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Trigeminal Neuralgia: Understanding the pathogenesis and review of treatment modalities.

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ABSTRACT

Trigeminal neuralgia is usually caused by demyelination resulting from vascular compression of trigeminal sensory fibers within either the nerve root or the brainstem. Other causes where demyelination is involved or implicated include multiple sclerosis, compressive space occupying masses in the posterior fossa. These focal demyelination areas have close apposition of demyelinated axons and an absence of intervening glial processes. It is this anatomical arrangement that coupled with pulsatile vascular indentation which favors the ectopic generation of spontaneous nerve impulses and their ephaptic conduction to adjacent fibers, and increased spontaneous nerve activity. Decompression results in separation of demyelinated axons and their release from focal distortion leading to rapid relief of symptoms in most patients with vessel-associated trigeminal neuralgia. Anticonvulsants, such as carbamazepine, phenytoin, gabapentin, lamotrigine, oxcarbazepine, and topiramate are the mainstay of pharmacotherapy of this condition. These medications are initially effective for pain control in 90% patients. When the patients become refractory to the pharmacotherapy surgical interventions are warranted. On the basis of clinical studies microvascular decompression seem to be the most effective treatment in terms of patient satisfaction and cost effectiveness. The peripheral procedures have higher recurrence rate and complications and have relatively lower long term cost effectiveness.

Keywords: Trigeminal neuralgia, pathogenesis, modalities

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INTRODUCTION

Classical trigeminal neuralgia has an annual incidence of ~4.5 per 100 000[1-2]. The condition is characterized by recurrent episodes of intense, lancinating pain localized to small areas of the face. The condition is usually first seen in middle or old age, but young adults and children can also be affected[3-5]. Attacks are triggered by mild sensory stimulation of so-called trigger zones which may be located anywhere along the distribution of trigeminal nerve and usually last only seconds but may recur repeatedly after short refractory period. The stimuli could be light touch, draughts of wind, eating, drinking, washing, shaving and even applying make-up. Initially, the neuralgic episodes occur in bouts, with subsequent spontaneous remission that may last months or years. In time, however, attacks become more frequent and the pain more sustained[6].

Etiology

A wide majority of cases are caused by compression of the trigeminal nerve root close to its point of entry into the pons, by an aberrant loop of artery or vein. This was first recognized as a cause of trigeminal neuralgia by Jannetta[7] and is now thought to account for 80–90% of cases[8-15].An arteriovenousmalformation[16, 17]or a saccular aneurysm[18]may be rare causes of vascular compression of the nerve root.Other compressive lesions that can cause trigeminal neuralgia include vestibular schwannomas[19], meningiomas[20, 21], epidermoid cysts[22, 23] and various other cysts and tumours[22, 24-26].In quite a few reported cases, the neuralgia was contralateral to the side of the mass lesion[20, 25, 26].Fujimaki and colleagues described two interesting case of recurrent trigeminal neuralgia in whom the neuralgia was caused by hardening and subsequent compression of nerve root by the prosthetic material which was used in the course of microvasculardecompression[27].Trigeminal neuralgia may be a result of bony compression of the nerve, e.g. due to an osteoma[28] or deformity resulting from osteogenesis imperfect[29].Schwannomas arising from the trigeminal nerve root may present with typical trigeminal neuralgia[30].Trigeminal neuralgia is a well-recognized complication of multiple sclerosis[31-34]where a plaque of demyelination encompasses the root entry zone of the trigeminal nerve in the pons[35-39]. Rarely, trigeminal neuralgiais seen in patients with Charcot–Marie–Tooth disease where peripheral nerve demyelination occurs[40].Vascular compression of the trigeminal nerve root may contribute to trigeminal neuralgia even in patients with demyelinating disorders; compression of the root entry zone by a blood vessel has been demonstrated in a sizeable minority of patients with multiple sclerosis and trigeminal neuralgia[37, 38]and in an occasional patient with Charcot–Marie–Tooth disease[37].In many such cases, decompression of the nerve

root leads to relief of symptoms. The principal infiltrative causes of trigeminal neuralgia are carcinomatous deposits within the nerve root, gasser an ganglion and nerve[41] and trigeminal amyloidomas[42, 43].In the vast majority of cases, trigeminal neuralgia is a sporadic disorder. Familial occurrence has been reported in Charcot–Marie–Tooth disease[40].A family with trigeminal and/or glossopharyngeal neuralgia affecting several individuals in three generations was described by Knuckey and Gubbay[44], and Duff and colleagues[45] described a family with seven affected family members in two successive generations. A further inherited disorder in which there is a theoretical risk of trigeminal neuralgia is autosomal dominant hypertension and brachydactyly. Naraghi and colleagues, who had previously mapped this disorder to chromosome 12p, reported that the hypertension was consistently associated with neurovascular anomalies, consisting of loops of posterior inferior cerebellar or vertebral artery that compressed the ventrolateral aspect of the medulla[46].Small numbers of patients have been reported in whom trigeminal neuralgia was associated with a small infarct[47-49] or angioma in the brainstem.

Pathogenesis of TN

There is a plethora of discussions related to pathophysiology of TN in the literature, the pain being ascribed variously to hyperactivity or abnormal discharges arising from the gasserian ganglion, the 'injured' nerve root and the trigeminal nucleus within the brainstem[34, 50-53].Smith and McDonald demonstrated that many experimentally demyelinated nerve fibres in the dorsal spinal white matter of the cat were spontaneously active, discharging either in small bursts or steadily at 15–45 impulses per second for many hours[54]. Focal deformations of the spinal cord in the region of demyelination increased the level of activity in fibres already discharging, and apart from that, also transiently induced activity in fibres that had previously been electrically silent. When implied to the vascular compression of the trigeminal nerve root, these observations raise the possibility that pulsatile compression of demyelinated axons by an overlying blood vessel may be responsible for initiating the aberrant impulses in some patients. As far as the subsequent spread of impulses is concerned, Hilton, Love and colleagues argued that the close apposition of demyelinated axons in regions of vascular compression should facilitate the ephaptic transmission of nerve impulses[36, 55]. Observations in patients with multiple sclerosis further support this mode of spread of impulse. A correlation has been shown to exist between abnormal brainstem trigeminal evoked potentials and presentation with TN or dysaesthesiae in patients with multiple sclerosis[33]. However, the rapid clinical and electrophysiological recovery after surgical decompression of the affected nerve root questions the central role for demyelination in the development of TN.

On the basis of experimental studies by Smith and McDonald[54], it can be implied that the rapid relief of clinical symptoms probably reflects the cessation of the ectopic generation of impulses and of their ephaptic spread to adjacent fibres caused by release from compression. Also, the separation of demyelinated axons that were previously compacted together prevents ephaptic cross-talk. Another aiding effect of the decomperssion surgery is the reversal of conduction block of relatively large-calibre, fast conducting fibres that are not demyelinated. In compression of low to moderate severity, large-calibremyelinated fibers seem to be more susceptible than smaller fibers to conduction block[56, 57]. Reversal of conduction block in these larger fibres would account for the rapid fall in conduction latencies across the trigeminal nerve root as soon as it is decompressed.

The pathogenesis of certain phenomena related to TN still remains unclear like occasional triggering of attacks by stimuli outside of the area of innervations of the trigeminal nerve, and even by bright lights or loud noises[13], which must involve central pathways. Another such phenomena is the occurrence of a refractory period of seconds to minutes after an attack of TN, during which further attacks cannot be provoked[58]. Experimental studies by Smith and Hall[59]have shown that the length of time for which nerve fibres are refractory to further excitation increases after demyelination in both the PNS and the CNS[60], but the duration of the refractory period in these experimental studies is much shorter than that in patients with TN. The explanation to this could be that there are other factors could conceivably delay the restoration of membrane potentials and excitability after an episode of TN like impaired mitochondrial generation of adenosine triphosphate (ATP) in an environment of focal endoneurial ischaemia due to the nerve root compression. This results in delay in the restoration of ionic gradients after a burst of discharges, and also leads to the paucity of extracellular fluid and increased longitudinal resistance to ionic current between closely juxtaposed demyelinated axons. However, it may be suggested that it is the remyelination of the nerve that helps to ensure the sustained relief of symptoms. Remyelination may also be the reason for spontaneous remission of TN in some patients. The role of remyelination is further emphasised by the failure of microvascular decompression to relieve symptoms in patients with very long-standing disease, in whom severe local depletion of oligodendrocytes and astrocytes prevent effective remyelination after decompressive surgery. Love et al suggested that the failure of microvascular decompression in some patients could be caused by aberrant remyelination in the compressed nerve root[55], thus preventing the separation of groups of apposed axons after decompression.

Pharmacotherapy review

CBZ is the gold standard for treatment of TN. Its superiority is well established by three placebo controlled crossover studies involving 151 patients[61-63].These studies, and its subsequent wide-spread use in TGN, made CBZ something of a gold standard against which other drugs have been compared in subsequent controlled trials. These drugs include tizanidine, baclofen, pimozide, tocainade, and oxcarbazepine and none have been shown to be superior to CBZ (Table 1). Phenytoin is considered the second drug of choice in TN. It was Bergouignan who discovered in 1942 that phenytoin was effective in preventing pain paroxysms in this condition[76]. However, long term use of phenytoin for treating epilepsy is on the decline due to its numerous side-effects. The advantage of using gabapentin is that serious side-effects are rare and it is generally well tolerated. Lamotrigine was compared to placebo as an add-on medication to either CBZ or phenytoin and the results were found to be superior in the lamotrigine treated group compared to those on placebo[77].There have not been any placebo controlled studies of clonazepam but it can be used for short term pain relief in patients not controlled with other medications. However, one weak study suggests that clonazepam is of value in treatment of TN[78].A pilot study involving topiramate-placebo crossover found that topiramate showed was effective in TN but in the confirmatory study topiamate did not show any effect[79].

Table 1: Summary of Results of Clinical Trails/Controlled Clinical Trials of Drug Treatment of Trigeminal Neuralgia

Study	Drugs Used	Total No. of Patients	Total No. of Patients Benefited (%)
Tomson[65]	CBZ	8	100
Farago[66]	CBZ analogues: (i) Dihydroketo	13	100
	(ii) Dihydromono-hydroxy	11	
Zakrzewska et al[67]	Oxcarbazepine	15	100 Benefited initially 80 Patients required surgery
Lindstrom [68]	Tocainide and CBZ	12	—
Lechin et al[69]	Pimozide and CBZ	48	100 Benefited with pimozide 56 Benefited with CBZ
Vilming[70]	Tizanidine	6	Effects of tizanidine were
	CBZ	6	inferior to those of CBZ
Merren[71]	Gabapentin	60	65
Delvaux et al[72]	Lamotrigine	25	100
Steardo et al[73]	Baclofen	25	All patients were improved by 68.61
Fromm[74]	Baclofen	60	30
Parmar[75]	Baclofen	20	65
Fromm et al[76]	L-Baclofen and racemic baclofen	9	66.6

Abbreviation: CBZ, carbamazepine.

Table 2: Success Rate of Peripheral Procedures

Procedure	Study	N	IPR (%)	PFD (months)	Recurrence rate (%)
PN	Haliasos et al [85]	47(56 PN's)	78.7	30.2	14.9
	Shah et al [86]	50	70	24–60	12(24 months)
	Freemont and Millac[87]	26(43 PN's)	97	26.5	18(12 months) 52 (24 months)
	Murali and Rovit[88]	40	79	Up to 60	12.5 (24 months)
CT	Zakrzewska[89]	29(83 CT's)	72	Up to 12	37(12 months)
AI	Grant [90]	331	79.7	13.6	NA
	McLeod and Patton [91]	49(278 inj)	90	11	NA
	Shah et al [92]	100 (250 inj)	86	10–56	14
	Fardy et al [93]	68	NA	13	NA
GI	Erdem and Alkan[94]	157	98	48	38
	Wilkinson [95]	18(60 inj)	87	9	63(12 months)
BI	Piovesan et al [96]	13	100	2	NA
	Zu´n˜iga et al [97]	12	100	2	NA
	Borodic and Acquadro[98]	11	73	2–4	NA

Abbreviation: PN peripheral neurectomy, AI alcohol injection, CT cryotherapy, GI glycerol injection, BI botulinum injection, N patient number, inj injections, FU follow up, IPR immediate pain relief, PFD pain free duration, IO infra-orbital, IA inferior-alveolar, LB long-buccal, NA not available

Table 3: Success rate of percutaneous procedures

Procedure	Study	N	IPR (%)	PFD (months)	Recurrence rate (%)
PBC	Skirving and Dan [99]	496	100	80.8	19.2
	Liu et al [100]	290	91.3	18.7	5.2
	Mullan and Litchor[101]	61	97	80	20
	Kouzounias et al [102]	61	85	20	50 (21 months)
	Park et al [103]	58	92	18	16
GR	Xu-hui et al [104]	3,370	73.6	60	35
	Saini [105]	552	96	24	28 (12 months)
	Steiger[106]	122	84	59	41
	Pollock [107]	98	73	28.7	16.7
	Pickett et al [108]	97	78	20	59
RFT	Wu et al [109]	1,860	78.8	24	25 (24 months)
	Kanpolat et al [110]	1,600	97.6	57.7	42.3
	Loveren et al [111]	700	81	61	20
	Fouad[112]	312	100	12	13.5
	Tronnier et al [113]	206	NA	25	75
	Latchaw et al [114]	96	NA	53	35
	Yoon et al [115]	81	87	26	74

Abbreviation: PBC percutaneous balloon compression, GR glycerol rhizotomy, RFT radiofrequency thermocoagulation, N patient number, FU follow up, IPR immediate pain relief, PFD pain free duration, NA not available

Table 4: Success rate of open surgical procedures

Procedure	Study	N	IPR (%)	PFD (months)	Recurrence rate (%)
MVD	Tyler-Kabara et al [116]	1,918	98.2	60	25
	Barker et al [117]	1,155	98	70	30
	Sindou et al [118]	362	86	80	15.1
	Kondo [119]	279	94.8	86.1	8.3
	Bederson and Wilson [120]	246	NA	83	17
	Zakrzewska et al [121]	245	90	60	21 (60 months)
	Olson et al [122]	156	93	74	18
	Lee et al [123]	146	96.5	89	8.6
	Zakrzewska and Thomas [124]	65	NA	62	38
	Sun et al [125]	61	NA	82	18
	Mendoza and Illingworth [126]	60	NA	71	18
	Walchenbach et al [127]	58	80	71	29
PSR	Bederson and Wilson	86	83	22.8	12
	Zakrzewska et al	60	88	84	28
	Adams et al [128]	57	84.2	54	5.7
	Klun[129]	42	86	NA	49

Abbreviation: MVD microvascular decompression, PSR partial sensory rhizotomy, N patient number, FU follow up, IPR immediate pain relief, PFD pain free duration, NA not available

Table 5: Success Rate Of Stereotactic Radiosurgery

Study	N	IPR (%)	PFD (months)	Recurrence rate (%)
Kondziolka et al	503	89	50	43
Verheul JB et al	285	80	12	40 (60 months)
Maesawa et al	220	85	15.4	16.6
Kano H et al	193	72	49	53
Smith ZA et al	169	71.3	28.8	19.5 (13.5 months)
Pollock et al	117	86	8	20
Young et al	110	88	33	34
Urgosik et al	107	80.4	58	25
Rogers et al	54	89	6.7	21
Shen et al.	32	84	21	7 (12 months) 15 (36 months) 11 (58 months)

Abbreviation: N patient number, FU follow up, IPR immediate pain relief, PFD pain free duration

Of the non-epileptic drugs, the best evidence is that for baclofen for alleviating TN[80]. Clomipramine, a potent 5-HT reuptake blockade agent was compared to a less powerful 5-HT reuptake blockade agent (amitriptyline) to test the hypothesis that brain 5-HT is a mediator of pain sensation by Carasso et al[81].He concluded that clomipramine was better than amitriptyline in treating TN and also it was better tolerated. Subcutaneous sumatriptan(agonist at 5HT1B/1D)

is a more promising medication that may be useful for rapid alleviation of TN82. Intranasal lignocaine was also reported to be effective for alleviating maxillary division TN in a placebo controlled crossover study[83].

Surgical treatment review

According to the European Federation of Neurological Societies (EFNS) guidelines on neuropathic pain assessment and the American Academy of Neurology (AAN) guidelines, patients who are not benefited by the effective doses of CBZ or oxycarbazepine are the ideal candidates for surgical intervention[84].The major criterion in selection of any surgery remains the success rate. Among the peripheral procedures, the maximum immediate pain relief (IPR) and longest pain fee duration (PFD) have been observed with peripheral neurectomies (PNs). Because of associated sensory losses, PNs are less in use and their mention in current literature is progressively fading (Table 2).

Studies involving alcohol injections (AI) have reported immediate pain relief in the range of 79-90% (Table 2). However the pain free duration averaged to around a year only. Injection of glycerol is a difficult pocedure which also results in marked swelling. However, the procedure is relatively painless when compared with AI[93].Among the peripheral injections, botulinum injections have shown the most promising results as far as immediate relief fom pain is concerned (Table 2). Cryotherapy(CT) gives about half the median time to recurrence as compared to AI[93]. However, the sensory loss observed with CT is usually reversible[89].

The literature review for the percutaneous procedures suggests that more patients have been managed by radiofrequency thermocoagulation (RFT) than percutaneous balloon compression (PBC) and glycerol rhizotomy (GR); presumably because of consistently higher IPR[109-112, 115].PBC has shown acceptable results with respect to IPR and PFD with lower recurrence rates (Table 3). The IPR reported in various studies range form 85%-100%[100-103].However, the PFD of these studies show significant variation ranging from 18 months to 80.8 months (Table 3). PBC can produce significant bradycardia and hypotension during the procedure and has higher incidence of motor dysfunction. GR has both low IPR and shorter PFDs[104-109].

Open procedures provide the highest patient satisfaction rate with respect to IPR and PFD (Table 4). These procedures are the only ones targeted towards alleviating the underlying cause of TN. Despite the inherent risks of craniotomy, MVD remains a popular treatment for TN. The overall IPR for MVD is more than 90 % with PFD of more than 5 years PSR is advocated when neurovascular contact at the trigeminal root is absent (Table 4). However, partial sensory rhizotomy (PSR) results are slightly comparatively less successful than those obtained after

MVD (Table 4). Highest post-operative anesthesia and hearing loss has been reported with PSR[129, 130]. In long term analysis, MVD appears to be a cost effective modality[131-134].

In recent past, stereotactic radiosurgery (SRS) has acquired a major role in treatment of TN. Up to 90 % of the patients treated with SRS achieve an IPR, though after a latency of several days to weeks[135]. Early recurrences are common with SRS(Table 5).However, the procedure may be repeated after the recurrence. The success rate of this procedure has improved significantly with the advancements in imaging modalities.

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