months preoperatively. It is unlikely that the entire trigeminal root had been killed by the glycerol because the patient did not experience dense numbness before surgery and still had some sensation after partial rhizotomy. Perhaps necrosis was heaviest on the root surface from where the biopsy sample was taken.

All patients had experienced severe pain preoperatively, severe enough to warrant intracranial surgery. We believed that it was futile and ultimately misleading to try to quantify the relative severity of preoperative pain and we do not know, therefore, whether the extent of root injury correlated with the severity of the patients’ symptoms. Qualitatively, the clinical presentation of patients who ultimately proved to have had clear microvascular compression and corresponding histopathological findings was no different from those who had minor or no vascular contact and a relatively preserved root structure. Finally, there was no obvious relationship between the spatial extent of pain (that is, pain in one, two, or three trigeminal divisions) and the degree of injury subjacent to the offending blood vessel (Table 1).

Control Tissue

The degree and type of axonal injury in biopsy samples is best appreciated by a comparison with control tissue. Although the contrast is most stark when compared with tissue taken from a healthy young animal that had been fixed optimally by vascular perfusion, even in this material occasional fibers (especially those with the CNS type of myelin) displayed some myelin crenulation and delamination. Dysmyelination occurred in a larger proportion of fibers taken from fixed human cervical root samples (all having the PNS type of myelin; Fig. 4C). Interestingly, tissue from patients with intervertebral disc herniation was very similar. Either the herniation in these cases occurred away from the location where the tissue was taken, or disc herniation (which is extradural) triggers relatively modest neuropathological conditions.

A serendipitous opportunity to observe essentially normal human trigeminal root was provided by the patient in Case 7. In this one patient, root compression was recorded at surgery, but only minor dysmyelinating changes were observed histologically. A retrospective check of the surgical notes in this case revealed that the presence of a collateral artery precluded obtaining a biopsy specimen in the center of the area of microvascular compression and, thus, the sample was taken just laterally, no more than 1 mm from the main site of compression. Similarly, in the case of glossopharyngeal neuralgia that we examined, intact fascicles were located closely adjacent to damaged ones. The images shown in Fig. 4A and C, therefore, reflect the normal state of craniospinal root tissue, including normal changes brought about by aging and artifacts caused by our tissue fixation protocol. Correspondingly, the changes shown in Figs. 1 through 3 reflect veridical effects of microvascular compression.

Finally, certain changes seen at the torn edge of the biopsy specimens can be attributed to a mechanical (dissection) artifact rather than a compression injury, on the grounds that similar changes occurred in control tissue. This includes fibers in which myelin was wrenched off the axon, leaving either partly exposed axolemma or torn axons with extruded axoplasm (for example, Fig. 1, thin arrow). Interestingly, some torn myelin lamellae in the control tissue had already formed closed bubbles (liposome-like froth) during the few seconds between sample dissection and fixation. Control samples torn (teased) off roots that had already undergone fixation, both in human and rat material, displayed certain artifacts not observed in biopsy samples such as myelin lamellae that were split and stretched into a form resembling a spider’s web. These and other gross processing artifacts rendered this material unsuitable for comparative purposes.

Discussion

Trigeminal Root Injury in TN

Massive injury to nerve fibers was found in the trigeminal root subjacent to sites of microvascular compression in patients with TN, and its severity was clearly graded with the degree of compression noted by the surgeon during the operation. In several patients, however, vascular contact was minor and injury minimal. We are aware of only one earlier case report on TN in which compression damage to the trigeminal root was documented in material obtained intraoperatively. 35 Massive pathological changes were observed, which are consistent with our observations. In that study the authors also noted several additional cases of typical TN in which no microvascular involvement and no root lesion was found. Together, these observations strongly support the contention that microvascular compression can damage trigeminal root fibers in patients with TN, and they define the nature of the lesion. Major challenges posed by the data are the need to account for TN pain in those patients in whom root compression and axonopathy are minimal and to explain the distinctive pain symptomatology.
observed in patients with TN in terms of axonopathy when it is present (see introductory remarks).

For obvious reasons we could not excise and examine portions of the trigeminal root that were expected to be healthy. Nonetheless, our data support the conclusion that root damage was focal, directly related to vascular contact, and in line with the degree of compression and discoloration seen during surgery. First, the larger samples all had areas of relatively intact axons adjacent to the zone of injury, indicating that the biopsy extended slightly beyond the area of severe injury. Assuming that most samples were taken roughly from the center of the area of vascular contact, as intended, the main area of damage would have been only 1 to 2 mm across, involving no more than approximately one quarter of the root in most cases. Second, data obtained in Case 7 revealed that axons were mostly intact at positions only marginally set off from the site of microvascular contact. The focal nature of the root injury is also consistent with the localized distribution of pain in TN. Likewise, it explains the relatively small changes in trigeminal somatosensory evoked potentials in patients with TN, and their limited sensory deficit.

Our observations are generally consistent with those in many earlier reports of ultrastructural change following mechanical injury (including compression) to peripheral nerves and spinal/cranial roots. The myelin sheath is particularly sensitive and undergoes graded changes from minor dysmyelination to frank disintegration as trauma becomes more severe. One peculiarity of the trigeminal root material was the apparently inefficient removal of myelin debris. In addition to myelin damage, there was clear axonal loss in the most severely affected parts of the root. Interestingly, there were equally prominent signs of axonal sprouting, confirming that the sensory cell soma in the TG survives axotomy.

Two detailed neuropathological studies are available on excised TGs and closely adjacent parts of the trigeminal nerve and sensory root in patients who underwent surgery for TN. This work was carried out in the early days of electron microscopy, a period when gangliectomy was still used in the management of TN. Although it was not stated explicitly by the authors, it is unlikely that the specimens examined included the portion of root located near the pons, where microvascular compression is most commonly observed. Both studies revealed considerable pathological changes, notably dysmyelination, some frank demyelination, and some axonal loss. Such changes were seen in essentially all patients suffering from TN, including those who had not undergone any previous neurolytic procedure. The authors were well aware of the need to factor in processing artifacts and normal aging changes unrelated to TN pain. Pathological changes were more prevalent in patients with TN than in controls (age-matched postmortem material), although even in patients the pathological conditions were much more serious than those found in our material; for example, Kerr and Miller typically needed to scan three to four tissue blocks to reveal convincing changes (see discussion on p 312 of that study).

**Root Disease and Pain**

According to Beaver and Kerr, and their colleagues, nearly all patients with TN had significant TG injury. In the light of current knowledge, however, a significant proportion of these patients must also have had a compression injury at the trigeminal root. This was not reported, presumably because the proximal root is not exposed for gangliectomy and was, therefore, not available for histological analysis. For the same reason, we did not have access to TG tissue from our patients. Had we examined the TG in our patients, no doubt we also would have observed pathological changes. Indeed, root compression itself probably causes retrograde changes in the TG, although the reverse is not the case. In patients with primary damage to the TG one would not see what we observed of focal root injury restricted to a zone immediately subjacent to a compressing blood vessel. Rather, in these patients one would have observed intact roots (if the TG injury were primarily demyelinating) or anterograde (wallerian) degeneration with axonal loss (if TG somata or axons had been killed).

In the absence of quantitative data on pain intensity we cannot comment on the possible correlation between degrees of injury and pain. In several patients, however, there was minimal overt injury, but enough pain to justify a major neurosurgical procedure. Hilton, et al., also reported five such cases. We propose two possible explanations. First, in some individuals, minimal root injury may be enough to yield significant pain. Second, and more likely, patients with TN without root injury may be ones in whom the primary disorder is located in or near the TG. For patients with a primary root compression lesion, MVD is the treatment of choice, although other options are also viable. For patients with TN whose primary lesion is located in the TG, partial rhizotomy is a rational default procedure. Either way, the pain mechanism is probably the same. As discussed later, the specific afferent pathophysiological characteristics that we believe underlie TN pain are expressed both in axons of the trigeminal root and in axons and neuronal somata of the ganglion.

Adams has argued that microvascular contact with trigeminal roots and root injury do not specifically cause TN, but rather reflect normal changes related to aging. Our patients were relatively young (53 ± 9 years of age), histopathological changes were observed in all patients with microvascular contact, and the degree of injury was graded with the degree of compression. Moreover, severe changes were restricted to the quadrant of the root that directly abutted the offending vessel. Finally, microvascular compression (as distinct from mere vascular contact) appears to be common in patients with TN and rare in individuals without TN. We conclude that damage caused by trigeminal root compression is a sufficient condition to induce symptoms of TN, although it is not a necessary condition.

**Mechanism of Pain Paroxysms in TN: the Ignition Hypothesis**

Assuming that root and/or TG lesions are, indeed, the usual cause of TN, how do they induce the characteristic symptomatology of TN? An answer is provided by the ignition hypothesis. The key is the discovery that sensory neurons frequently become electrically hyperexcitable when injured and a source of abnormal spike discharge. In cases of TN, such ectopic pacemaker activity could arise in the following: 1) dys- or demyelinated root ax-
ons; 2) swollen endbulbs and sprouts at the end of severed axons; and 3) axotomized cell somata within the TG. When ectopic firing occurs spontaneously, as it frequently does, 20 it presumably gives rise to background paresthesias and burning sensations, as reported by some patients with TN. 27,30 Other injured sensory neurons are silent, but have a hair-trigger threshold such that momentary stimulation induces a burst of spontaneous firing lasting for seconds or even minutes. This triggered activity, or neuronal afterdischarge, 6,20,49 is proposed in the ignition hypothesis to be the cause of the pain paroxysms associated with TN. Although afterdischarge is set off by an external stimulus, the spiking itself is self-sustaining, a reflection of the intrinsic repetitive firing tendency of injured afferent neurons. 6,7,20 Afterdischarge bursts may also occur without any obvious trigger stimulus.

As long as neurons with ectopic afterdischarge fire independently, the sensation they evoke is expected to resemble a prolongation of the sensation normally evoked by the trigger stimulus. The intense paroxysms of pain experienced by patients with TN and their sudden onset indicate that something must be synchronizing the afterdischarge bursts in large numbers of TG neurons. The ignition hypothesis proposes that synchronization of afterdischarge is a result of neuron-to-neuron crossexcitation 60 at the site of root compression or in the TG. Two well-established processes probably contribute to the synchronization: ephaptic crosstalk and “crossed afterdischarge.” 20

One of the striking observations in our biopsy material and in that of Hilton, et al., 35 were groups of axonal profiles devoid of myelin sheaths, in close apposition to one another without an intervening glial process. Close membrane apposition is a pathological condition known to facilitate axon-to-axon crossexcitation. 2,17,24,45,50,62,64 Thus, momentary stimulation of a facial or intraoral trigger point innervated by one or more members of such a coupled group might activate the entire group, resulting in a pain paroxysm.

The second synchronizing mechanism, crossed afterdischarge, is probably even more important for TN paroxysms because it affects a much larger proportion of afferent neurons. Crossed afterdischarge is a newly discovered form of nonsynaptic, nonephaptic coupling that occurs both within sensory ganglia and at sites of nerve injury. Specifically, impulse activity evokes nonsynaptic release of a neurotransmitter(s) and/or K+ ions into the interstitial space. These mediators move by diffusion and excite intrinsic burst activity (afterdischarge) in neighboring neurons. 3,4,21,49,57,66 As is the case with ephaptic crosstalk, a brief stimulus at a peripheral trigger point could be enough to evoke a massive synchronous afterdischarge by this mechanism. 60

According to the ignition hypothesis, the effects of both synchronizing mechanisms may be augmented by positive feedback; that is, each new neuron recruited following the initial trigger stimulus tends to recruit activity in additional neighboring neurons. These, in turn, elicit activity in still more neurons. The resulting chain reaction is felt as a paroxysmal explosion, the characteristic lightning attack of TN. 60 It should be noted that crossed afterdischarge is preferentially triggered by activity in Aβ afferents, those that are activated by light touch. 2,5 Correspondingly, pain paroxysms in TN are typically triggered by light touch stimuli and not by pinch. 1,3,5 Moreover, both ephaptic contact and crossed afterdischarge support the spread of activity from Aβ touch afferents to nociceptors. 1,24 Such spread is presumably what renders TN paroxysms painful. Central sensitization is unlikely to play a major role in TN because tactile allodynia and hyperalgesia are not usual symptoms. 44

Finally, one wants to account for the characteristic electrical shocklike quality of pain paroxysms in TN. Everyday electrical shocks evoke high-frequency (50 or 60 Hz) activity in all types of afferents simultaneously. This is the neuronal activity that gives rise to the shocklike sensation. Paroxysms of ectopic afterdischarge, amplified and synchronized by ephaptic crosstalk and crossed afterdischarge, are expected to evoke just this pattern of activity.

Self-sustaining afterdischarge in sensory neurons does not usually persist for more than a few tens of seconds. The mechanism that stops the burst is hyperpolarization due to a Ca2+-activated K+ conductance activated by Ca2+ entry during the burst. 5 The burst-triggered hyperpolarization, which may last for several minutes, also renders the cell less responsive than normal to subsequent trigger stimuli. This is the proposed explanation of the refractory period that occurs in TN, the observation that following an attack a second attack cannot be triggered until 2 to 3 minutes have passed. 46 The hair-trigger nature of paroxysmal bursts may also account for the sometimes prolonged remissions that are a characteristic of TN. Long-term processes such as partial remyelination, or normalization of membrane channel marshaling, 20 may bring the triggering level below threshold for long periods of time.

**Treatment Modalities in Light of the Ignition Hypothesis**

The ignition hypothesis accounts for the major positive and negative signs and symptoms of TN, and for its pathogenesis following microvascular root compression. 60 The same neuronal changes (ectopic hyperexcitability, afterdischarge, and crossexcitation) are also known to develop in sensory ganglia following either axotomy or direct trauma to the ganglion. 7,68,70 The ignition hypothesis, therefore, works equally well for cases in which there is no microvascular root compression but there is a TG lesion. 60 In the case of root compression, ignition may be exacerbated by the pounding of the arterial loop on the compression site, a region known to be abnormally mechanosensitive. 15 The cardiac rhythm expected by this pounding is presumably obscured by the long time constant imposed by neuronal afterdischarge. Removal of the vessel by MVD surgery provides immediate relief; long-term relief presumably results from root recovery, primarily due to remyelination.

The ignition hypothesis also accounts for the effectiveness of medical treatment. Anticonvulsant medications such as carbamazepine, phenytoin, and lamotrigine are membrane stabilizers (Na+ channel blockers) that suppress ectopic neural firing. 12,14,20,60 This action occurs in the PNS, over and above the role these agents play in suppressing seizure activity in the CNS. As the lesion progresses, ever increasing doses of these drugs are required until CNS side effects such as nausea and sedation become intolerable and surgical intervention is required. Membrane stabilizing drugs that are excluded from the CNS might prove an alternative therapeutic strategy.

A key prediction of the ignition hypothesis that distinguishes it from hypotheses based on a CNS cause 6 is the presence of paroxysmal discharge in primary afferent neu-
rons serving areas of the face to which pain is referred. This prediction might be verified by referral to microneurographic recordings from peripheral nerve branches. Another approach is to detect effector consequences of antidromic activity in peripheral nerves, such as neurogenic inflammation. Indeed, Nurminko and associates recently reported finding cutaneous vasodilation in patients with TN during paroxysmal attacks with the aid of laser-Doppler flowmetry. Verification of the ignition hypothesis is not merely of academic interest, but it suggests specific new avenues for the development of novel treatment modalities.

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