Gamma Knife rhizotomy-induced histopathology in multiple sclerosis–related trigeminal neuralgia

Clinical article


¹Section of Neurosurgery and ²Department of Pathology and Diagnostic Services, University of Manitoba, Winnipeg, Manitoba, Canada

Object. In this report, the authors describe the pathological changes in the human trigeminal nerve after Gamma Knife radiosurgery.

Methods. Three trigeminal nerves of patients with multiple sclerosis (MS)–related trigeminal neuralgia (MS-TN) after Gamma Knife radiosurgery and other ablative procedures were examined by a neuropathologist. These cases were compared with 3 patients with typical TN who underwent partial surgical rhizotomy following recurrent symptoms after gasserian injury procedures, as well as with autopsy specimens from patients with and without MS-TN.

Results. The three irradiated MS-TN specimens exhibited axon loss, demyelination, myelin debris, and fibrosis. Mild lymphocytic infiltrate was present in all 3 samples from MS-TN patients. The nonirradiated trigeminal nerve samples were generally well myelinated with rare degenerating axons. The microscopic findings in trigeminal nerve autopsy specimens were normal in patients without TN, with MS but not TN, and MS-TN.

Conclusions. The inflammation observed in MS-TN specimens collected following Gamma Knife radiosurgery has not previously been described in the literature. These data provide new insight into the changes that occur in trigeminal nerve following stereotactic radiosurgery.

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Key Words • trigeminal neuralgia • multiple sclerosis • Gamma Knife • rhizotomy • histopathology • radiosurgery • peripheral nerve • stereotactic radiosurgery • pain

Trigeminal neuralgia (TN) is a potentially disabling source of craniofacial pain with an annual incidence of 4–5 per 100,000 that increases with advancing age.¹⁸ As defined by the International Headache Society, TN consists of characteristic, stereotyped paroxysmal attacks of pain lasting from seconds to 2 minutes and affecting one or more divisions of the trigeminal nerve.⁹ It is usually caused by pulsatile vascular compression of the affected trigeminal root by tortuous or aberrant vessels. A small subset of TN cases (2%–4%) is related to multiple sclerosis (MS)¹⁰ thought to be caused by demyelination of trigeminal projections within the CNS.¹⁴,²¹

A variety of treatment options are commonly employed for TN, including: 1) pharmacotherapy, 2) microvascular decompression (MVD) surgery, 3) injury to the intracisternal portion of the trigeminal nerve by stereotactic radiosurgery or 4) partial surgical rhizotomy (Dandy procedure), 5) percutaneous rhizotomy at the region of the gasserian ganglion (via balloon compression, radiofrequency, or glycerol rhizotomy), or 6) peripheral nerve block or injury.¹ The success of rhizotomy procedures tends to correlate with new trigeminal sensory deficits and is attributed to the degree of nerve injury.¹⁶ In prior small case series authors have described trigeminal nerve histopathological features in typical TN (due to vascular compression)²,⁴,⁵,⁸,¹¹,¹²,¹⁶,¹⁷ and MS-related TN (MS-TN),¹,⁴,¹⁰,¹⁴,¹⁵,²¹ as well as after radiosurgery in primates⁸,²⁵ and humans.⁷,²⁴

In this report, we describe the histopathological findings in 3 patients with medically refractory MS-TN who underwent partial surgical rhizotomy following failure of both percutaneous and Gamma Knife rhizotomies. These observations are compared with findings in 3 patients who had typical TN and underwent partial surgical rhi-

Abbreviations used in this paper: MS = multiple sclerosis; TN = trigeminal neuralgia.
Trigeminal neuralgia histopathology

but had not undergone prior radiosurgery.

Methods

The research ethics board at the University of Manitoba approved this retrospective analysis. Three specimens of trigeminal nerves were obtained during partial surgical rhizotomy for the treatment of refractory MS-TN in patients who had previously undergone Gamma Knife radiosurgery. None of the patients received immune modulating therapy. Three trigeminal nerve specimens were also obtained in a similar manner from patients with refractory TN who had neither MS nor radiosurgery for comparison. Clinical details and prior interventions are listed in Table 1. Trigeminal nerves from 4 autopsy subjects with and without TN and MS are presented as a reference (Table 2).

Stereotactic radiosurgeries were performed with a Gamma Knife. A maximal dose of 80 Gy delivered via a 4-mm collimator was prescribed to the proximal trigeminal nerve root, with the 20% isodose line slightly encroaching on the brainstem surface (Fig. 1). A second Gamma Knife dose was prescribed to the same or slightly distal point in 2 patients.

Partial surgical rhizotomies were performed through a standard retrosigmoid craniectomy with patients in the lateral decubitus position after general anesthesia was induced; intraoperative neurophysiological monitoring was used throughout. The trigeminal nerve root was visualized via an anterosuperior approach over the cerebellum. No active neurovascular compression was noted; 1 patient had neurovascular compression discovered 1 year prior with transient pain relief. The caudal piece of the por-

tio major was removed en bloc from the brainstem entry point, distally to a length of 3–4 mm. The excised portion corresponds to the area previously targeted as the Gamma Knife isocenter. There were no intraoperative difficulties in any of the cases. All patients were discharged to home and reported persistent pain relief on follow-up.

All surgical specimens were sent from the operating theater in glutaraldehyde directly to the department and reported persistent pain relief on follow-up. Additional trigeminal nerve roots obtained during routine autopsies were similarly prepared.

Results

The normal trigeminal nerve from an autopsy specimen exhibited large axons myelinated by oligodendro-
cytes in the central portion and by Schwann cells in the peripheral portion. Through the transitional zone, axons were not myelinated and were surrounded by astroglial cell processes filled with intermediate filaments. The extracellular compartment contained only loosely organized material and minimal collagen (Fig. 2). These features are similar to those previously described in normal human material21,20,22 and nonhuman primates.19 The trigeminal nerves and pons from an individual with TN and from a patients with MS but not TN and a patient with MS-TN were also examined (Table 2). None of these samples exhibited inflammation, and no evidence of myelinated axon loss was observed in the trigeminal nerve.

The trigeminal nerve was examined from 3 patients who had typical TN but no MS or radiosurgery and who underwent exploratory posterior fossa cranietomies. No major vascular loop was identified. The trigeminal nerve of 1 patient (a 62-year-old male) had a small “tag” of tissue inferiorly, which was biopsied; the other 2 patients underwent partial rhizotomies of the proximal nerve. Examination of the sample from the 62-year-old male, who had undergone many interventions, showed peripheral and transitional zone nerve with rare swollen degenerating axons and microglia with myelin debris (Fig. 3). There were no lymphocytes or demyelination. The trigeminal nerve from a 44-year-old patient with typical TN but no MS or radiosurgery was microscopically normal. The third patient, a 65-year-old female, had a small superficial focus of demyelinated axons in the peripheral portion and activated microglia in the central portion.

The trigeminal nerve sample from the first MS-TN patient, who had undergone Gamma Knife treatments 12 and 16 months prior (80 Gy each), included both peripheral and central nerve portions. The outer sheath was fibrotic with corpora amylacea. At the ultrastructural level, collagen was abundant in the peripheral portion. Through the transitional zone, axons and transitional zone nerve with rare swollen degenerating axons and microglia with myelin debris (Fig. 3). There were no lymphocytes or demyelination. The trigeminal nerve from a 44-year-old patient with typical TN but no MS or radiosurgery was microscopically normal. The third patient, a 65-year-old female, had a small superficial focus of demyelinated axons in the peripheral portion and activated microglia in the central portion.

All surgical specimens were sent from the operating theater in glutaraldehyde directly to the department of pathology and processed for electron microscopy. Additional trigeminal nerve roots obtained during routine autopsies were similarly prepared.

TABLE 1: Patient information*

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Age (yrs), Sex</th>
<th>MS</th>
<th>TN</th>
<th>Gasserian Rhizotomies</th>
<th>MVD</th>
<th>Gamma Knife (dose)</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Balloon</td>
<td>Glycerol</td>
<td>RF</td>
<td>MVD</td>
</tr>
<tr>
<td>Typical TN</td>
<td>62, M —</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>7</td>
<td>7</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>44, M —</td>
<td>3</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>3</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>65, F —</td>
<td>11</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>none</td>
</tr>
<tr>
<td>MS-TN</td>
<td>60, F 18</td>
<td>8</td>
<td>5</td>
<td>4, 3</td>
<td>7, 6, 5</td>
<td>—</td>
<td>12 mos (80 Gy); 16 mos (80 Gy)</td>
</tr>
<tr>
<td></td>
<td>48, M 15</td>
<td>7</td>
<td>2</td>
<td>2, 1</td>
<td>—</td>
<td>5</td>
<td>21 mos (80 Gy)</td>
</tr>
<tr>
<td></td>
<td>53, F 40</td>
<td>9</td>
<td>9</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>6 yrs (80 Gy); 4 yrs (70 Gy, distal)</td>
</tr>
</tbody>
</table>

* All numeric values are years prior to surgical rhizotomy unless otherwise specified. MVD = microvascular decompression; RF = radiofrequency; — = not applicable.
like inclusions. Scattered large axons had thin or absent myelin, and there were rare degenerating axons. Mild chronic inflammation was evident with rare scattered lymphocytes, hypertrophic microglia, and macrophages containing myelin debris, mainly in the central portion. There was approximately 25% loss of myelinated axons. Blood vessels had thickened walls (Fig. 4A–C).

The trigeminal nerve sample from the second MS-TN patient, treated with Gamma Knife 21 months prior, spanned the transitional zone. The central portion had a few thinly myelinated large central axons, rare axon degeneration, oligodendrocytes with lysosomal debris, rare lymphocytes, occasional reactive astrocyte processes with small Rosenthal fibers, and mild perivascular fibrosis (Fig. 4D and E). The peripheral region seemed to be better myelinated than the central region.

The trigeminal nerve sample from the third MS-TN patient, who had been treated with Gamma Knife 4 and 6 years prior, also spanned the transitional zone. The nerve was atrophic with reactive astroglia processes, and had small foci of perivascular lymphocytes and debris-filled macrophages in the central portion. The peripheral portion exhibited some collagen accumulation. Schwann cells myelinated less than half of the normal proportion of axons (Fig. 4F).

Discussion

Classical TN is initially responsive to pharmacotherapy but later often becomes medically refractory. In many patients TN will ultimately progress and require a variety of surgical rhizotomy or nerve ablative procedures for pain relief. Some TN sufferers undergo multiple procedures for recurrent pain, especially if their TN is unrelated to vascular compression, as in the MS-TN population.

The cisternal portion of the trigeminal nerve traverses the CSF space between the semilunar ganglion in Meckel’s cave and the superolateral pons, and enters the superolateral pons at the root entry zone. The nerve comprises a portio major that contains sensory fibers and a portio minor containing the motor fibers. The central to peripheral transition zone occurs approximately 1–2 mm lateral to the pons (the first quarter of the cisternal portion of the nerve).22 This is the most common site of vascular compression responsible for typical TN.

Ultrastructurally, the normal trigeminal nerve contains a mix of large axons myelinated by oligodendrocytes and Schwann cells in the central and peripheral portion, respectively, and small unmyelinated axons (there is a variable amount of irregularity in the myelin, even in

![Fig. 1. Gamma Knife target plan. Maximal dose of 80 Gy through a single 4-mm collimator with the 20% isodose line slightly encroaching on the brainstem.](image1)

**TABLE 2: Autopsy control cases: histological findings in the pons and trigeminal nerve**

<table>
<thead>
<tr>
<th>Age (yrs), Sex</th>
<th>MS</th>
<th>MS TN</th>
<th>Pons</th>
<th>Trigeminal Nerve(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65, M</td>
<td>no (control patient)</td>
<td>no</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>89, F</td>
<td>no</td>
<td>TN for “many years,” medical therapy only</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>30, M</td>
<td>MS for 4 yrs</td>
<td>no</td>
<td>multiple small demyelinated plaques, no inflammation</td>
<td>normal</td>
</tr>
<tr>
<td>63, F</td>
<td>MS for 25 yrs</td>
<td>TN for 3 yrs, glycerol rhizotomy 6 mos before death</td>
<td>demyelinated plaque in rt pons, no inflammation</td>
<td>normal</td>
</tr>
</tbody>
</table>

![Fig. 2. Electron micrographs of a normal trigeminal nerve obtained from an autopsy case. A: Central portion of trigeminal nerve where axons are surrounded by (dark) rings of myelin, which are proportionate to the axon diameter. B: Transitional zone of the trigeminal nerve where axons (ax) lack myelin and are surrounded by astrocyte processes (asterisk). Bar = 5 μm (A) and 50 μm (B).](image2)
normal controls. The axons in the transitional zone are unmyelinated and are surrounded by astroglial cells of the glia limitans. The extracellular compartment contains capillaries, fibroblasts, and no significant collagen.\textsuperscript{11,19,20}

TN is associated with dysmyelination and axonal tortuosity in the cisternal portion, with a variable degree of axonal loss.\textsuperscript{2,8,11,16} MS-TN has a similar morphological appearance\textsuperscript{3} with the addition of perivascular lymphocytes, lipid-laden macrophages, and plaques in the centrally myelinated nerve.\textsuperscript{4,8,21} Kondziolka et al. and Zhao et al. examined the trigeminal nerves of baboons and rhesus monkeys that underwent Gamma Knife radiation. There was no evidence of inflammation, but they noted focal myelin pallor and vacuolation without fibrosis, substantial large and small axonal loss, fragmentation, and swelling. Necrotic tissue was present in the irradiated region and included necrotic Schwann cells.\textsuperscript{13,25} Foy and colleagues noted similar findings in an irradiated facial nerve (compressed by a vestibular schwannoma) and also reported microvasculitis.\textsuperscript{6} Watanabe et al. described a microscopically normal trigeminal nerve 17 months and 3 weeks after receiving 85- and 70-Gy doses, respectively (noting that this patient had refractory TN and may not be representative).\textsuperscript{24} Szeifert and coworkers reported on 1 patient receiving 85- and 70-Gy doses, respectively (noting that this patient had refractory TN and may not be representative within the central component of the nerve root and more extensive following multiple rather than single radiosurgery treatments. These changes were also more pronounced than those previously described in specimens obtained from MS-TN patients not exposed to prior radiosurgery rhizotomy (Table 3).

### Conclusions

Multiple sclerosis–related TN can be a debilitating condition that often requires multimodality treatment, including multiple nerve-injury procedures for pain relief. We have presented the histopathological findings in 3 patients with medically refractory MS-TN who underwent partial surgical rhizotomy following Gamma Knife radiosurgery rhizotomy. All of the specimens exhibited regional axonal loss, demyelination, residual myelin degeneration and demyelination, which is similar to previously described findings. The changes most commonly attributed to Gamma Knife radiosurgery were vascular wall thickening and fibrosis, as well as significantly more pronounced axonal and myelin injury compared to controls. The inflammation observed in both centrally and peripherally myelinated nerves in MS-TN specimens might be attributable to the MS and/or prior Gamma Knife treatments. This inflammation was not seen in prior simian models examined at 6 months postirradiation; however, the present study assessed nerves obtained 1–6 years after irradiation. Some authors have hypothesized that MRI evidence of enhancement seen in some patients after Gamma Knife treatment might reflect endothelial injury with an unknown component of inflammation.\textsuperscript{20}

We do not routinely obtain MR images immediately prior to rhizotomies, although preoperative MR images have demonstrated plaques within the brainstem, which is consistent with the pathophysiological changes of MS-TN. An alternative theory explaining this inflammation could be related to irradiation-induced blood-brain barrier degradation, allowing MS-related inflammation to extend peripherally.

The limitations of this study are the small sample size and the complex interplay of multiple pathologies. Unfortunately, we were unable to obtain a nerve root from a living patient with MS-TN who had not undergone radiosurgery as a comparative surgical specimen; however, the autopsy specimens are consistent with the surgical samples. Although we assessed a small number of samples, this is the only case series describing changes in the trigeminal nerve root following radiosurgery for MS-TN. We endeavored to differentiate the changes caused by MS, TN, prior ablation, and Gamma Knife rhizotomy based on our control cases and prior descriptions of the histopathological features of TN and MS-TN. The inflammatory and injury findings observed following radiosurgery in the MS-TN samples was more impressive within the central component of the nerve root and more extensive following multiple rather than single radiosurgery treatments. These changes were also more pronounced than those previously described in specimens obtained from MS-TN patients not exposed to prior radiosurgery rhizotomy (Table 3).

### TABLE 3: Summary of histopathological findings in the trigeminal nerve and attributed etiologies

<table>
<thead>
<tr>
<th>Finding</th>
<th>Gasserian Rhizotomy*</th>
<th>MS*</th>
<th>Gamma Knife Rhizotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>axon loss</td>
<td>rare</td>
<td>rare</td>
<td>25%–50%</td>
</tr>
<tr>
<td>thinned myelin</td>
<td>absent</td>
<td>present</td>
<td></td>
</tr>
<tr>
<td>fibrosis</td>
<td>absent</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>inflammation</td>
<td>absent</td>
<td>rare</td>
<td>present</td>
</tr>
</tbody>
</table>

* Based on historical reports and autopsy controls.
bris, fibrosis, and vascular thickening, confirming prior findings in animal models. Additionally, MS-TN was associated with mild lymphocyte infiltration. These findings provide insight into the changes that occur in the trigeminal nerve following Gamma Knife radiosurgery in patients with MS-TN.

Acknowledgment

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Disclosure

Dr. Del Bigio holds the Canada Research Chair in Developmental Neuropathology. The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following: Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Kaufmann, Phillips. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kaufmann. Administrative/technical/material support: Phillips, Del Bigio. Study supervision: Kaufmann, Del Bigio.

References

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Address correspondence to: Anthony Kaufmann, M.D., M.Sc., F.R.C.S.C., GB-137, 820 Sherbrook St., Winnipeg, MB R3A 1R9, Canada. email: akaufmann@hsc.mb.ca.