

Detection of Neurovascular Compression in Trigeminal Neuralgia by high-resolution Magnetic Resonance Angiography

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DECLARATION

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Abstract

Trigeminal neuralgia (TGN, tic douloureux) refers to sudden severe paroxysms of severe lancinating pain on one side of the face involving one or more branches of the trigeminal nerve (CN V) which usually lasts a few seconds to a few minutes. Attacks of excruciating lancinating pain, which usually lasts a few seconds to about two minutes, and often triggered by stimuli such as talking, drinking, brushing teeth, shaving, chewing and touching the face but occur spontaneously. There is often a “trigger point” which elicits pain.

The cause of trigeminal neuralgia is multi-factorial, with about 10% of cases being due to local lesions such as tumors, arachnoid cysts, or a demyelinating plaque affecting the pons at the root entry zone. In 1934, an American Neurosurgeon, Walter Dandy, suggested that “idiopathic” trigeminal neuralgia might be due to compression of the fifth cranial nerve at the pons by a pulsating blood vessel based on his observations at exploratory craniotomy in a patient with TGN in whom he expected to find a tumour but instead observed arterial compression of the nerve by a looping artery and no other cause. This area where the trigeminal nerve enters the pons is referred to as the root entry zone and the theory suggests that pulsatile irritation of the nerve at the pons results in damage to the nerve and, subsequently pain. The theory was not widely accepted, even after the publication of Jannetta’s large series of surgical exploration of the posterior fossa in which neurovascular compression of the fifth cranial nerve was seen in 96% of cases of recalcitrant trigeminal neuralgia. Prior to the publication of our method and papers NVC could not be demonstrated by imaging.

Purpose

To determine whether high resolution MRI with a Time-Of-Flight Magnetic Resonance Angiographic approach could reliably depict the vascular anatomy of the posterior fossa in the region of the pons and trigeminal nerves, and determine whether neurovascular compression of the nerve (NVC) was present in TGN patients but not in controls.

Methods

High-resolution 3D MRA was carried out with the imaging volume centred over the pons in

patients with TGN, controls and patients with multiple sclerosis. Imaging was conducted in a superconducting 1.5-T magnet (Siemens Magnetom, Erlangen, Germany) with the patient positioned in the head coil. A standard sagittal localizer (250/15, [TR/TE], two excitations) yielding seven 5-mm-thick slices with a 2.5 mm inter-slice gap was obtained. An FISP 3D sequence [35/7, flip angle 15deg, 55mm slab, 64 partitions, 22 cm field of view, 256 x 256 matrix] centered axially over the pons was prescribed from the midline slice. A parallel saturation slab was placed superiorly to eliminate venous flow. The effective slice thickness and in-plane resolution were both 0.9 mm. Intravenous contrast agent (Gadopentate dimeglumine, 0.1mmol/kg) was administered to patients in whom arterial contact was not confirmed on unenhanced MRA, to delineate the veins as veins which are saturated on non-contrast MRA.

Sagittal and coronal mean-planar-reconstructions (MPRs) were constructed along with axial oblique MPRs when necessary.

Results

MR images vascular contact with the trigeminal nerve at the pons was identified in 70% of 40 nerves on unenhanced imaging in patients with idiopathic trigeminal neuralgia and in a further 15% following injection of contrast medium. Contact between the nerve and two vessels at the pons was seen in 10% of cases, and deformity of the nerve was present in 30% of cases. In the control group, vascular contact with the nerve was identified in 8% of 114 nerves. NVC was also identified in the majority of patients with TGN associated with multiple sclerosis, in whom demyelinating plaques along the trigemino-thalamic tract were absent. There was excellent correlation with surgical findings.

Conclusion

NVC of the trigeminal nerve can be reliably demonstrated in patients with TGN, most commonly by the superior cerebellar artery. Vascular contact between the nerve and an adjacent artery is not specific for TGN, occurring in 7-14% of the population although distinct differences between vascular compression in TGN and vascular contacts in asymptomatic subjects are evident. Surprisingly, NVC was also present in the majority of patients with multiple sclerosis and trigeminal neuralgia, indicating that MS must not be

accepted as the cause of TGN in symptomatic patients with an MS history.

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Finally, I would like to thank all the patients who kindly participated in the study.

DEDICATION

To my family

James and Margaret Meaney, my parents, deceased.

John Meaney, my only brother, deceased and my sister, **Mary Meaney**.

Briena Staunton, my aunt and Godmother, deceased.

Jacqueline Ann Meaney, my fabulous wife.

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ABBREVIATIONS

1.5T	1.5 Tesla
3.0 T	3.0 Tesla
7.0T	7.0 Tesla
ADC	Apparent Diffusion Coefficient
AICA	Anterior Inferior Cerebellar Artery
BB	Black blood
CBZ	Carbamazepine
CFD	Computational Fluid Analysis
CISS	Constructive Interference in the Steady State
CN IX	Cranial Nerve IX (glossopharyngeal)
CN V	Cranial Nerve V (trigeminal)
CN VII	Cranial Nerve VII (facial)
CN X	Cranial Nerve X (vagus)
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
FA	Fractional Anisotropy
FFE	Fast Field Echo
FIESTA	Fast Imaging Employing Steady sTate Acquisition
FISP	Fast Inflow with Steady state Precession
FOV	Field of view
Gd DTPA	Gadolinium Diethylene Triamine Pentacetic Acid
GRE	Gradient-recalled-echo
MIP	Maximum Intensity Projection
MIP	Maximum Intensity Projection
MPR	Mean Planar Reformat

MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MRTA	Magnetic Resonance Tomographic Angiography (same as MRA)
MRV	Magnetic Resonance Venography
MS	Multiple Sclerosis
MTS	(Magnetisation Transfer Saturation)
MVD	Microvascular Decompression
NVC	Neurovascular Compression
REZ	Root Entry Zone
SCA	Superior Cerebellar Artery
T1W	T1 Weighted
T2W	T2 Weighted
TDP	Trigeminal Deafferentation Pain
TE	Echo time
TGN	Trigeminal Neuralgia
TOF	Time-of-flight
TONE	Tilted Optimized Nonsaturating Excitation
TR	Repetition time
TZ	Transitional Zone
V1	Ophthalmic division of CN V
V2	Maxillary division of CN V
V3	Mandibular division of CN V
WSS	Wall Shear Stress
WSSR	Wall Shear Stress Ratio

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Trigeminal Neuralgia

Trigeminal Neuralgia is a disorder characterized by episodes of severe lancinating facial pain in one or more of the three divisions of the fifth cranial nerve (CN V, the trigeminal nerve)[2-14].

An individual attack, which may occur in paroxysms, usually lasts from a few seconds to several minutes or hours, but these can repeat for hours with very short intervals between attacks. In other instances, fewer attacks are experienced daily[3, 4, 9-13].

There is often a trigger area on the face so sensitive that minor stimuli such as touching or even air currents can trigger pain; however, frequently the pain occurs spontaneously without any apparent trigger. TGN severely affects lifestyle as it can be triggered by common activities such as chewing, eating, drinking, talking, smiling, putting on makeup, shaving and tooth brushing. The attacks are frequently described as having a stabbing electric shock, burning, sharp, pressure, crushing, exploding or shooting nature that may become intractable.

The pain also tends to occur in cycles with remissions lasting months or even years, and tends to worsen in frequency and severity over time. Bilateral TGN is rare (1%) and usually occurs sequentially rather than synchronously[15, 16]. Pain, localised to one division initially (most commonly the maxillary division, followed by the mandibular division and rare in the ophthalmic division), may migrate to additional branches over time or may remain stable. The severity of the pain makes it difficult to wash the face, shave, and perform good oral hygiene. The pain has a significant impact on activities of daily living and some patients live in fear of when they are going to get their next attack of pain and how severe it will be which can lead to severe depression and anxiety.

However, not all people will have the symptoms described above and there are variants of TN. One of which is atypical TGN, ("trigeminal neuralgia, type 2" or trigeminal neuralgia with concomitant pain), a more prolonged lower severity background pain described more as a burning or prickling pain rather than a shock, and which may be present for over 50% of the time.

Trigeminal pain can also occur after an attack of herpes zoster, and post-herpetic neuralgia has the same manifestations as in other parts of the body[17]. Trigeminal deafferentation pain (anesthesia dolorosa) (TDP), occasionally complicates intentional damage inflicted on a trigeminal nerve following surgical manipulation of the nerve[18-28]. Unlike classic TGN, this pain is usually constant and burning and associated with objective numbness. TDP is very difficult to treat as further interventions are usually ineffective and possibly detrimental as they may lead to further complications[20].

History of Trigeminal Neuralgia

Trigeminal neuralgia (TGN) is one of the most common diseases of cranial nerves, the most frequently diagnosed form of chronic facial pain and has a prevalence of 1-4 per 100,000 in the population. Trigeminal neuralgia as a medical entity has been known since ancient times, having been described by Arateus in the first century AD[29].

The first clear description of trigeminal neuralgia was given in 1671. The sufferer was Johannes Laurentius Bausch (1605-1665), a physician philosopher and municipal

counsellor of Schweinfurth, Franconia. In 1652 Bausch founded and became the first president of the Imperial Leopoldian Academy of Natural Sciences[29]. He suffered from what classically sounds like severe trigeminal neuralgia affecting his right maxilla and radiating into the forehead. This is described in detail in his eulogy by the secretaries of the Academy, Dr. Johannes Michael Fehr and Elias Schmidt and reported in the second volume of the publications of the Academy covering the year 1671. In this eulogy the authors give a history of Bausch's youth, his development, his merits and the foundation of the Academy[29]. They then continue:

Joh. Lauren. Bausch had suffered for four years ... from a harassing, sharp, shooting pain in his right maxilla. The pain varied in intensity. It was less at times: at others retracted deeply into the issues or even completely disappeared. However, on the 5th of November 1664 the pain was so intense that our beloved master became bedridden. Suddenly, like a lightning flash, the pain penetration his jaws and his brain. He was almost unable to speak and was incapable of taking any solid food. Scurvy complicated the neuralgia. He struggled manfully against his new ailment but could never overcome it completely. During June 1665 he could again leave his home and enjoy the fresh air. New hope of recovery seemed to appear with the beginning of fall. However, the pain returned and became worse and worse. Emaciation gradually occurred. On the 15th of December 1665 he ... expired, faithful to his Lord.

This brilliant description of major trigeminal neuralgia in a man of European fame obviously stimulated a watch for other cases. In a series of letters to Dr. John Mapleton in December 1677, the English philosopher and physician John Locke describes the experience with this condition as it affected in Countess of Northumberland, wife of the British Ambassadors to France.

.... on Thursday night last I was sent for it to my lady Ambassadice, whom I found in a fit of such violent and exquisite torment, that (though she be, as you know, a person of extraordinary temper, and I have seen her even in the course of this distemper endure very great pain with a patience that seemed to feel noe thing), it forced her to such cries and shrieks as you would expect from one upon the rack, to which I believe hers was an equal torment, which extended itself all over the right side of her face and mouth. When the fit came, there was, to use my Lady's own expression of it, as it were a flash of fire all of a suddaine shot into all those parts, and at every one of those twitches which made her shreeke out, her mouth was constantly drawn to the right side towards the right eare by repeated convulsive motions, which were constantly accompanied by her cries.... These violent fits terminated on a suddaine, and then My Lady seemed to be perfectly well, excepting only a dull pain which ordinarily remained in her teeth on that side, and an uneasiness in that side of her tongue which she phansied to be swollen on that side, which yet as I looked on it, as I often did, had not the least alteration in it ..., though it were one of her great complaints that there was a scolding liquor in her fits shot into all that half of her

tongue. She had usually a presentation of the fit by a little throbbing upon her gum of the lower jaw, where she had this summer a tooth drawn; and a like throbbing in the upper jaw just over against it.... Speaking was apt to put her into these fits; sometimes opening her mouth to take anything, or touching her gums, especially in the places where she used to finde these throbbings; pressing that side of her face by lying on it were also apt to put her into fits. These fits lasted sometimes longer, sometimes shorter, were more or less violent, without any regularity and the intervals between them at the longest not halfe an hour, commonly much shorter. At night when I was cald, I saw noe roome for anything else to be done but to endeavour to give her present ease by topical anodyne applications to those parts where guns were the first beginning of her fits appeare, which had soe good an effect that that night she had two or three howers rest together without any fits, besides some other little intervalls of sleepe. But the next day the fits returning.

Paris 22nd December 1677.

In 1677, John Locke had identified the major clinical features of TGN and the moniker “*tic douloureux*” was coined in 1756 by a French physician, Nicolaus Andre, referencing the facial spasms that may accompany the attacks. English physician John Fothergill in 1773 further defined the major clinical features of TGN and the disease is often referred to as Fothergill’s disease. His description was as follows:

The affection seems to be peculiar to persons advancing in years, and to women more than to men.... The pain comes suddenly and is excruciating; it lasts but a short time, perhaps a quarter or half a minute, and then goes off; it returns at irregular intervals, sometimes in half an hour, sometimes there are two or three repetitions in a few minutes.... Eating will bring it on some persons. Talking, or the least motion of the muscles of the face affects others; the gentlest touch of a hand or a handkerchief will sometimes bring on the pain, whilst a strong pressure on the part has no effect.

Between 1821 and 1829, Charles Bell established that the trigeminal and facial nerves had separate functions. Bells contribution allowed tic douloureux to be localized to the trigeminal nerve, which led to the ultimate evolution of the name of the disease as **trigeminal neuralgia** (TGN).

Since these earlier times reference to TGN in the literature occurred with increasing frequency although there was lack of clarity between this condition and other causes of facial pain such as that of dental origin.

A big breakthrough in the understanding of the cause of trigeminal neuralgia come in 1934, with Walter Dandy's neurosurgical observation that vessels compressing the nerve were present in TGN during posterior fossa exploration[30]. Despite his observation and the fact that he observed that the vessels might be responsible for TGN, he did not suggest that removing the vessels could be curative and MVD was not carried out for many years. It was not until 1967 with the publication of Janetta's surgical series that

NVC of the nerve as the cause of most cases of “idiopathic” TGN started to gain traction[31]. Although Jannetta widely publicized his results, acceptance of the theory was limited to a few enthusiastic physicians, notably neurosurgeons, unsurprising considering the many dissenting voices, even from within the field of neurosurgery, and the fact that examination of the neurovascular relationships of the trigeminal nerve in subjects without TGN (controls) was impossible. This was largely owing to the fact that the cranium was largely a “black-hole” prior to the introduction of CT, but CT even to this day cannot clarify the neurovascular relationships and therefore could not shed light on the subject. Even with the introduction of MRI (with its superior contrast resolution) into clinical practice in the mid 1980’s, the spatial and contrast resolution required to visualize the trigeminal nerve and small posterior fossa arteries at sub-millimetre resolution would not be available for another 10 years. Therefore, the “black-hole” of the posterior fossa neurovascular relationships remained beyond the imaging capability of even the best available modalities until the mid 90’s and the medical profession remained largely skeptical about a causative role of NVC in TGN.

As a result, for the next 2 centuries following its description, TGN has been investigated extensively by scientists and clinicians from such different fields as pathophysiology, neuromorphology, dentistry, neurology, neurosurgery, neuroradiology, and psychiatry. This was at least in part because 80-90% had no convincing identifiable cause (“idiopathic”) and therefore the patients had no natural “home” in any one specialty. This thesis provides objective imaging evidence that confirms the long-held but hitherto unproven theory that the majority of “idiopathic” cases are indeed secondary to neurovascular compression of the nerve by an adjacent vessel, usually the caudally

looping superior cerebellar artery and that acceptance of this disease as anything other than a specific syndrome with an identifiable, treatable cause is inappropriate.

Epidemiology of TGN

TGN is frequently both misdiagnosed and underdiagnosed. In 1968, Penman reported the US prevalence of trigeminal neuralgia as approximately 107 men and 200 women per 1 million people, a recurring theme in the literature where females appear to be affected approximately twice as commonly as males[10]. By 1993, Mauskop noted approximately 40,000 patients have this condition at any particular time in the US, with an incidence of 4.2-27 new cases per 100,000 per year, with an incidence of approximately 15,000 cases per year[32]. There is an estimated lifetime prevalence of 0.16–0.3% in population-based studies. In 90% of patients, the disease begins after age 40 years, with a typical onset in middle and later life and an average age of presentation of 53 years[32]. There are occasional reports of trigeminal neuralgia in the paediatric literature[33]. No geographic tendency or racial differences have been found for trigeminal neuralgia. TGN has been reported in approximately 1% to 2% of patients with multiple sclerosis and there is a higher incidence of bilateral trigeminal neuralgia associated with MS which occurs at a younger average age[15, 16, 34]. Likewise, patients who present with the disease at a younger age are more likely to suffer from multiple sclerosis[34]. Approximately 10% are associated with tumours[35-37].

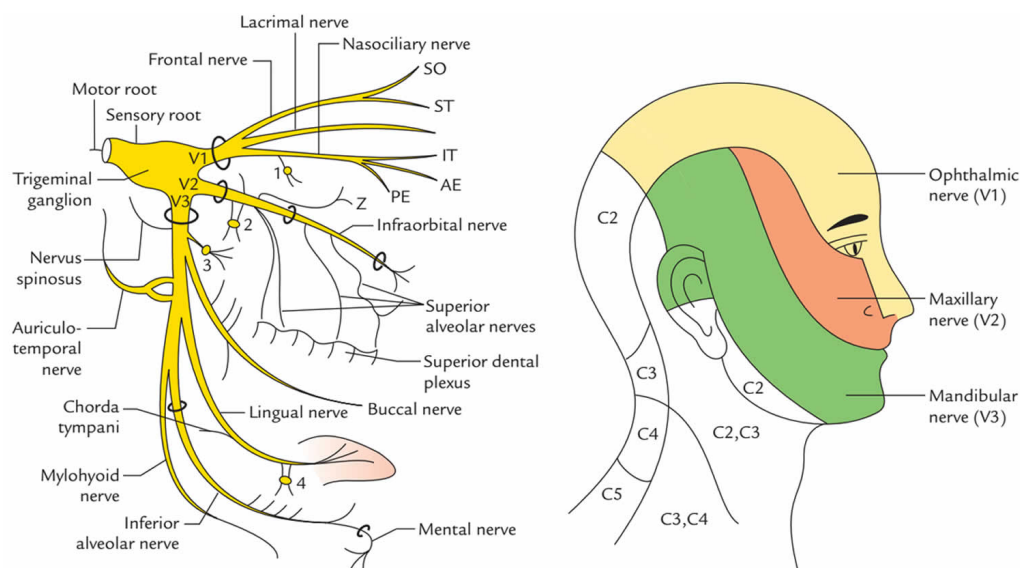
Anatomic Considerations

It is clear that lesions anywhere along the cisternal portion of the nerve and pathology within the central distribution of the nerve through the various ganglia and interconnections can cause trigeminal neuralgia but that historically identifiable lesions were identified in a minority of cases only[15, 34-40]. A review of the relevant anatomy now follows[10, 37, 41-57].

Anatomy of the Trigeminal Nerve

The trigeminal nerve is probably the most complex of the cranial nerves. Its name – trigeminal from tri-(three), and geminus (twin), three twins or thrice-twinning, deriving from the fact that each nerve has three major branches. The nerve serves both sensory (it's major function) and motor functions[4, 46, 58-60].

Fig. 1: Anatomy of the Trigeminal nerve



Sensory portion of the trigeminal nerve

The sensory portion of the trigeminal nerve transmits tactile, proprioceptive and nociceptive information from the face and mouth. Immediately adjacent to the sensory root, a smaller motor root (providing a secondary motor function) emerges from the pons just above the sensory root at the same level[46].

As the nerve is predominantly a sensory nerve, its course is described towards the pons.

The ophthalmic (V1), maxillary (V2) and mandibular (V3) branches enter the skull through three separate foramina, the superior orbital fissure, the foramen rotundum and the foramen ovale. The ophthalmic nerve (V1) carries sensory information from the scalp and forehead, the upper eyelid, the conjunctiva and cornea, the nose (including the tip of the nose, except alae nasi), the nasal mucosa, the frontal sinuses and parts of the frontal meninges. The maxillary nerve (V2) carries sensory information from the lower eyelid and cheek, the nares and upper lip, the upper teeth and gums, the nasal mucosa, the palate and roof of the pharynx, the maxillary, ethmoid and sphenoid sinuses and part of the meninges. The mandibular nerve (V3) carries sensory information from the lower lip, the lower teeth and gums, the chin and jaw (except the angle of the jaw, which is supplied by C2-C3), parts of the external ear and parts of the meninges. The mandibular nerve carries touch-position and pain-temperature sensations from the mouth. The chorda tympani, which emerges from one of its branches—the lingual nerve – at the level of the

petrotympanic fissure before joining the mastoid segment of the facial nerve

conveys afferent special sensation from the anterior 2/3 of the tongue.

After entering the skull, the three trigeminal branches immediately pass into Meckel cave (located only a few mm away from each of the three foramina transmitting the trigeminal branches), which is located within the lateral wall of the cavernous sinus, and fuse to form the trigeminal ganglion (also called the Gasserian or semilunar ganglion). The trigeminal ganglion is analogous to the dorsal root ganglia of the spinal cord, which contain the cell bodies of incoming sensory fibers from the rest of the body. From here, the trigeminal nerve exits as a solitary structure, flattened in the supero-inferior direction as it exits the cavernous sinus, with gradual transition to medio-lateral flattening towards the pons. The nerve, with an average length of 18 mm, traverses the pre-pontine cistern and enters the pons[61-63]. The CSF filled pre-pontine cistern is also the location of relevant vascular structures such as the basilar artery, superior cerebellar artery, anterior inferior cerebellar artery and petrosal vein and its tributaries.

Motor portion of the trigeminal nerve

Trigeminal nerve also serves a motor function, innervating the muscles of mastication, the tensor tympani, tensor veli palatini and the anterior belly of digastric. Motor fibers pass through the trigeminal ganglion without synapsing on their way to peripheral muscles, their cell bodies located in the nucleus of the fifth nerve, deep within the pons. The motor root is much smaller than the sensory root[46, 64].

Relevant central neuroanatomy

The trigeminal nerve enters the pons and fibers pass directly posteriorly to the spinal trigeminal nucleus, deep within the medulla, which receives information about touch, pain and temperature from the ipsilateral trigeminal nerve. The spinal trigeminal nucleus also receive sensory inputs transmitted by other cranial nerves - pain information from the facial (VII), glossopharyngeal (IX) and vagus (X) nerve. Thus the spinal trigeminal nucleus receives input from cranial nerves V, VII, IX and X[46, 60].

Trigeminal tracts

Figure 2: Anatomy of the Trigeminal Tracts

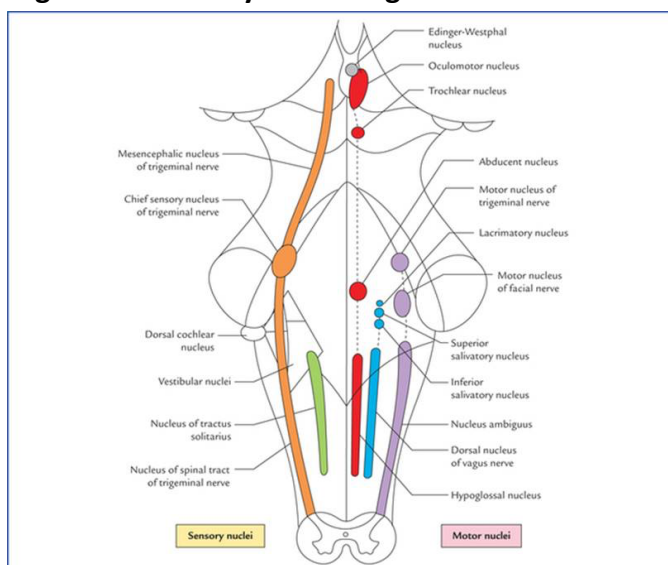


Fig 2: Courtesy of Nuclei, Functional Components and Distribution of Cranial Nerves – Textbook of Clinical Neuroanatomy. 2 ed. www.doctorlib.info. (FIG. 9.2 Surface projection of cranial nerve nuclei on the dorsal aspect of the brainstem. Motor nuclei are shown on the right side and sensory nuclei on the left side). No copyright infringement is intended.

The **sensory trigeminal nerve nuclei**, are the largest of the brain stem nuclei, extending through the whole of the midbrain, pons and medulla, caudally as far as the high cervical spinal cord. They project to the ventral posteromedial nucleus

(VPM) in the contralateral thalamus via the ventral trigeminal tract[7, 41, 44, 46, 57, 60, 64].

The nucleus is divided into three parts, from rostral to caudal in humans:

1. The mesencephalic nucleus

- The mesencephalic nucleus is involved with reflex proprioception from the periodontium and muscles of mastication, to prevent biting down sufficiently hard to damage a tooth. Nerves in the periodontal ligaments sense tooth movements and afferent fibers from muscle spindles located within the masticatory muscles are stimulated by stretching during hard jaw muscle contraction. The mesencephalic nucleus is considered as a sensory ganglion embedded within the brainstem as it is the only central nervous system structure to contain the cell bodies of first order sensory neurons and is thus neuroanatomically unique.

2. The chief sensory nucleus (main or principal sensory nucleus)

- This is a group of 2nd order neurons consisting of cell bodies in the caudal pons. It receives light touch sensation from the face and, via first order neurons of the trigeminal nerve, conscious proprioception from the jaw. Most sensory information crosses via the anterior trigeminothalamic tract to the contralateral ventral posteromedial nucleus of the thalamus but sensation from the oral cavity travels to the ipsilateral thalamic ventral posteromedial nucleus via the dorsal trigeminothalamic tract.

3. The spinal trigeminal nucleus

- This medullary nucleus receives information from the ipsilateral face (crude touch, pain and temperature) but the facial, glossopharyngeal and vagus nerves also convey pain information to the spinal trigeminal nucleus. The spinal trigeminal nucleus has three parts, from rostral to caudal:
 - Pars Oralis (pons to hypoglossal nucleus) is continuous with the principle sensory nucleus of V and associated with the transmission of fine touch from the mouth and face.
 - Pars Interpolaris (hypoglossal nucleus to obex) which is associated with the transmission of tactile sensation and dental pain.
 - Pars Caudalis (obex to C2) receives nociception and heat sensations from the head

Although touch-position information from the body ends up in the ventral posterolateral nucleus of the thalamus, touch-position information from the face accesses the ventral posteromedial thalamus nucleus. From these areas, information projects to the parietal lobe primary somatosensory cortex in the postcentral gyrus where sensation is organized somatotopically.

There is also an anatomically separate (trigeminal) motor nucleus, located on the medial side of the chief sensory nucleus[64].

Vascular anatomy of the pre-pontine cistern around the trigeminal nerve:

The Superior Cerebellar Artery

The superior cerebellar arteries are the most rostral pair of infratentorial vessels, originating from the tip of the basilar artery (98%) or occasionally from the proximal posterior cerebral artery[61, 65, 66]. It arises usually as a solitary trunk but is duplicated in up to 14%[65]. From its origin in the interpeduncular cistern, the first segment of the superior cerebellar artery (interpeduncular-crural or pontomesencephalic segment) takes a lateral course from the basilar artery to reach the anterolateral portion of the brain stem), lying caudal to the emerging root of the oculomotor nerve, which separates it from the proximal segment of the posterior cerebral artery. It continues posterolaterally around the cerebral peduncle and traverses the crural (pre-pontine) cistern, continues posteriorly through the ambient cisterns where it's medial relation is the midbrain, it's caudal relation the cerebellar peduncle, and passes laterally over an overlapping cuff of cerebellum[61, 65, 66].

As the artery passes posteriorly and caudally, in most patients (>85-90%) it does not make contact with the trigeminal nerve. In a small number of case (and notably patients with TGN), the artery passes medial to the nerve and its caudal loop gets lodged within the axilla of the nerve[1, 61, 67, 68]. When this happens, there is no way for the artery to release itself and in patients in whom pulsatile damage to the nerve results in TGN, it is only by surgical manipulation of the artery away from the nerve by interposition of an inert "spacer" that this situation can be rectified.

The Anterior Inferior Cerebellar Artery (The AICA)

The Anterior Inferior Cerebellar Arteries is the third of 3 paired arteries that supply blood to the cerebellum (the other two being the SCA and the posterior inferior cerebellar artery, the PICA). The Anterior Inferior Cerebellar Arteries arises from the basilar artery and is usually smaller than the posterior inferior cerebellar artery[61, 68]. It passes laterally and inferiorly over the pons, close to the 7th/8th cranial nerves near the internal auditory meatus. At this point the internal auditory artery gives off two branches to supply the cerebellar hemisphere, the medial of which courses along the lobule of cerebellum and which anastomoses with branches of the PICA. The second branch pursues a lateral course around the upper pole of the flocculus, across the middle cerebellar peduncle and then to the superior and inferior semilunar lobules of the cerebellum to anastomose with branches of the SCA and PICA[69].

With atherosclerotic elongation that occurs with age, and with deviation from the expected anatomical course for whatever reason (e.g. anatomical variation) the SCA and AICA can edge ever closer to the trigeminal nerve. The fact that the normal course of the anterior inferior cerebellar artery is more remote from the trigeminal nerve than the normal course of the SCA explains why the SCA is more commonly responsible for NVC in TGN than the AICA.

Superior Petrosal Vein

The superior petrosal vein (Dandy's vein) is part of the venous drainage system in the posterior cranial fossa, draining the anterior aspect of the cerebellum and brainstem. Unlike the arteries, the petrosal venous system is a venous plexus

with inconstant anatomy. The superior petrosal vein drains into the superior petrosal sinus, a dural venous sinus that empties into the cavernous sinus[58].

Neurovascular Compression Syndromes

A neurovascular compression (NVC) syndrome is a disorder caused by compression of cranial nerves by adjacent blood vessels, most commonly an artery. The most common neurovascular compression syndrome is trigeminal neuralgia (TGN). Other NVCs include hemifacial spasm (secondary to compression of the facial nerve, cranial nerve VII) and possibly vestibulocochlear neuralgia (cranial nerve VIII), glossopharyngeal neuralgia (CN IX) and tinnitus[70-75]. NVCs may coexist with one another[76].

Definitions: Neurovascular “contact” versus neurovascular “compression”, the Root Entry Zone, the Transitional Zone and the “axilla”

Because the narrow CSF space is traversed by cranial nerves and blood vessels, especially in the prepontine cistern, contact between vessels and nerves are common but despite this, NVC syndromes are extremely rare. The prevalence of TGN is estimated at around 1-3:10,000 of the population whilst contact between the nerve and an adjacent artery (almost always the superior cerebellar artery) is present in 7-15% of the asymptomatic population[1, 2, 68, 77].

Therefore, the term “contact” is used when there are no symptoms whereas the term “compression” is used in patients with TGN (notwithstanding the fact that they may appear identical).

The type of neurovascular contact is important in determining whether a neurovascular contact results in symptoms. Arteries are much more likely to cause

symptomatic NVC syndromes and can induce focal demyelination within the nerve as a result of higher pressures and greater pulsatility during each cardiac cycle, veins less so[71, 78-82].

Also, the location of the neurovascular contact along the nerve is a critical factor. It is believed that central myelin is more susceptible to pressure effects than peripheral myelin[52, 83]. At some point along the nerve, central myelin gives way to peripheral myelin and it is believed that this transitional zone (TZ, defined as the junction between central and peripheral myelin) has increased mechanical vulnerability to local trauma. The TZ occurs at a different location on each cranial nerve but for the trigeminal nerve is no further along the nerve than its midpoint[84-86].

Transition from central to peripheral myelination of the trigeminal nerve:

Significance of the Transitional Zone (TZ) and Root Entry Zone (REZ)

At some point along the cisternal portion of the nerve (i.e. that part suspended in CSF between the REZ and the cavernous sinus), there is a transition from “central” to “peripheral” myelin. This point is called the transition zone and is regarded as being within 5mm of the entry point of the nerve (REZ) in almost all individuals. Its significance lies in the fact that there is increased mechanical vulnerability at this location, which is of particular interest in the context of symptomatic NVC syndromes such as TGN. At the transitional zone, the insulating sheath surrounding the axons transitions from that derived from oligodendrocytes (i.e., central myelin) to that derived from Schwann cells (i.e., peripheral myelin). Although the transition zone is neither visible to the operating surgeon nor to the radiologist on high resolution imaging, it can be clearly defined pathologically in excised nerves or in autopsy specimens. A histologic study found that the maximum observed length of the centrally myelinated segment was 48% of the cisternal segment of the trigeminal nerve[52, 57]. This metric is particularly useful because the entire cisternal portion of the nerve is well appreciated on MR images, and, by dividing the cisternal segment of the trigeminal nerve into posterior and anterior halves, clinicians can determine whether any encroaching blood vessels are likely to fall on the central myelin (posterior half, where NVC is thought to be important) or peripheral myelin (anterior half, where NVC is thought to be less relevant).

The length and location of the TZ varies between cranial nerves, with the

vestibulocochlear (CN VIII) having a TZ located more distally along the nerve comparison with the Trigeminal (V), Facial (VII), and Glossopharyngeal (IX) nerves[48, 87].

The Root Entry Zone (REZ) and Transitional Zone (TZ)

The term “root entry/exit zone” (REZ) is a vague term used in the context of NVC syndromes. In some publications, it is often used as a synonym for the TZ, whereas in other publications, the term “REZ” is used to define the portion of the nerve that includes the TZ, the central myelin root portion, and the adjacent brain stem surface. Although this author and his co-workers favour the latter, it must be appreciated that as the TZ cannot be defined by gross inspection either by the surgeon or radiologist, the length of the REZ is uncertain, however, for practical purposes is regarded as the part of the nerve (several mm) closest to the pons. Strictly speaking the TZ is the more relevant and vulnerable anatomic structure, but as it cannot be identified, the more practical term REZ is used[7, 16, 22, 26, 57, 78, 79, 81, 86, 88-96].

The “Axilla”

The trigeminal nerve also has unique anatomy that lends itself to significant compression, namely, an “axilla” (the angle between the pons and trigeminal nerve) in which a vessel (almost always the superior cerebellar artery) can become lodged as a result of atherosclerotic vessel elongation during life[1, 77]. Because of the narrow angle between the nerve and the pons, once the artery impacts on the axilla, it can only be dislodged by surgical intervention. We believe that the responsible vessel gets “jammed” into this angle (usually by bad luck as a result of caudal looping

of the superior cerebellar or cranial looping of the anterior inferior cerebellar artery) and that once this occurs there is simply no way out and that it is the constant pulsatile irritation of the nerve at this area that results in nerve damage and ultimately trigeminal neuralgia.

Another factor is that owing to the nature of surgical dissection, the relationships of the compressing vessels to the trigeminal nerve may be altered during posterior fossa exploration, so when the surgeon refers to vessels in the “REZ”, correlation with imaging may be imperfect owing to alteration in relationships during surgery. Thus, the concept of the “axilla” is a much more practically relevant and important concept.

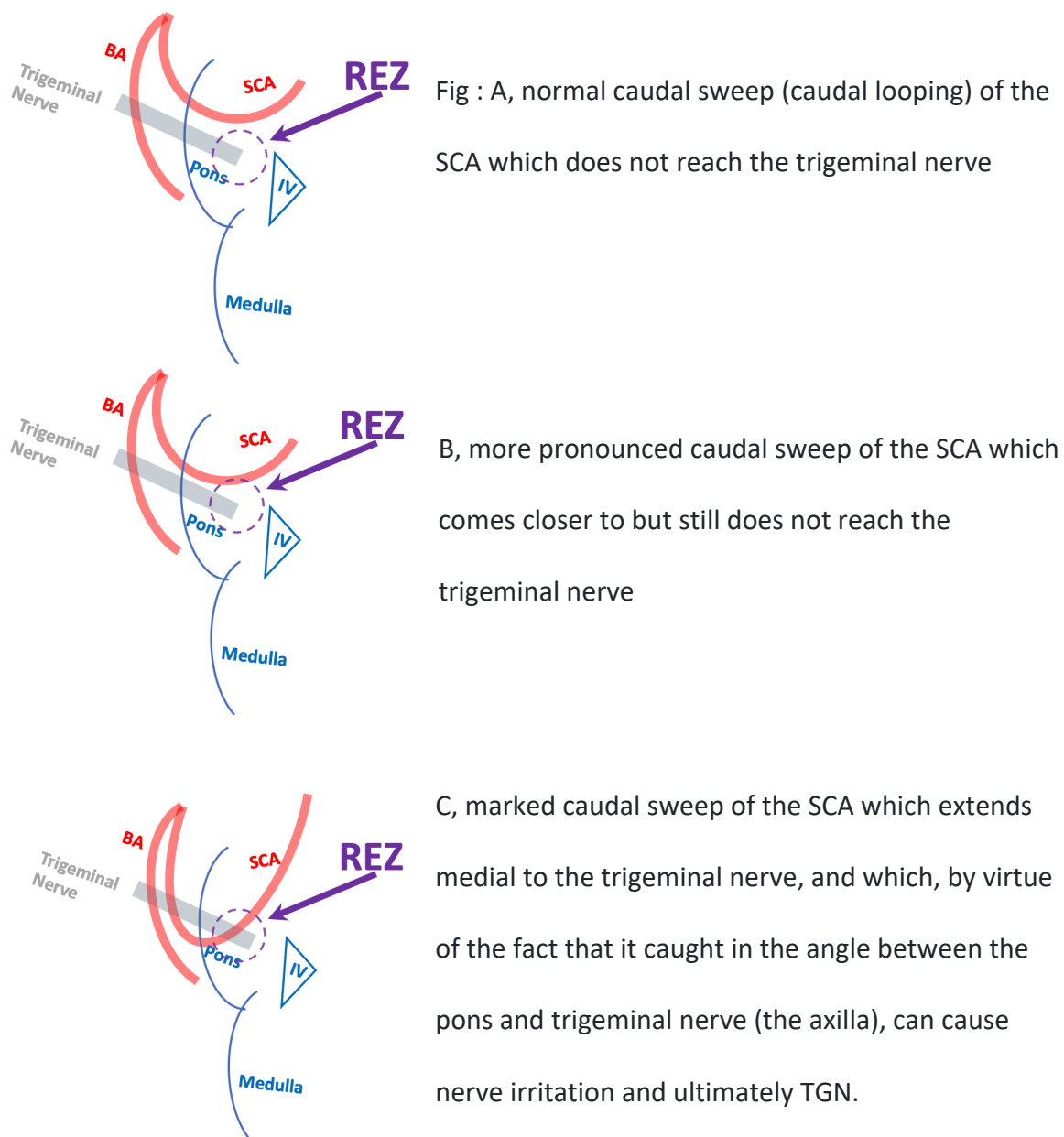
Why do arteries become lodged within the axilla

It is accepted that elongation of the SCA occurs as a part of the generally increasing atherosclerotic elongation of arteries that occurs with age[65, 97]. Because of the location of the trigeminal nerve caudal to and posterior to the origin of the SCA which under normal subjects describes a caudal loop, atherosclerotic elongation of the artery with age results in the artery edging ever closer to the nerve. In many instances the artery passes along the lateral side of the nerve and adjacent pons and does not contact it. In other instances, the artery simply makes contact with the nerve along its superior aspect but again does not have any effect on the nerve[67, 80]. However, in a small number of instances the artery becomes lodged in the axilla and which in a subset of patients leads to TGN[1, 77]. A vessel simply sitting on the nerve would probably slide off the nerve during systolic motion, whereas this could not happen with nerve impaction in the axilla. However, we emphasize that it is the

location of the artery in the axilla/REZ per se that leads to symptoms, and although this normally occurs as a result of atherosclerotic elongation, it can also occur within normal arteries in young subjects simply as a more caudal sweep of the artery than occurs in most subjects.

This is shown graphically in the following diagram.

Figure 3:– Neurovascular relationships of the Trigeminal Nerve



Pathogenesis of trigeminal neuralgia

Theories of genesis of TGN must account for the observation that lesions at multiple discrete anatomically separate sites, for example neurovascular compression of the nerve outside the brain (peripheral cause) and demyelinating plaques at numerous different sites along the trigeminal pathway in multiple sclerosis (central cause) are implicated in trigeminal neuralgia[53, 57, 84-86, 88].

The most compelling explanation emphasises peripheral aetiology with central structures being involved in pathogenesis[7, 57, 85, 86]. That is, trigeminal neuralgia occurs in individuals when disease or irritation of the trigeminal nerve causes increased firing to the point of triggering paroxysmal discharges in the trigeminal nuclei, but only in patients with central nervous system susceptibility. Neurovascular compression (typically by the superior cerebellar artery) causes chronic nerve irritation leading to focal demyelination of nerve fibers which then start firing ectopically. Histologically, focal demyelination, axonal atrophy or hypertrophy, and damage to both Schwann cells and peripheral myelin around the transition zone, have been described in the REZ resulting from vascular compression. In order to reconcile these changes with the paroxysmal nature of the pain which is so characteristic of the condition, it is proposed that partially damaged neurons at the TZ trigger are hyperexcitable, making them prone to bursts of spontaneous activity which is facilitated by the physical proximity of the neurons to the nerve root compression site. Increase in post-trigger neuronal activity recruits additional neighborhood neurons leading to a rapid accumulation of electrical activity, which can be amplified by ephaptic interaction along neurons surrounded by damaged myelin sheath within nerve fibers which are therefore at closer range[52, 57].

Support for this comes from the therapeutic relief provided by carbamazepine, baclofen, and phenytoin, which act centrally and depress excitatory synaptic transmission in the spinal trigeminal nucleus which could serve to prevent paroxysmal discharges in this nucleus, and which might be the mechanism by which the drugs prevent attacks, regardless of cause[6, 98, 99]. The finding that carbamazepine, baclofen, and phenytoin also markedly facilitate the segmental inhibition of interneurons in the spinal trigeminal nucleus (a negative feedback type of inhibition), suggests another way in which these drugs may prevent paroxysmal discharges in this nucleus[6, 100-102]. Facilitation of this negative feedback mechanism could serve to dampen the response of the trigeminal nucleus to abnormally increased firing of the trigeminal nerve without affecting the response to normal firing. This would prevent the paroxysms of tic douloureux without impairing normal sensory perception. If this is the case, one may also speculate that a failure of this negative feedback mechanism may be part of the pathogenesis of trigeminal neuralgia[57, 84].

Reasons why NVC as a cause of TGN was not widely accepted

Many of the reasons why NVC was not widely accepted as a cause of TGN related to the fact that this small corner of the posterior fossa remained the exclusive domain of a tiny number of neurosurgeons practicing MVD and remained a “black hole” for cross-sectional imaging such that the neurovascular relationships of the trigeminal nerve in TGN and in controls could not be established.

In a nutshell:

1. Visualization of the relationships of the trigeminal nerve to the posterior fossa vessels remained the domain of a tiny number of neurosurgeons, and even amongst neurosurgeons there was some scepticism as to the relevance of the finding and significance of NVC[103-105]. The relationships of the vessels to the nerves could only be explored “in-vivo” on the symptomatic side in patients with TGN undergoing MVD. Also, owing to ethical and other issues related to the manipulation required to expose the nerve and operation length, clarification of the neurovascular relationships of the trigeminal nerve in patients undergoing posterior fossa exploration for other reasons was not possible.
2. Historically, the excellent cure rate from MVD was questioned by dissenters who pointed to the high incidence of surgical rhizotomy and potential damage to the nerve by the operating neurosurgeon as accounting for symptomatic improvement or cure[22, 104]. Essentially skeptics were saying “aren’t vessels present contacting/compressing the nerves in all subjects?”
3. Prior attempts to clarify neurovascular relationships of the trigeminal nerve in asymptomatic controls primarily came from post-mortem data, either without

any attempts to compensate for brain and vessel sagging post-mortem or with an attempt to better simulate in-vivo conditions by perfusion of the posterior fossa arteries at physiological pressures[67, 80]. A single paper reported the caudal looping pattern of the SCA on catheter angiography in patients with TGN although the position of the nerve could only be inferred from anatomical landmark reference (highly unreliable owing to absence of soft tissue landmarks on this projection technique) was published[97]. Clearly, these methods were highly flawed.

4. Prior to our first paper reporting the neurovascular relationships of the trigeminal nerve in TGN and in normal controls, no cross-sectional high-resolution 3-D study had reported the relationships in-vivo[1, 77, 106]. This was because historically no imaging modalities were able to image the brain, cranial nerves and posterior fossa at required resolution, and even with the introduction of computed tomography (CT) into practice in 1972, poor nerve-vessel-CSF contrast confounded by artefact from the dense petrous temporal bones precluded interrogation of the relevant area. Even with the introduction of MRI several years later, the high-resolution techniques required to deliver sub-millimetre tissue resolution of the nerves and small posterior fossa arteries did not come for another 10 years[107-110].

Possibility of introducing a high-resolution imaging method to detect NVC in TGN:

Understanding flow effects and principles of Magnetic Resonance Angiography

Unlike X-ray angiography where injection of a contrast agent is required to outline a vessel, magnetic resonance angiography generates images of blood vessels by manipulation of signal within the vessel lumen and by reprojecting the high signal voxels representing the lumen into a 3 dimensional image by applying a maximum intensity projection algorithm (MIP) to give a conventional “angiographic” type image[107-110].

Although contrast in conventional MR images depends principally on image parameters such as longitudinal relaxation time (T1), transverse relaxation time (T2), and proton density (PD), MR images are also sensitive to flow related effects[110]. Essentially non contrast MRA uses these flow-induced signal variations in the lumen, regarded as a nuisance and source of artefact on spin-echo imaging, to generate an “angiogram”, albeit acquired non-invasively and which furthermore can be used to obtain quantitative information about blood flow velocity and direction (not relevant to this thesis)[110].

Requirements for MR imaging of NVC

In order to devise an imaging test that would allow demonstration of NVC in TGN, we propose that the following conditions must be met:

- Clear definition of the nerve from its exit/entry point to/from the pons.
- Clear definition of the small posterior fossa arteries, notable the SCA and AICA.
- Clear differentiation of the nerve from the CSF and adjacent arteries.
- High spatial resolution (minimum of 1mm isotropic voxels).
- Ability to reconstruct images in multi-planar reformat along the nerve (axial oblique and sagittal) and across it (coronal).
- Ideally, the ability to differentiate arteries from veins.

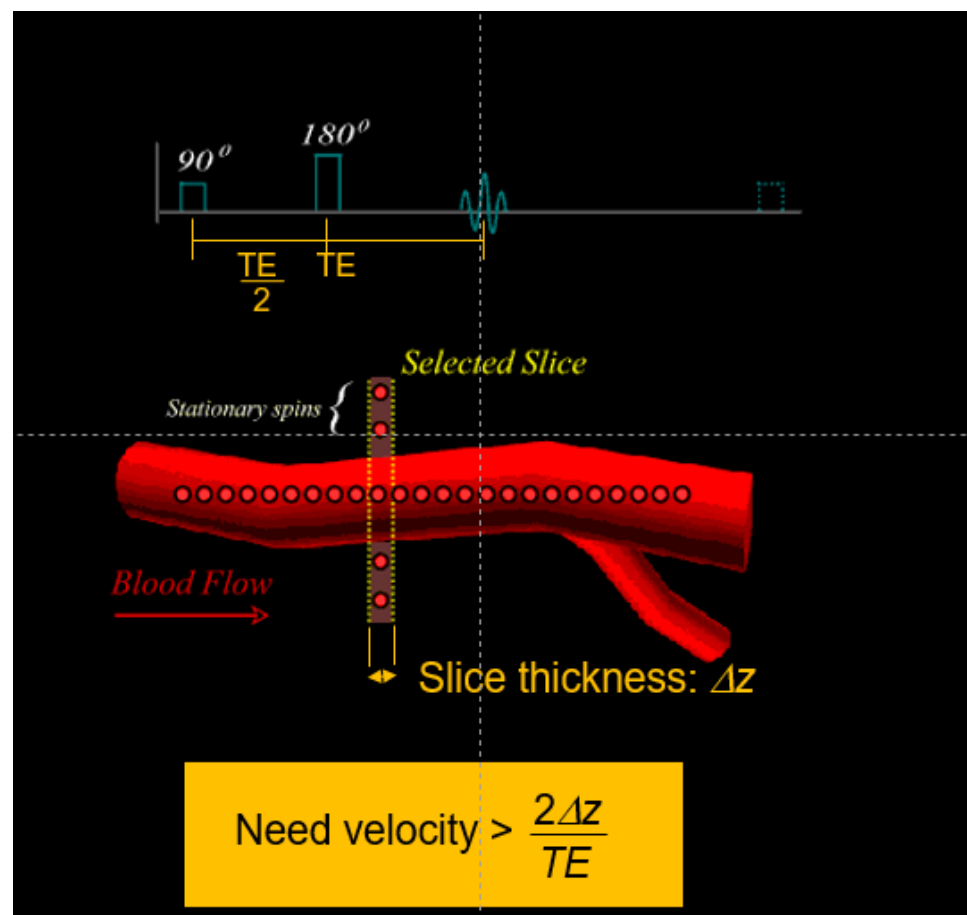
Black blood and Bright blood MRA: Concept of spin washout versus flow related enhancement

Black blood effect

Basically blood flow appear either as bright or dark on MRI images depending on whether spin-echo or gradient-echo acquisitions are acquired. A basic spin-echo pulse sequence (see fig) uses 2 slice selective radiofrequency pulses as shown in the diagram above (90 degrees and 180 degrees pulses). A signal is only produced if the tissue within a voxel receives both pulses. Motion of the blood through the image slice during the time $TE/2$ between the two pulses causes “washout” of the blood excited by the 90-degree pulse from the image slice so that it does not receive the

180-degree pulse. This washout maybe partial for slow venous blood, resulting in only a partially reduced signal, or may be total, as with faster arterial blood resulting in total signal loss (black blood effect). This explains why blood flowing at a high velocity perpendicular to the imaging plane produces a lower signal than the surrounding stationary tissues, when spin-echo pulse sequence are employed and is the basis of the so-called “black-blood” effect, the image appearance of which is referred to as a flow void (or signal void) which is a characteristic of spin-echo imaging. It's also called a washout effect and it is most pronounced on T2 weighted imaging because of the long echo times used.

Figure 4: Basis of Spin-echo (Black Blood) MRA:



In spin echo black blood MRI, blood flowing through the imaged slice in a time less

than $TR/2$ is not affected by both the 90-degree and 180-degree slice selective pulses, and will appear dark (image courtesy Dr. Gerard Boyle, Medical Physicist, St. James's Hospital, Dublin).

Bright blood effect

Although the signal of blood flowing rapidly out of the measured slices reduces with spin-echo sequences, when gradient-echo imaging is employed the opposite effect occurs and spins flowing into the slice generate a higher signal than the surrounding tissues. This effect is referred to as inflow enhancement and is the basis of time-of-flight magnetic resonance angiography (TOF MRA). With gradient-echo pulse sequences, blood flowing at a high velocity perpendicular to the imaging plane produces a higher signal than the surrounding stationary tissues. With gradient echo (GRE) techniques (see Fig), a single RF pulse is repeated at each TR which causes the tissue within the imaging slice to become partially saturated. With successive RF pulses rapidly delivered (as occurs with TOF MRA), recovery of stationary tissues is incomplete when the next RF pulse is delivered and the available signal emanating from the stationary tissues is reduced (this is good as the stationary tissues don't then get reprojected by the MIP algorithm). However, for blood vessels, motion of the blood through the slice replaces the partially saturated blood with fresh blood that has not been excited, yielding bright vessels. The bright depiction of flowing blood, however, requires the use of flow rephasing techniques called gradient motion rephasing (GMR) in order to overcome the effects of spin dephasing due to transverse magnetization. It is the combination of bright vessels as a result of flow-

related enhancement (time of flight effect) coupled with reduced background (brain tissue) from rapid RF pulsing, that facilitates extraction of the arteries into an “angiogram” by application of a Maximum Intensity Projection (MIP) algorithm.

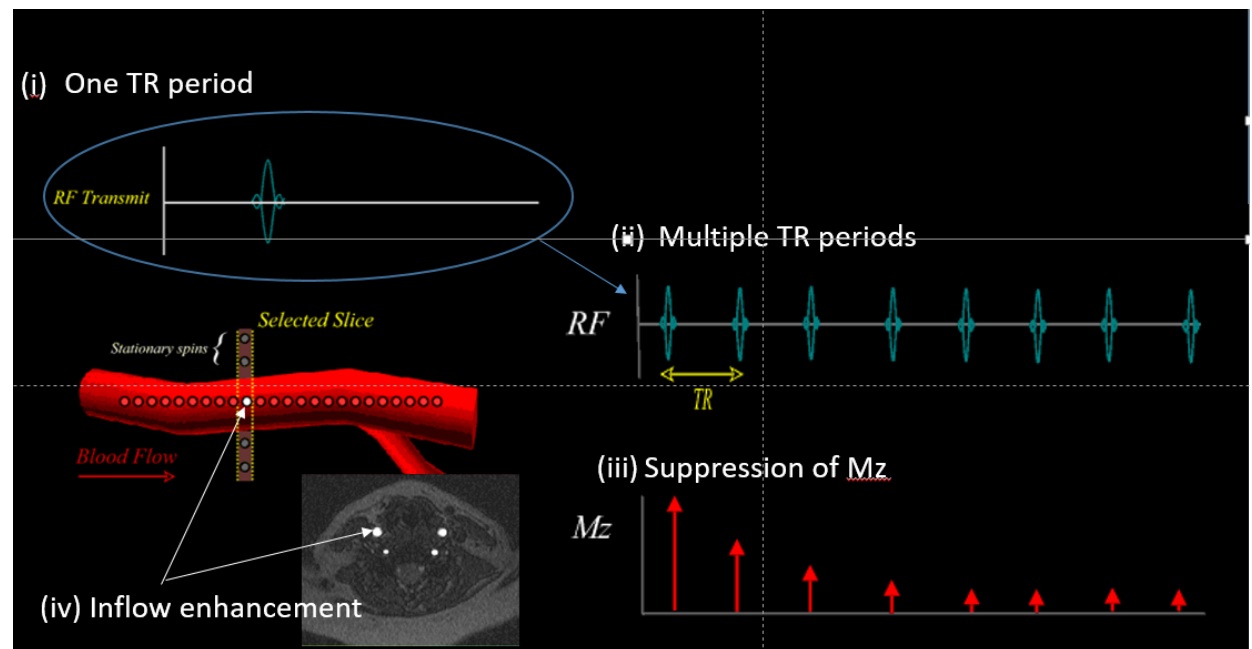


Fig 5: TOF MRA:

In TOF a gradient echo (GRE) sequence is used. (i) In a single TR period in a GRE, a single slice selective excitation pulse is applied, (ii) Any real sequence will consist of many TR periods, and over the initial RF applications (iii) longitudinal magnetization of spins in the slice will be suppressed, and recovers somewhat by the end of each TR, eventually settling to a reduced, steady level. (iv) The effect on stationary tissue is to suppress signal, whereas blood flowing into the slice ‘fresh’ is exposed to a lower number of excitations and will appear hyperintense (image courtesy Dr. Gerard Boyle, Medical Physicist, St. James’s Hospital, Dublin).

2 candidates for imaging of the neurovascular anatomy at isotropic high resolution

Table 1: Black blood versus bright blood MRA

	TOF MRA (Bright blood)	Dark Blood (T2W or balanced sequences)
CSF	Dark	Bright
Nerve	Intermediate (between CSF and artery)	Low (not as dark as nerve)
Arteries	Bright (brightest structure on the images)	Dark (darkest structure on the images)
Veins	Yes with Gadolinium	Yes (same signal as arteries)
Differentiate arteries from veins	Yes (veins visible post- Gad)	No (with difficulty)
Reproject vasculature	Yes (MIP)	No
Isotropic reformats	Yes	Yes
Time efficiency	Good	Good

MRI sequence employed

TOF MRA, performed with a heavily T1W spoiled gradient-echo sequence, was chosen for this study owing to the perceived advantages and institutional experience and bias[107, 108, 110].

Advantages of TOF MRA

Time-of-flight MRA is one of the oldest MR angiographic methods and traces its origins back to 1988[107]. With TOF MRA, a fast spoiled-gradient-echo acquisition is employed. The repetition time, TR, is optimized to allow maximal inflow and a time of approximately 35msec is appropriate. TOF MRA is a cross-sectional method that demonstrates arteries as high signal structures owing to “inflow”. The blood vessels are extracted from the 2D images into a 3D reprojection by applying a Maximum Intensity Projection (MIP) algorithm which extracts all pixels with a value substantially greater than background (more than 2 standard-deviations greater). Obviously the greater the contrast between the vessels and the brain parenchyma (and nerves), the better the reprojected MIPs of the intracranial vasculature. The rapid RF pulsing results in “saturation” of the brain parenchyma although the outline of the parenchyma and nerves remain clearly visible. Many advances in intracranial TOF MRA such as TONE (tilted optimized non-saturating excitation) and MTS are based on methods for eliminating the background (brain and cranial nerve) signal although this would be counterproductive for evaluation of NVC syndromes[110]. As blood flow within arteries is primarily directed towards the head, and venous signal towards the foot, a superior saturation slab is placed to eliminate venous signal. In reality, veins, particularly the small petrosal veins and tributaries in the pre-pontine cistern, become saturated and therefore invisible because of the rapid RF pulsing, an unexpected but welcome advantage which gives arteriography

(without venography).

TOF MRA and flow patterns within different territories

Since TOF MRA is based on complex flow phenomena, physiological conditions of flow in vessels differ throughout the body and have a large impact on the applicability of the method. However, within the brain, advantageous conditions such as disposition of the arteries of the posterior fossa over a short craniocaudal extent (which allows use of a small imaging volume with less saturation), nearly laminar flow, constancy of flow throughout the cardiac cycle (making ECG triggering unnecessary which would complicate patient set-up and prolongs scan time), and high velocity of arterial flow (50-100 cm/sec) assure excellent “inflow” and therefore good vessel background contrast which in turn facilitates moderate acquisition times. Consequently, TOF MRA has proven to be a robust and versatile method for noninvasive imaging of brain vessels, particularly around the circle of Willis (but is less effective for imaging arteries outside the brain e.g. the peripheral circulation where slower flow, marked reduction in flow during diastole and long region of interest negatively impact). The major limitations of time of flight MRA therefore are less pronounced within the brain, making it ideal for intracranial MRA.

Intracranial MR Venography (MRV)

Recall that TOF MRA is optimized to capture fast flow (arterial) but that veins are also present in the imaging volume but are rarely visualized on (unenhanced) MRA. The reason for this is twofold; firstly, as blood flow velocities are much lower in veins

they become rapidly “saturated” and therefore indistinguishable from CSF signal, secondly; a saturation pulse is placed cephalad to the imaging volume to further suppress signal from veins. This has an added advantage as it eliminates signal within larger venous structures (the major venous sinuses) in which pulsatile flow occurs and which can result in substantial artefact propagated in the phase-encoding direction. However, it is crucial to depict posterior fossa veins as veins and not arteries are the cause in 10-15% of cases. Even if the saturation pulse, designed to suppress flow from superior to inferior (venous flow) is eliminated, the small veins of the posterior fossa are poorly demonstrated owing to saturation effects as a result of slow flow.

Visualization of the veins can be easily achieved by repeating the acquisition after injection of a standard dose of a Gadolinium contrast agent (Magnevist, Schering/Berlex 0.1mmol/kg) injected as a bolus. Given the short intravascular half-life of gadolinium (approximately 7 minutes), venous concentration will be sufficiently high for the duration of the scan (or at least for the contrast-defining central lines of k-space) to deliver exquisite venous depiction[108, 111].

Parameter optimization for TOF MRA

The maximum slab thickness should be kept as small as possible and matched the size of the vessel region of interest. Selection of the TR is a trade-off between keeping saturation effects to a minimum (mandates longer TRs) and keeping scan times acceptable (mandates lower TR), in practice TR=35msec is a good compromise and has been validated in prior studies of visualization of the intracranial arteries

with TOF MRA. An out of phase echo time was used (6.9msec).

Flip angle also affects intravascular signal with higher flip angles giving better signal at the entry side of the imaging volume but at the expense of more rapid saturation of blood within the volume and therefore reduced conspicuity of vessels closer to the exit side of the volume. Smaller flip angles give lower signal at the entry side which progressively diminishes throughout the imaging volume. A flip angle of 15-degrees was chosen, again as a compromise and again validated in prior studies of visualization of the intracranial arteries with TOF MRA. A novel software advance, tilted optimized non-saturating excitation (TONE) is a method that gives an acceptable tradeoff and varies the flip angle over the slab to minimize saturation (uses a lower flip angle at the entry site and a higher angle at the exit side) to boost signal, and was employed. Bandwidth is optimized based on other parameters[108-110, 112].

Materials and Methods:

The study group consisted of four different cohorts:

Group 1: Patients with TGN in whom MVD was planned and in whom MRA was performed[1].

Over a 12-month period, 42 patients with severe trigeminal neuralgia who were unresponsive to conservative treatment were referred to our institution for imaging. Patients with conditions known to cause trigeminal neuralgia independent of neurovascular compression were excluded (two patients with multiple sclerosis and one with a large tumour deforming the trigeminal nerve in the cerebellopontine angle). One patient had bilateral trigeminal neuralgia, giving a total of 40 nerves within the group of symptomatic patients.

Group 2: Controls[1]

A total of 114 nerves were examined in asymptomatic control subjects, 38 contralateral to the side of pain in the symptomatic patients, and 76 nerves in 38 age- and gender-matched volunteers. There was no gender predilection in either group. The average age was 63 years among the symptomatic patients (median = 55) and 60 years among the control group (median = 50). The 38 asymptomatic controls were specifically recruited for the study and not undergoing MR examination for any reason other than to evaluate the posterior fossa neurovascular relationships.

Group 3: Surgical group[77]

To assess whether vascular compression of the nerve could be demonstrated preoperatively, high definition magnetic resonance tomographic angiography (MRTA) was performed in 50 consecutive patients, five of whom had bilateral TGN, prior to posterior fossa surgery. The imaging results were compared with the

operative findings in all patients, including two patients who underwent bilateral exploration.

Group 4: Patients with TGN associated with other conditions where NVC was not anticipated (Multiple Sclerosis, Charcot Marie Tooth syndrome and 2 children)[33, 77, 113]

Table 2: Details of the TGN study patients(Group 4) [113]:

	Duration of MS (Yrs)	Age	Side and Division(s)	Pathology	Treatment	Outcome
1	5	40	Right V1,V2,V3	Vessel	MVD	Pain free
2	12	54	Left V2	Plaque	CBZ	Partial control
3	25	54	Left V3	Vessel	Alcohol	Pain free
4	20	60	Left V2V3	Epidermoid tumour	Surgery	Partial control
5	36	71	Bilateral Left V1, Right V2	Single vessel left, 2 vessels right	Left – RFL Right - MVD	Died
6	25	44	Bilateral Left V3, Right V3	Vessel	Alcohol	Pain free
7	20	40	Left V1V2	2 vessels	Nerve block	Pain free

MVD = Microvascular decompression

CBZ = Carbamazepine

RFL = Radiofrequency lesion

Miscellaneous group 4 patients

One patient with Charcot Marie Tooth syndrome and 2 children, all of whom had severe TGN[33, 77].

MR Protocol

MR images were obtained with a superconducting 1.5-T magnet (Siemens Magnetom, Erlangen, Germany).

Localiser

After the patient was positioned in the head coil, a standard sagittal localizer (250/15, [TR/TE], two excitations) yielding seven 5-mm thick slices with a 2.5 mm interslice gap was obtained.

MRA

A FISP 3D (Fast Inflow with Steady-State Precession) sequence [TR 35msec, TE 7msec, flip angle 15deg, 55mm slab, 64 partitions, 22 cm field of view, 256 x 256 matrix, cantered axially over the pons was prescribed from the midline slice. A parallel saturation slab was placed superiorly to eliminate venous flow. The effective slice thickness and in-plane resolution were both 0.9 mm.

Image preparation for interpretation

The individual axial images were inspected, and, after identification of the trigeminal nerves, volume editing was done to include the trigeminal nerves, the pons, and the region of the trigeminal ganglia. If the nerve was not identified in its totality from the pons to the petrous apex where it enters the cavernous sinus on axial images, axial oblique reformats were constructed to demonstrate the entire length of the nerve on the axial images.

From these axial images, a stack of reformatted images orthogonal to the nerve, were constructed in the coronal plane, perpendicular to the midline, such that the axilla and point of entry to the pons appeared symmetric on both sides, to the greatest extent possible.

All reformats were contiguous (i.e. no gap between images).

Images were windowed to optimally demonstrate both the nerve and the high signal arteries and all images were printed to hard copy film.

Maximum Intensity Projections (MIPs)

The location of the basilar artery was identified on the source images and the vertebral and basilar arteries and their branches were edited from the entire volume by use of a cuboid sub-volume editing tool. Images were windowed to accentuate the arteries at the expense of all other tissues and a Maximum Intensity Projection (MIP) algorithm was applied with reprojection of images in the coronal (AP) plane at 3 degrees intervals from minus 45 degrees to plus 45 degrees (the mid image was in the straight AP direction) for a total of 30 images.

The exact same image presentation protocol was followed for patients who also underwent post-contrast imaging.

Image review

All examinations were reviewed by two experienced radiologists, one of whom was the applicant, who had no knowledge of the clinical details.

All images were evaluated for

- Visibility of the trigeminal nerves
- Presence of a vessel lodged within the axilla*
- Name of the artery (if present) by tracing it back to its parent artery (the basilar artery in cases of arterial compression by either the SCA or AICA)
- Cases were classified as “single” or “double” compression.
- In patients who underwent post-contrast imaging also (for venous

compression), the type of vessel responsible (if present) was also identified.

- In instances of NVC being identified on post-contrast imaging, comparison of the pre-contrast images was performed to clarify whether the vessel responsible was a vein or an artery that had been “saturated” on unenhanced MRA.
- In patients with NVC, deviation of the nerve from its normally straight course, distortion of the nerve, and nerve grooving were also recorded.

*The examination was regarded as positive if definite contact (no intervening CSF) could be seen between the trigeminal nerve and a vessel in the axilla (the space bounded by the trigeminal nerve laterally and pons medially). As the coronal images show the entire circumference of both trigeminal nerves on a single image, those were used as the final arbiter in all cases.

The positive examinations in both groups were reviewed by both radiologists together to determine the number and nature of the vessels involved, and all images for the presence or absence of distortion of the nerve.

The examination was repeated after injection of gadopentate dimeglumine (Magnevist, Schering AG, Berlin, Germany) in 10 of 12 patients with negative findings on the unenhanced scan, in an attempt to demonstrate veins around the trigeminal nerve at the pons and to show small arteries in which blood had become indistinguishable from adjacent brain tissue. However, two patients with normal findings on the unenhanced scan declined the injection.

Statistical analysis

The difference between the two groups regarding the prevalence of vascular contact

with the nerve at the pons was highly significant ($p < .001$, Pearson's chi-squared test), as was the difference between the incidence of deformity of the nerve ($p < .001$) and contact between the nerve and two vessels ($p < .001$).

Results:

Group 1: Patients with TGN[1]

Over a 12-month period, 42 patients with severe trigeminal neuralgia who were unresponsive to conservative treatment were referred to our institution for imaging. Patients with conditions known to cause trigeminal neuralgia independent of neurovascular compression were excluded from this group (two patients with multiple sclerosis and one with a large tumour deforming the trigeminal nerve in the cerebellopontine angle). One patient had bilateral trigeminal neuralgia, giving a total of 40 nerves within the group of symptomatic patients. A total of 114 nerves were examined in asymptomatic control subjects, 38 contralateral to the side of pain in the symptomatic patients, and 76 nerves in 38 age- and gender-matched volunteers. There was no gender predilection in either group. The average age was 63 years among the symptomatic patients (median = 55) and 60 years among the control group (median = 50).

The preganglionic segment of both trigeminal nerves was clearly seen throughout its entire subarachnoid course in all symptomatic and control nerves when the multiplanar reconstruction capabilities were used.

In the symptomatic group, a looping vessel was seen in contact with the trigeminal nerve on the symptomatic side in 28 of 30 patients on the unenhanced images. Of the 10 patients with initially normal findings in whom contrast enhanced imaging was performed, a vein was identified contacting the nerve at the pons on the symptomatic side in four instances. In two further patients a small vessel (subsequently identified at surgery as an artery in both cases) was seen. In the symptomatic group, vascular contact was by a single vessel in 30 instances and by

two vessels in four cases (10%), resulting in 38 instances of neurovascular compression in the 34 patients with positive studies. The offending vessel was the superior cerebellar artery in all cases in which a single artery was involved (Figs. 2 and 3) and a combination of the superior cerebellar artery and anterior inferior cerebellar artery in all four cases (Fig. 4) with compression by two vessels. The petrosal vein was responsible for all cases of venous contact with the nerve (Fig.). Overall, the vessels shown by MR varied between 0.9 mm and 2.7 mm. Distortion of the preganglionic segment of the nerve on the symptomatic side was identified in 30% (12/40) of patients with trigeminal neuralgia. In the symptomatic group, the site of contact between the superior cerebellar artery and nerve was superior, superomedial, or medial in all cases, with an arterial loop descending into the axilla for a variable distance. In all four cases in which contact between the nerve root and two vessels was apparent, the site of contact between the anterior inferior cerebellar artery and the nerve was inferior or medial in all cases. The pattern of venous contact was more variable, with contact around three fourths of the nerve circumference in one patient (Fig. 5), superiorly in one, medially in one, and inferiorly in the remaining case. Vascular contact with the lateral aspect of the nerve only was not encountered.

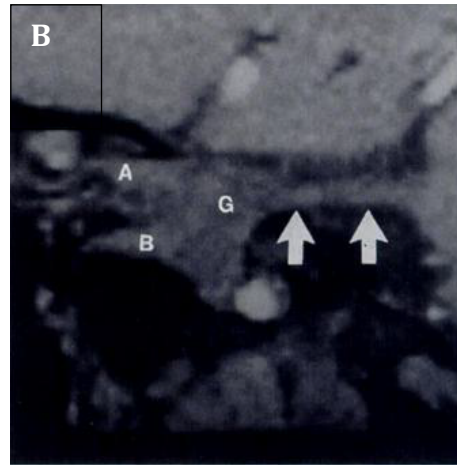
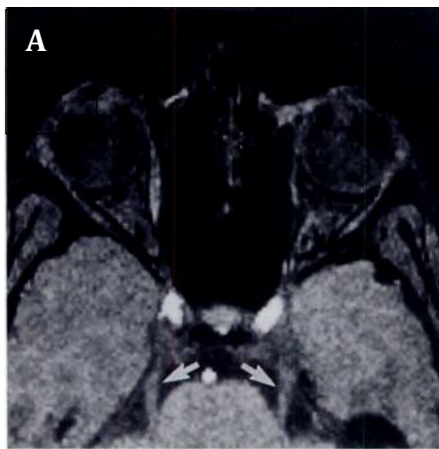
Group 2: Controls[1]

A total of 114 nerves were examined in asymptomatic control subjects, 38 contralateral to the side of pain in the symptomatic patients, and 76 nerves in 38 age- and gender-matched volunteers. The controls were specifically recruited for the study and not undergoing MR examination for any reason other than to evaluate the posterior fossa neurovascular relationships.

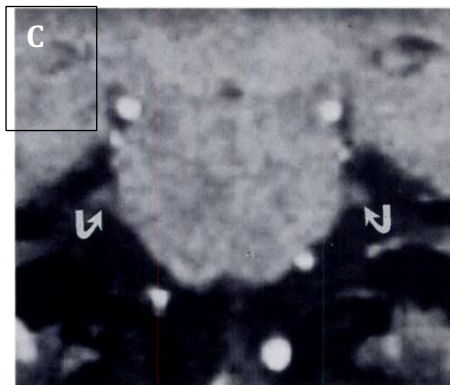
In the control group, vascular contact with a trigeminal nerve at the pons was identified in eight instances on the unenhanced images. This was on the asymptomatic side in two patients with trigeminal neuralgia and in a further six instances in the asymptomatic subjects. In one patient with trigeminal neuralgia in whom contrast enhancement was given, a further vessel was identified in contact with the nerve at the pons on the asymptomatic side. Neither distortion of the nerve by the blood vessel nor contact with two vessels was seen in any control subjects. The site of vascular contact was superior on medial in all control; subjects the superior cerebellar artery was implicated in all instances in which vascular contact was identified on the unenhanced images. In the last case in which the enhanced images revealed contact between the nerve and a vessel on the asymptomatic side in a patient with trigeminal neuralgia, the nature of the vessel was uncertain, but probably represented a vein. The pattern of vascular contact in the control subjects was identical to that seen in those symptomatic patients who had single-vessel contact without distortion of the nerve.

Fig. 6: a-d. Normal.

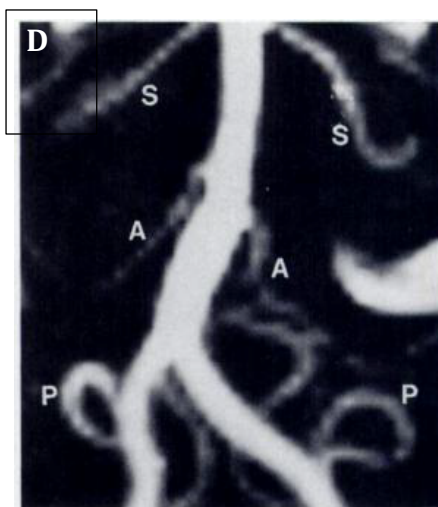
A, Axial image shows both trigeminal nerves (arrows).



B, Sagittal multiplanar reconstruction of MR Image along right trigeminal nerve shows nerve (arrows) in its entire subarachnoid course. Ganglion (G) is indicated. Note also first (A) (ophthalmic) and second (B) (maxillary) divisions of the nerve.

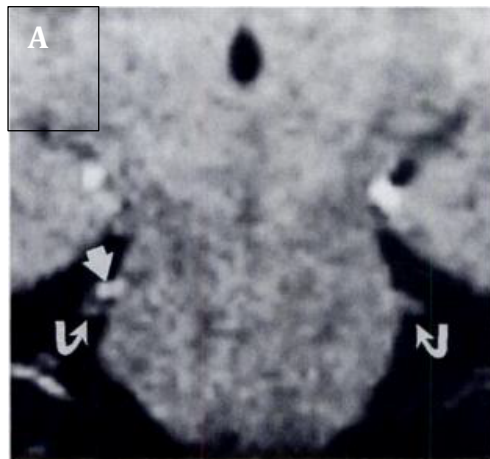


C, Coronal MR image shows both trigeminal nerves (arrows) at level of pons. Note absence of vascular contact with nerve.

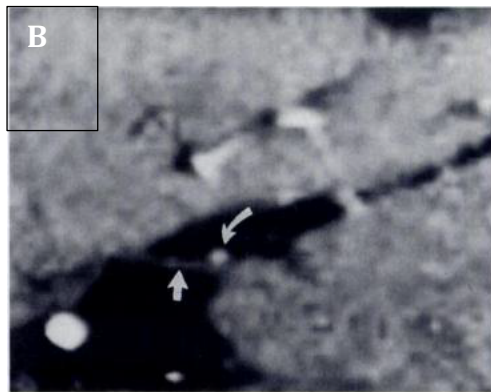


D, Maximum-Intensity-projection angiogram of posterior fossa vessels shows superior cerebellar (S), anterior inferior cerebellar (A), and posterior inferior cerebellar arteries (P) well.

Fig 7: 58-year-old woman with right-sided trigeminal neuralgia[1].

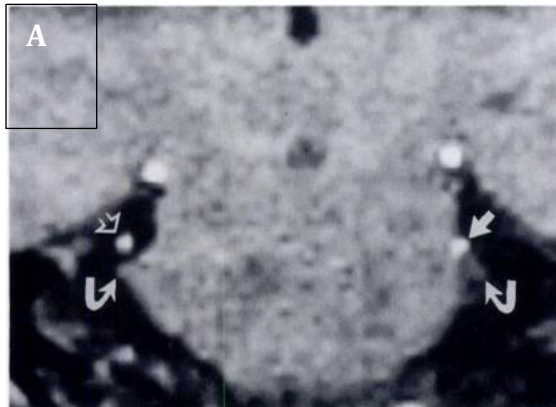


A, Coronal MR image of pons shows both trigeminal nerves (curved arrows). Note artery in contact with right trigeminal nerve at pons (straight arrow). Appearance on left side is normal.

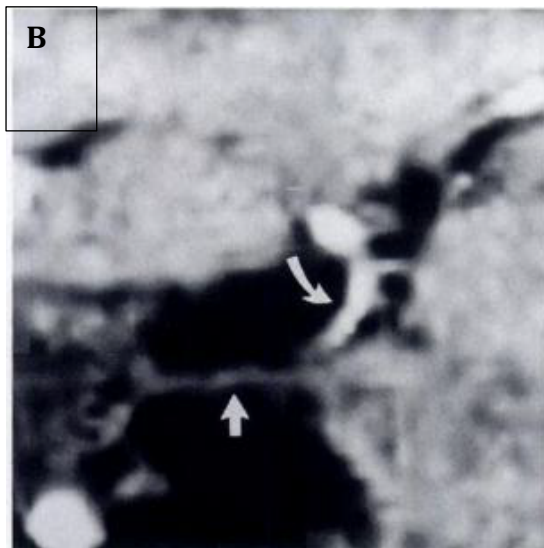


B, Sagittal MR image shows right trigeminal nerve (straight arrow) and vessel intimately in contact with the nerve at the pons (curved arrow).

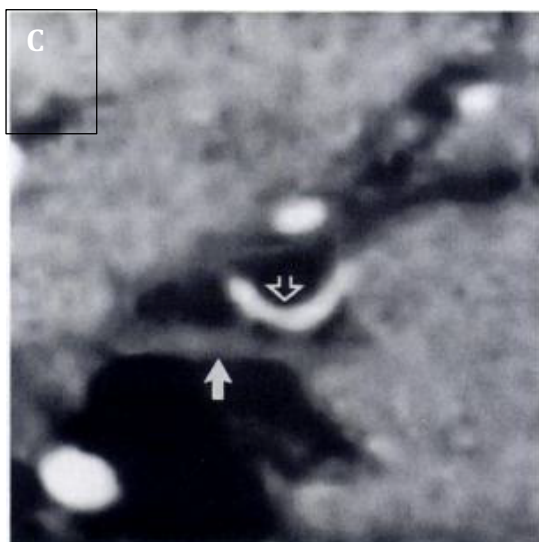
Fig 8: 37-year-old female patient with left trigeminal neuralgia[1].



A, Coronal MR image of pons shows both trigeminal nerves at level of pons (curved arrows). On the symptomatic (left) side, the superior cerebellar artery (solid straight arrow) contacts the nerve in axilla. On right side, the superior cerebellar artery (open arrow) comes very close to nerve, without actually touching it.

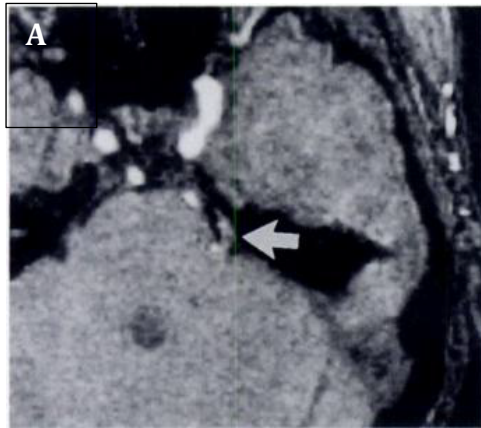


B, Sagittal image along left trigeminal nerve (straight arrow). Superior cerebellar artery (curved arrow) contacts nerve superiorly at pons. (Coronal image showed that vessel, after crossing superior aspect, passed downward to lodge in the axilla - see A.)

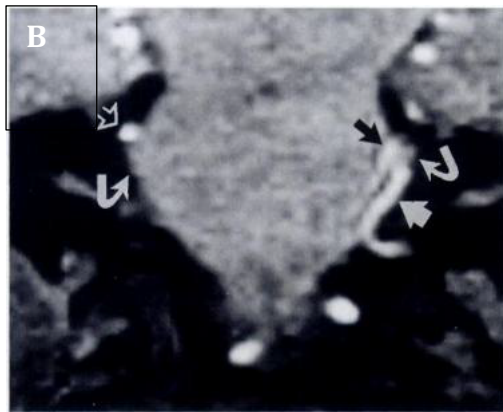


C, Sagittal MR Image along right trigeminal nerve (solid arrow) shows superior cerebellar artery (open arrow) passing very close to nerve but appearing to be separated from it by thin rim of CSF. Although appearances on this projection alone are potentially misleading, by combining information from this and coronal image, It is possible to appreciate close proximity of vessel to, but absence of actual contact with, the right trigeminal nerve.

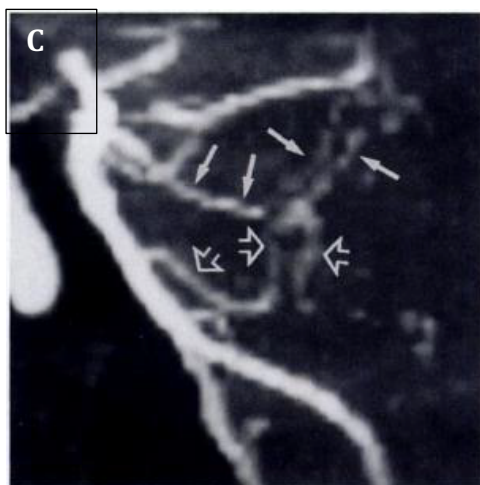
Fig 9: 26-year-old patient with left trigeminal neuralgia[1].



A, Axial MR image shows lateral bowing of left trigeminal nerve (arrow) by a vascular loop.

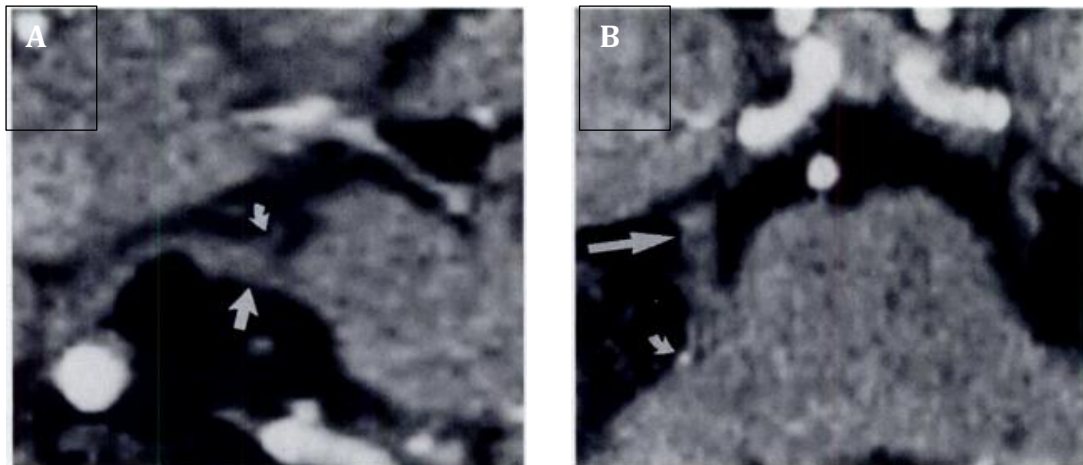


B, Coronal MR image shows both trigeminal nerves (curved arrows). On left side, nerve is sandwiched between superior cerebellar artery above (black arrow) and a cranially looping anterior inferior cerebellar artery below (solid straight white arrow). Right superior cerebellar artery (open arrow) also makes contact with right trigeminal nerve superiorly on the asymptomatic side.

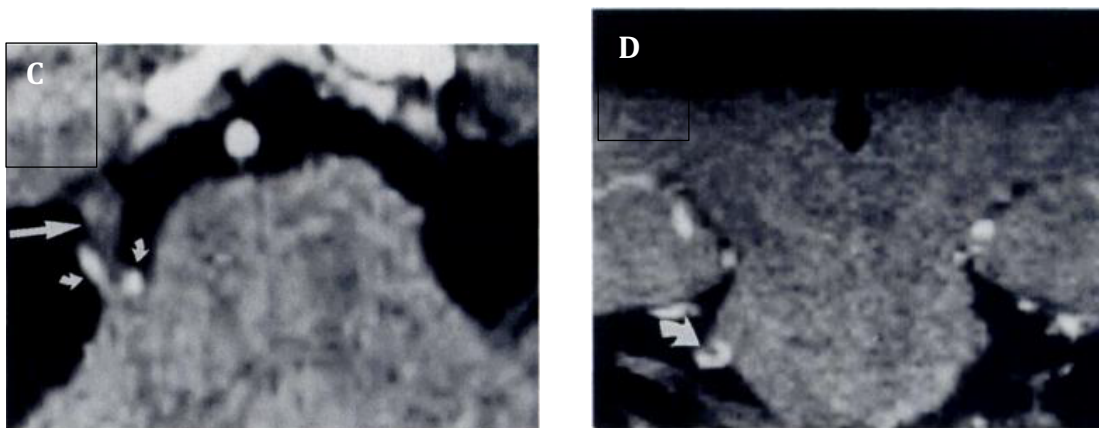


C, Maximum-intensity-projection angiogram (rotated 30deg. to left) shows caudal looping of the superior cerebellar artery (solid arrows), which bifurcates where the anterior Inferior cerebellar artery (open arrows) forms a prominent cranial loop. The site of nerve compression is between the two loops where they approximate one another.

Fig. 10. 64-year-old patient with right trigeminal neuralgia[1].



A and B, Unenhanced sagittal (A) and axial (B) MR images of right trigeminal nerve showing no evidence of vascular contact with nerve (straight arrows) at pons. Small vessel (curved arrow) (B) behind and lateral to nerve on axial unenhanced image represents a branch of the petrosal vein (sometimes seen on unenhanced images) and is of no significance. Note small projection from superior aspect of nerve (curved arrow) (A) with signal intensity slightly lower than that of adjacent nerve. This was subsequently shown on enhanced images to represent saturated blood within the petrosal vein (C and D).



C, Enhanced axial MR image shows intense enhancement in petrosal vein (curved arrows), which contacts nerve (straight arrow) both laterally and medially in axilla.

D, Enhanced coronal MR image showing the right trigeminal nerve (curved arrow) encircled around at least half its circumference by the petrosal vein.

Group 3: Surgical group[77]

High definition magnetic resonance tomographic angiography (MRTA) was performed in 50 consecutive patients, five of whom had bilateral TGN, prior to posterior fossa surgery. The imaging results were compared with the operative findings in all patients, including two patients who underwent bilateral exploration. Vascular compression of the trigeminal nerve was identified in 42 of 45 patients with unilateral symptoms and on both sides in four patients with bilateral TGN. In the last patient with bilateral TGN, neurovascular compression was identified on one side, whilst on the other side the compressing superior cerebellar artery was separated from the nerve by a sponge placed during previous surgery.

There was full agreement regarding the presence or absence of neurovascular compression demonstrated by MRTA in 50 of 52 explorations, but. In one case of disagreement between the surgical and MRTA findings, surgery revealed distortion of the nerve at the pons by a vein that MRTA had predicted to lie 6 mm remote from this point. In the second patient, venous compression was missed; however, this patient refused gadolinium-enhanced imaging and venous compression could not be assessed.

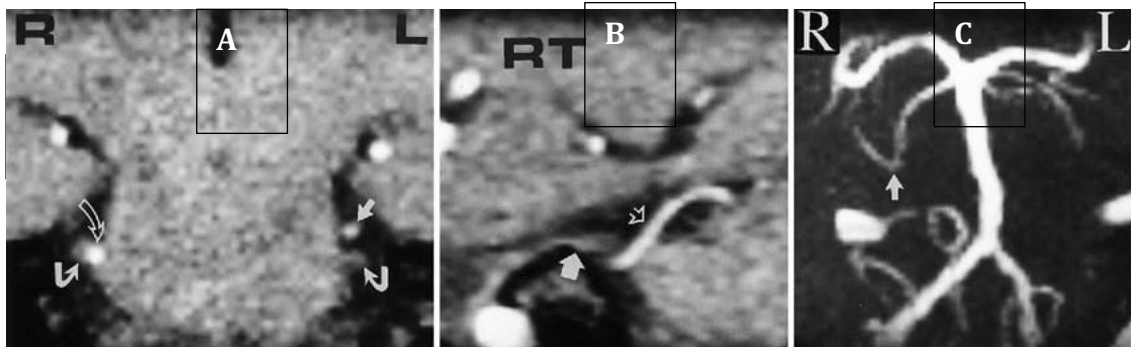
MRTA misclassified four vessels compressing the trigeminal nerve as arteries rather than veins which were disclosed at surgery

In nine cases, MRTA identified neurovascular compression of the trigeminal nerve by two arteries.

MRTA successfully guided surgical re-exploration in one patient in whom a compressing vessel was missed during earlier surgery but confirmed on re-exploration prompted by positive MRTA. MRTA also prompted exploration of the

posterior fossa in two patients with multiple sclerosis and one patient with Charcot-Marie-Tooth syndrome and bilateral TGN, all of whom had neurovascular compression identified preoperatively (see below).

Fig 11: Surgical case: 67-year-old patient with right trigeminal neuralgia[77].

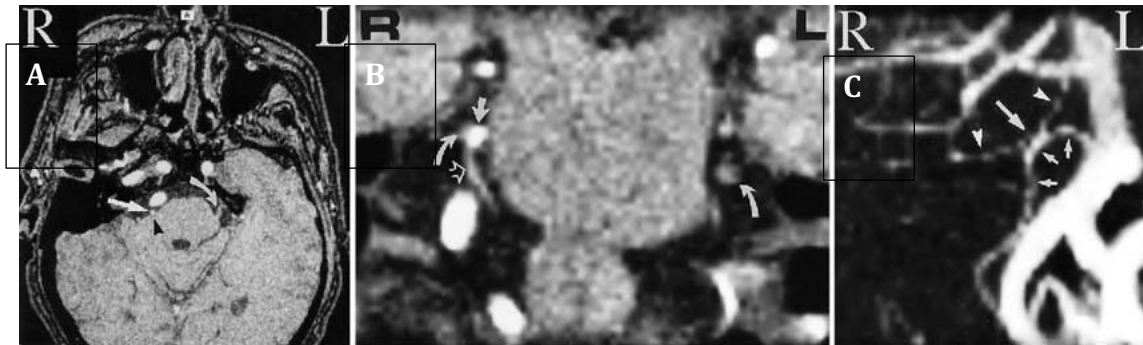


A: Magnetic resonance tomographic angiogram (MRTA). Both trigeminal nerves are indicated by curved arrows on this coronal reconstruction. Note compression of the right trigeminal nerve (which appears semilunar in cross-section due to grooving) in the axilla by the superior cerebellar artery (SCA) (curved open arrow). Note a clear separation of the left SCA (straight arrow) from the left trigeminal nerve.

B: Sagittal MRTA reconstruction along the right trigeminal nerve confirming compression of the nerve (solid arrow) by the SCA (open arrow).

C: Maximum intensity projection angiogram showing caudal looping of the right SCA. The site at which the vessel compressed the nerve is indicated (arrow).

Fig 12: Surgical case: 78-year-old patient with right trigeminal neuralgia[77].

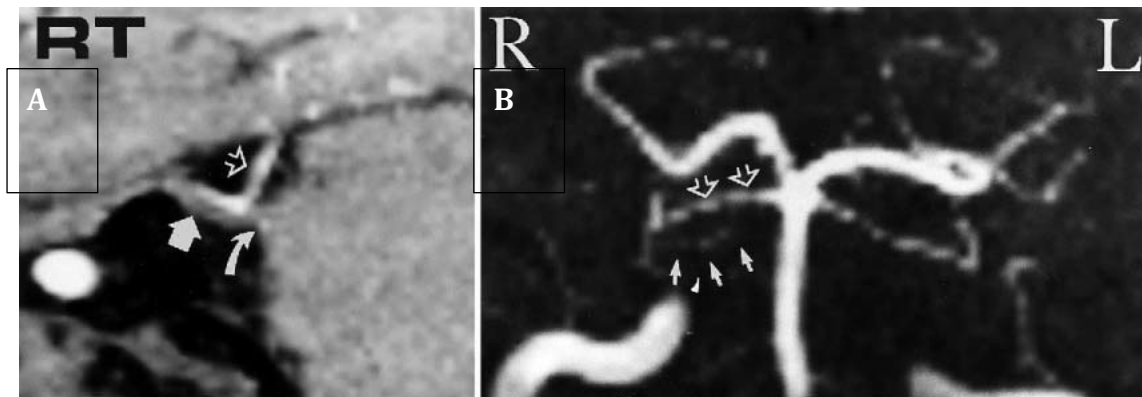


A: Magnetic resonance tomographic angiogram (MRTA). Axial slice at the level of mid pons showing the left (curved arrow) but not the right trigeminal nerve. At the expected site of the right trigeminal nerve there is a small artery (straight arrow) behind the basilar artery, which is deviated to the right side at approximately the site of the axilla of the nerve. As the symptomatic nerve is not seen, neurovascular compression cannot be confirmed or excluded.

B: Coronal MRTA reconstruction showing elevation, distortion, and grooving of the right trigeminal nerve (compare both nerves, curved arrows) by an upwardly looping anterior inferior cerebellar artery (AICA) (open arrow). A further vessel is seen medial to the nerve (solid straight arrow). Further slices (not shown) confirmed the presence of compression of the nerve between two vessels.

C: Maximum Intensity Projection angiogram (rotated 30° to right anterior oblique position) shows a caudally looping superior cerebellar (arrowheads) and cranially looping AICA (short arrows), which approximate one another in the prepontine cistern. The site at which the nerve was compressed between these two vessels is indicated by the long straight arrow.

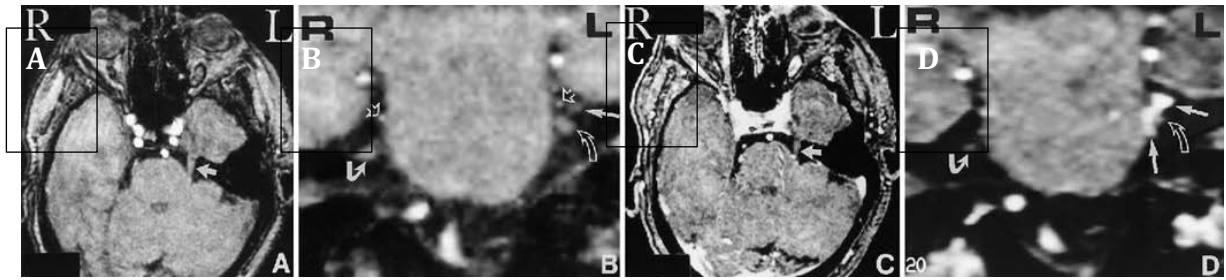
Fig 13: Surgical case: 45-year-old patient with right trigeminal neuralgia[77].



A: Magnetic resonance tomographic angiogram, sagittal reconstruction, along the right trigeminal nerve showing compression of the nerve (straight solid arrow) at the pons by the superior cerebellar artery (SCA) above (open arrow) and a further small vessel inferiorly (curved arrow).

B: Maximum intensity projection angiogram showing the SCA (open arrows) and confirming that the second vessel inferiorly (straight arrows) represents a second small branch of the SCA rather than the anterior inferior cerebellar artery.

Fig 14: Surgical case: 53-year-old patient with left-sided trigeminal neuralgia[77].



A: Unenhanced axial slice showing no definite evidence of vascular compression of the left trigeminal nerve (arrow).

B: Unenhanced coronal reconstruction showing what appear to be normal trigeminal nerves bilaterally (right trigeminal nerve, solid curved arrow; left trigeminal nerve, open curved arrow). Both superior cerebellar arteries are quite small (open straight arrows). On the left side note the presence of unopacified blood within the petrosal vein (straight arrow) above the nerve.

C: Enhanced axial slice at same level as A, showing the presence of an enhancing vascular structure compressing the nerve (arrow) in the axilla. Further slices confirmed that this represents the petrosal vein.

D: Enhanced coronal reconstruction at the same level as B. There is no evidence of compression of the right trigeminal nerve (curved solid arrow). On the left side there is compression of the trigeminal nerve (open curved arrow) by the enhancing petrosal vein (straight arrows). The nerve is considerably reduced in size confirming the presence of grooving. The enhanced scan confirms that what appeared to represent the left trigeminal nerve on the unenhanced coronal image (B) actually represented a combination of the grooved trigeminal nerve and the petrosal vein. In retrospect the “nerve” in B has a slightly dumb-bell appearance consistent with a vein-nerve composite opacity.

Table 3: Group 4:

MS patients with TGN, one patient with Charcot Marie Tooth syndrome and two children with severe intractable TGN[33, 77, 113].

Demographic data of patients with TGN and MS:

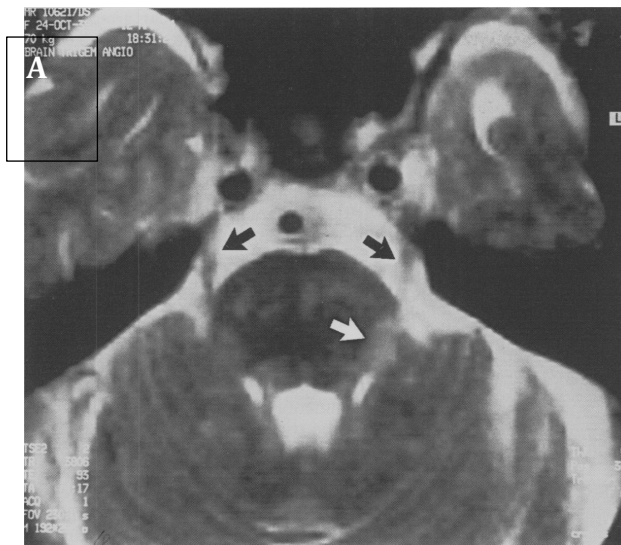
	Duration of MS (Yrs)	Age	Side and Division(s)	Pathology	Treatment	Outcome
1	5	40	Right V1,V2,V3	Vessel	MVD	Pain free
2	12	54	Left V2	Plaque	CBZ	Partial control
3	25	54	Left V3	Vessel	Alcohol	Pain free
4	20	60	Left V2V3	Epidermoid tumour	Surgery	Partial control
5	36	71	Bilateral Left V1, Right V2	Single vessel left, 2 vessels right	Left – RFL Right - MVD	Died
6	25	44	Bilateral Left V3, Right V3	Vessel	Alcohol	Pain free
7	20	40	Left V1V2	2 vessels	Nerve block	Pain free

MVD = Microvascular decompression, CBZ = Carbamazepine, RFL = Radiofrequency lesion

Table 4: Demographic data of 2 paediatric patients.

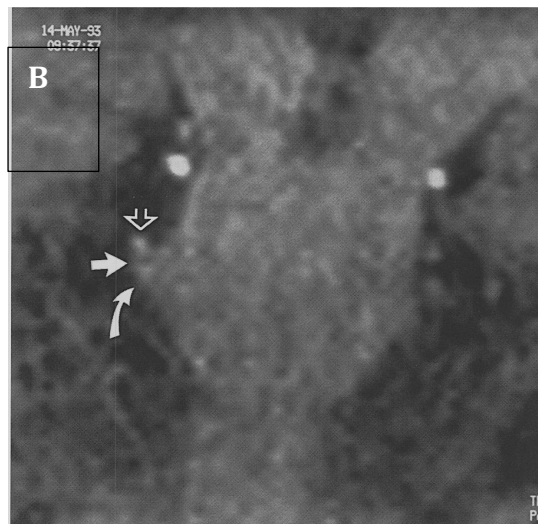
	Age	Sex	Duration of Symptoms	MTRA findings	Treatment
Case 1	9yrs	M	22 months	SCA compression + probable venous compression	MVD x 3 explorations.
Case2	12yr	M	2 months	Venous compression with nerve grooving	MVD x 2 explorations

Fig 15: TGN and MS: (patient 2)[113]

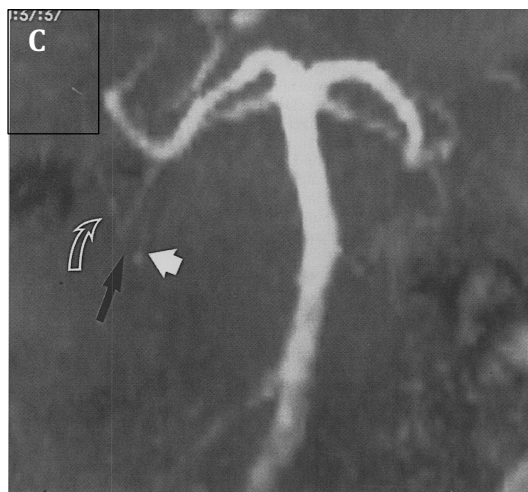


T2 weighted magnified image at the level of the pons. Both trigeminal nerves are visible as low signal intensity structures (black arrows) suspended within the high signal CSF. Note high signal intensity plaque (white arrow) extending posteriorly from the left trigeminal nerve root entry zone.

TGN and MS: (patient 5)



(A) Coronal MRTA showing the right trigeminal nerve (straight arrow), barely visible because of pronounced compression, sandwiched between the superior cerebellar artery above (open arrow), and another vessel below (curved arrow), presumably a branch of the anterior inferior cerebellar artery.



(B) Maximum intensity projection angiogram showing caudal looping of the superior cerebellar artery (open curved arrow) and a further small vessel inferiorly (solid white arrow). The site at which the nerve was compressed between these two vessels is indicated (black arrow)

Statistical analysis for Groups 1-3

We found a high degree of agreement between the two observers regarding the presence or absence of vascular contact with the trigeminal nerve ($k = 0.91$), with complete agreement between them in the symptomatic patients and only mild disagreement in the control group.

For group 3, Sensitivity was 100%, specificity 100%, and positive predictive value 96%. Negative predictive value could not be adequately assessed.

Discussion:

In approximately 10% of patients with TGN, an identifiable cause such as a tumour compressing the nerve within the pre-pontine cistern, or multiple sclerosis, is present[3, 15, 34, 36-40, 57, 114-117]. In the remaining (majority of) cases, no cause was evident and was classified as “idiopathic”. However, in 1934, Walter Dandy observed vessels compressing and distorting the nerve and he proposed that compression of the nerve by an adjacent vessel was causative[9, 30]. His theory was later popularized by Gardner and Jannetta but despite a growing body of surgical evidence, the theory was not universally accepted[11, 71, 95, 118-121]. Essentially, for those who believed the theory no proof was necessary, but for those who did not, no objective proof was available.

Prior to performing our studies, it was observed at surgical exploration that NVC was present and presumed causative in the majority of patients with severe intractable “idiopathic” TGN who progressed to surgery, and that MVD was curative[78, 89, 91, 95, 122]. Although MVD had by this time evolved into an extremely safe procedure in experienced hands, scepticism of the notion of NVC was widespread and many clinicians were unwilling to refer their patients for neurosurgical assessment[5, 18, 21, 103-105, 123-127]. The surgical series reported in the literature represented a highly selected subgroup of the entire cohort with TGN, and there were huge gaps in knowledge, primarily related to the unavailability of a reliable imaging test that could both confirm NVC pre-operatively in TGN patients and exclude NVC in control nerves[89, 125, 128-130].

Therefore, most patients initially underwent drug treatment, which although initially

successful in the majority of cases, eventually failed[6, 85, 99-102, 131-134].

Patients then progressed to neuro-destructive procedures on the trigeminal ganglion, which were highly effective in many patients, but which usually ultimately failed[18-20, 23-25, 27, 28, 135, 136]. Only after several years were patients referred for surgical assessment and “exploratory” (i.e. no knowledge was available pre-operatively regarding the possibility of NVC) craniotomy[8, 16, 22, 26, 78, 79, 81, 91-94, 96, 103, 125, 128, 129].

These issues will now be discussed further. However, please note that it was not the intention to challenge the findings at posterior fossa exploration in patients with TGN in whom MVD is or was planned. Essentially, for the purpose of this thesis it is accepted that the reported incidence of NVC as observed by surgical exploration is correct. However, a short expose of surgical findings reported in the literature is made for context.

Table 5: Neurovascular compression disclosed at posterior fossa exploration performed for MVD in TGN.

Author	Year	Ref	Incidence of NVC (%)
Dandy	1934	[9]	30
Adams	1982	[103]	11
Van Loveren	1982	[19]	82
Richards	1983	[129]	90
Zorman	1984	[20]	74
Burchiel	1988	[79]	90
Bederson	1989	[22]	89

Hamlyn	1992	[80]	90
Barker	1994	[94]	96

NVC has been disclosed in the majority of patients in reported neurosurgical series with few exceptions. One of these exceptions is Dandy's original series where a 30% incidence was found, although Dandy in the 1930's suffered from the huge disadvantage of not having an operating microscope at his disposal (not invented until 1953)[9]. Another dissenting voice was that of Adams, who, in 1982 published a series of patients with an 11% incidence of NVC although his paper received heavy criticism and was not representative of the wider neurosurgical literature[103].

Overall NVC rates were between 74% and 96%.

The incidence of neurovascular contacts around the REZ (TZ/Axilla) in asymptomatic controls is between 15-30% in autopsy series[61, 67, 80]. Grooving and distortion/deviation of the nerve and double compression were not reported in any controls.

Autopsy series examining the neurovascular relations of the trigeminal nerve

In order to determine the relationship of the trigeminal nerve to the adjacent arteries in subjects without TGN, several anatomical studies were performed in autopsy subjects, the three most detailed of which are now discussed:

Hardy et al[61]

They examined 50 cranial nerves in 25 autopsies. After removal of the calvarium, the brainstem was transected at the level of the superior colliculi, the tentorium

cerebelli was sectioned along the straight sinus and retracted laterally and the cerebellar hemispheres were removed to expose the basal cisterns. Using magnification (x 3 to x 20) the arachnoid coverings of the basal cisterns were opened, and the trigeminal nerve was examined on each side.

Table 6: Neurovascular contacts:

Contact	No.	%
Artery making contact		
SCA	26	52
AICA	4	8
PICA	0	0
Basilar artery	0	0
Total	30	60
Site on SCA of Trigeminal Contact		
Main trunk	8	16
Caudal trunk	22	22
Rostral trunk	2	4
Caudal and rostral trunk	4	8
Marginal branch of caudal trunk	1	2
	26	52

Haines et al[67]

They compared neurovascular relationships of the trigeminal nerve in 40 nerves at autopsy and 40 nerves examined during microvascular decompression for TGN. They classified nerve-artery contacts as follows:

- **Compressing arteries:** Those within the “axilla”, those that grooved or distorted the nerve and those that passed through it.
- **Contacting vessels:** Those that lay in contact with the nerve but did not distort, groove or pass through it.
- **No contact:**

Control subjects:

They examined 40 cranial nerves in 20 autopsies. They employed a similar dissection approach to Hardy et al - removal of the calvarium, transection of the brainstem at mid-collicular level to remove the cerebral hemispheres, and sectioning of the tentorium cerebelli along the straight sinus with lateral retraction of the cerebellar hemispheres to expose the basal cisterns. Using magnification (x 3 to x 12.5) the arachnoid coverings of the basal cisterns were opened, and the trigeminal nerve was examined on each side, first with the arachnoid intact and then after careful removal of the arachnoid to prevent displacement of the arteries. The cadavers were examined within 18 hours of death and before fixation or perfusion of the cerebral vessels.

Symptomatic (TGN) patients

They reviewed video operating tapes, movies and photographs made for posterior fossa performed for microvascular decompression of the trigeminal nerve in patients who presented with classic TGN.

Table 7: Results: Classification of nerve-artery relationships

	Not touching			Touching			Compressing		
Patients	Total	Lt	Rt	Total	Lt	Rt	Total	Lt	Rt
#	6	6	3	2	1	1	32	16	16
%	15			5			80		
Cadavers									
#	26	11	15	10	6	4	4	3	1
%	65			25			10		

Table 8: Results: Classification of nerve-vein relationships

	Not touching			Touching			Compressing		
Patients	Total	Lt	Rt	Total	Lt	Rt	Total	Lt	Rt
#	23	11	12	9	4	5	8	5	5
%	57.5			22.5			20		
Cadavers									
#	27	13	14	9	5	4	4	2	2
%	67.5			27.5			10		

Table 9: Results: Classification of types of vascular compression

Series	Arterial	Venous	Mixed Arterial & Venous	None
Patients				
#	29	5	3	3
%	72.5	12.5	7.5	7.5
Cadavers				
#	3	3	1	33
%	7.5	7.5	2.5	82.5

The authors found that neurovascular *contact* was seen in 35% of the *cadavers*. The superior cerebellar artery was responsible for all of the arterial contacts (87% in Hardy & Rhoton's study) and most (10 of 14) contacts did not distort the nerve. In contrast, the patients with trigeminal neuralgia had a significantly higher proportion of arterial contact with the nerve (34 or 40, 85%) and all but two of the contacts distorted the nerve. Of 35 contacts with 34 nerves, 31 involved the superior cerebellar artery, 3 the anterior inferior cerebellar artery, and one the basilar artery (jointly with the superior cerebellar artery). There was a clear highly statistically significant association between the presence of trigeminal neuralgia and the presence of an arterial compressive lesion of the trigeminal nerve at the root entry zone.

The authors emphasized the importance of the configuration of the superior cerebellar artery which formed a deep caudal loop in most patients. This was seen in 22 of 40 patients with trigeminal neuralgia, but in none of the controls (nor in Hardy & Rhoton's cadaver study).

The authors acknowledged the many limitations of this study. For example, vessels at autopsy examination are not distended and perfused with pulsatile blood at arterial/venous pressure and clarification of compression of adjacent structures may be difficult because of this. The vessels may also change position during the process of exposing the brainstem even when due care is taken to avoid this. They state that this risk is greatest when the arachnoid was removed as was also the case in the autopsy study by Hardy and Rhoton. They also acknowledged that relying on video tapes and other photographic material for the patients with trigeminal neurology introduces further difficulties. They furthermore admitted that exposure of the nerve is more difficult during MVD than at autopsy and that loss of three-dimensional vision during recordings of iv-vivo dissection may explain why not all of the clinical cases deemed to show compression at the time of operation could be classified as showing compression on video tapes review. Also they noted a significant age difference between the cadaver series (mean 64.4 years) and the trigeminal neuralgia patients (mean 54.5 years) but argued that if anything, the greater age in the control group could potentially be associated with more atherosclerotic lengthening which would bias the results towards an increased number of Contacts. Lastly neither the cadaver nor the patient's series could be considered to be a random sample of their respective populations.

The authors concluded that they found *compression* of the nerve in 92.5% of TGN patients compared to 17.5% of cadavers (controls) and postulated that NVC of the trigeminal nerve was responsible for the majority of cases of "idiopathic" TGN.

Hamlyn et al[80]

In 1992, Hamlyn & King reported the surgical findings in 41 consecutive patients undergoing MVD for TGN and in the same paper reported posterior fossa exploration in cadavers using a sophisticated technique of posterior fossa blood vessel perfusion in fresh cadavers, to address the shortcomings of the prior autopsy studies and to allow the normal neurovascular relationships to be observed post-mortem under physiological (or near physiological) conditions.

Autopsy study:

The cadavers were positioned in the same way as surgical patients (head up and rotated, the neck flexed, and shoulders forwards and down) with skin incision, craniotomy and dural opening mirroring the operative method using a floor mounted microscope with identical optics. Cerebrospinal fluid was removed after the arachnoid was opened and bridging veins were controlled with titanium clips without diathermy. The trigeminal nerve was approached as for surgical patients. Extracranial cannulation of the carotid and vertebral arteries was performed and circle of Willis pressures were measured during perfusion. The pressure in both internal carotid arteries and opposite vertebral artery was within 5mm Hg of each other at a steady state. The superior cerebellar artery pressure measured on five occasions was also within 5 mm Hg.

In order to study the veins, the transverse sinus was cannulated distal to the torcular herophili and the pressure measured in the internal jugular vein on the right at its exit from the jugular foramen.

50 cadavers age and sex-matched to the clinical series were studied. 15 cadavers were used to develop the perfusion technique and other 5 cadavers with unexpected intracranial pathology giving a control group of 30 cadavers (60 nerves).

Definitions:

A simple grading system was employed as follows:

- “In contact”: It was further noted whether distortion and/or “grooving” of the nerve was present once the vessel was displaced.
- “Not in contact”:

Results: TGN patients:

NVC was present in 37/41 (90%). Compression was purely arterial in 28 (76%), purely venous in 4 (11%) and both in 5 (13%). In 36 of 37 cases there was marked distortion of the nerve and a groove remained in all 36 cases after dislodgement of the offending vessel. In only one case of venous compression was this not the case.

Table 10: Age and sex distribution of the clinical group

				Age	
Group	Female	Male	Median	Range	Quartile
Clinical	21	20	55	27-77	50-63
Anatomical	15	15	58	27-78	50-65

Table 11: Operative findings in clinical cases of trigeminal neuralgia

Vessel	# “in contact”	Compression at REZ	Groove in nerve
Artery only	28	20	28
Vein only	4	2	3

Artery & vein	5	3	5
Total	37	25	36

Table 12: Source, site and result of decompression in clinical cases

	Artery	Vein	Mixed	Total
NVC at REZ (22)				
none	14	1	1	16
minor	0	0	1	1
major	3	2	0	5
NVC beyond REZ				
none	6	0	1	7
minor	1	0	1	2
major	0	1	1	2
Totals	24	4	5	33

Table 13: Findings during perfusion in 30 control cadaver dissections

	In Contact	In Contact	Vessels “near”	
Source	REZ	Lateral (beyond REZ)	REZ	Lateral (beyond REZ)
Veins	2	0	2	2
SCA	1	0	3	0

AICA	0	1	0	1
Total	3	1	5	3

Cadavers:

In the 30 perfused cadaver dissections, median time from demise to dural opening was 17 hours (5-23 hours). 22 dissections were performed on the right and 8 on the left to match the clinical series. In all cases, all vessels became more tortuous with perfusion which continued to a point well beyond physiological pressures. Terminal arterial perfusion pressures of 200 mm Hg arterial pressure and venous pressure of 40 mm Hg were achieved and maintained for five minutes before final observations were recorded.

In 60% vessels were not in contact with the nerve over its length. In 13% (4 nerves), vessels were recorded “in contact” with the nerve (one SCA, one AICA, two veins – one at the REZ, the other lateral to it). In 8 nerves (27% of cases) vessels came close to but did not touch the nerve. Of the vessels “in contact” with the nerve only half were deemed so prior to perfusion and of the 8 vessels “near” the nerve only 3 were deemed so pre-perfusion. This represents an increase from 17% (prior to perfusion) to 40% (after perfusion) in the combined “in contact” and “near” groups, thus validating the methodology (and highlighting shortcomings in the prior studies performed without physiological perfusion[61, 67, 137].

None of the control nerves demonstrated “compression” and no grooves or distortions were found.

Neurovascular relationships at X-Ray angiography in TGN and in controls

In the absence of a cross-sectional modality that could demonstrate neurovascular

relationships of the trigeminal nerve, de Lange et al performed an angiographic study in 22 patients with trigeminal neuralgia (13 F/9M, 31-70yrs, 11 right sided and 9 left sided) and used as controls the findings on the contralateral (asymptomatic) side, and findings on angiograms from patients undergoing vertebral angiography for causes unrelated to TGN[62, 97]. To determine the value of angiography, all patients underwent posterior fossa exploration and microvascular decompression if NVC was confirmed, regardless of the angiographic results (in one patient surgery was terminated because of hemorrhage, but not before a compressing vessel was confirmed).

Catheter angiography was performed using either conventional intra-arterial biplane angiography or intra-arterial digital subtraction angiography. Cerebellopontine and trigeminal nerve tumours were excluded by computed tomography in all cases (MRI was not routinely available in 1985).

As catheter angiography gives vascular and bone landmarks only and gives no information about the location of nerves, the authors set about outlining the position of the trigeminal nerve from a series of autopsy dissections where the position of the trigeminal nerve was marked[62]. In each, the cerebral hemispheres were carefully retracted, and the tentorium excised following removal of the calvarium, so that trigeminal root could be identified. 5mm radio-opaque arterial clips were placed on the nerve, one where it emerges from the pons and one where it enters Meckel's caves at the petrous ridge apex. After the calvarium was replaced radiographs were taken in lateral, Towne and straight AP projections.

The authors noted the location of the radio-opaque arterial clips on the 3 projections, however, diagrams denoting the position of the various clips placed at

the proximal end of the nerve (the REZ) shows these to be distributed over an area measuring around 1cm in diameter on each side.

The authors introduced the useful concept of “trigeminal looping”, i.e. elongation of the artery which resulted in it running a more exaggerated caudal looping course to the point where it could lodge in the REZ/axilla. They inferred the position of the trigeminal nerve REZ, by mapping the position of the clipped trigeminal nerve REZ on the autopsy studies onto the angiograms acquired in-vivo.

Table 14: Patients with TGN: Trigeminal looping

Vessel identified on angiogram	Vessel identified at Surgery	# patients
Left SCA	Same	8
Right SCA	Same	8
Left and Right SCA	Left SCA	1
Left SCA and Left AICA	Same	1
Right AICA	Same	1
BA	Same	1
None	Vein	2

In summary, in TGN patients the authors implicated 21 arteries in 20 patients as being potentially responsible for NVC (2 cases were negative).

Controls: Trigeminal looping in 159 healthy individuals

In order to validate their approach, de Lange et al also presented findings in a control group of 159 consecutive normal vertebral angiograms of patients between 2 and 80 years of age (mean 44.4 years), were evaluated. These patients had no

history of TGN. Of these, 91 (57%) were female and 68 (40%) were male. In all cases conventional biplane film technique was used.

Table 15: Results: Trigeminal looping

Artery	Left	Right	Bilateral	Total (%)
SCA	20	21	10	51 (32.1)
AICA	6	3	0	9 (5.7)
BA	5	4	0	9 (5.7)
Total				69 (43.5)

In total, “trigeminal looping” identical to that found in TGN was present in 32.1% of nerves with a further incidence of “AICA looping” and “BA looping” in 5.7% each for a total of 43.5%.

Major flaw of this study:

The authors implicated “looping” vessels in the region of the REZ in 95% of patients with TGN but also in 43% of normal subjects. The mapping exercise that they performed where the presumed “location” of the nerve in relation to the looping vessel was inferred is flawed as the only relevant question “is there a vessel on the axilla/REZ of the trigeminal nerve or not” could not be answered (vessels “in the region of” the nerve don’t matter). Inspection of the diagrams denoting the location of the nerve give an approximate 1cm “region”, much greater than the size of the nerve. This accounts for the (apparent) over-estimate of “looping” vessels in controls, as it is highly likely that few of these vessels actually made contact with the nerve. Additionally, it was assumed that the point of compression of the nerve was

at the caudal-most point of the looping SCA (or at the cranial-most point of a looping AICA) but there is no reason why this should be the case. Notwithstanding the significant limitations, the approach was the “best possible” under the circumstances of absence of a high-resolution cross-sectional imaging test.

The issue of NVC in symptomatic TGN patients, control subjects in autopsy studies and the relevance of our 2 initial studies (Groups 1-3) in clarifying causation will now be discussed in the light of the state-of-the-art knowledge at that time.

Evidence from surgical series of MVD

In summary, by the mid 1990’s, two clear observations related to the role of NVC in TGN could be made:

1. NVC was present in the majority of operative cases and MVD produced immediate (in most patients) and lasting (in most patients) relief of TGN (with some dissent)[16, 22, 26, 67, 78, 81, 89, 91-95, 122, 129, 138].
2. NVC around the trigeminal nerve in controls (asymptomatic subjects) was thought to be uncommon.

A major limitation at this time related to the inability of imaging to demonstrate the neurovascular relationship of the trigeminal nerve preoperatively and the procedure stood alone amongst almost all other neurosurgical procedures in that posterior fossa craniotomy was entirely exploratory. There was literally no other neurosurgical procedure in the brain (or elsewhere) that was not guided by detailed pre-operative imaging.

Prior to our publications, the best anatomical information regarding the neurovascular relationships of the trigeminal nerve in patients without trigeminal neuralgia was autopsy, optimally performed shortly after time of death although interpretation of findings was beset with pitfalls, not least of which was that fact that the brain sags post mortem, the vessels collapse and the normal anatomical relationships are interfered with in order to expose this part of the brain[61, 67, 80]. The autopsy studies offered useful information regarding neurovascular relationships, discussed below, however, only one study was carried out under what could be considered anything close to normal physiological conditions. Hamlyn & King performed dissections in the same position as neurosurgical procedures for MVD were carried out and perfused the arteries and veins with fluid to return post-mortem intravascular pressures to near physiological levels[80]. Despite the limitations of prior autopsy studies, all studies showed a relatively low incidence of neurovascular contacts/compression along the nerve close to the pons in control subjects.

All of this changed with our first two publications which detailed a simple method for establishing neurovascular relationships in symptomatic patients with ultimate surgical validation, but, possibly more crucially, in controls, using a simple 3D TOF technique that was widely available (the scan that could be performed on any MRI scanner with the capability to perform diagnostic quality 3D intracranial MRA for aneurysm detection) [1, 77]. Although preliminary data was previously published on GRE imaging, we implemented a commercially available 3D TOF technique that gave highest possible resolution, isotropic submillimetre resolution and superior depiction of the artery-nerve relationships than prior reports[139]. A heavily T1W sequence 3D

FISP sequence (fast-inflow with steady-state precession) was employed by the author of the thesis. Images thus generated demonstrates CSF with low signal, nerves and brain parenchyma with intermediate signal and vessels (arteries) with very high signal. This combination of image contrasts provides the ideal medium in which neurovascular anatomy could be interrogated at sub-millimetre resolution, pixel by pixel around the proximal trigeminal nerve. Importantly, the neurovascular relationships were examined in vivo at high resolution under physiological conditions without administration of anaesthetic, in an MRI scanner without interference with the normal posterior fossa structures as a result of surgical dissection and brainstem retraction.

In our first study, we demonstrated that the trigeminal nerve was clearly identified bilaterally in all subjects. We also demonstrated that the superior cerebellar artery, an artery almost invariably present in all subjects, was clearly visible and we also demonstrated the AICA in the majority of subjects (and all of those in whom it was implicated at surgery)[1]. Our studies support NVC as the cause of TGN, beyond reasonable doubt, first, by confirming NVC in the majority of symptomatic patients and excluding it in control subjects with a highly statistical significance ($p < 0.001$). Although it could be argued that our confirmation of NVC in the symptomatic group simply confirmed what was known by (some) neurosurgeons for years, our control group of 114 nerves, which consisted of the nerve contralateral to the symptomatic side in 38 patients with unilateral TGN, and 76 nerves in 38 age and sex matched controls was a completely novel advance. We showed an 8% incidence of arterial contacts which despite largely tallies with prior anatomical data, despite previously

highlighted limitations of autopsy evaluation (although had we performed post-contrast MRV to examine the veins in all subjects this figure would have been appreciably higher)[1, 77].

Our 2nd study (group 3) was the first published paper with surgical-imaging correlation in a prospective large consecutive cohort of patients investigated with high resolution 3D pre-operative imaging although a prior study of 12 patients did report operative findings using an inferior oblique GRE reformat method[77, 140]. The exquisite nerve-vessel detail provided in our study, interrogated by 0.9mm contiguous slices allowed clear depiction of the anatomy in patients progressing to surgery, with excellent correlation with operative findings. Of the 52 explorations, the MRTA findings were deemed correct in 50 of 52 instances regarding the presence or absence of vascular compression. Vascular compression by two arteries was identified in eight patients undergoing exploration for the first time. In one patient in whom the SCA was decompressed at the time of previous surgical exploration, compression of the nerve by a second vessel (shown as the AICA on MRTA) missed at the time of the earlier operation, was identified and successfully decompressed with excellent outcome. This was also classified as a case of double compression, giving nine cases in all. In four cases in which the MR findings were prospectively interpreted as arterial compression, venous compression was found at operation (but these were still regarded as true positives as NVC was correctly predicted). In one patient, MRTA showed the presence of a large vein in contact with the trigeminal nerve some 6 mm remote from the pons, but no evidence of vascular contact with the nerve in the axilla; however, at surgery a large vein of identical configuration to that seen on the MR images was found to lie in the axilla and distort

the nerve. In another patient, absence of arterial compression was confirmed at surgery but venous compression of the trigeminal nerve at the pons, missed by MRTA, was found surgically, however, venous compression could not be commented on in this patient as gadolinium injection was declined. In another patient we misclassified double compression as being caused by two arteries although an arterio-venous fistula with mixed arterial-venous compression was identified at surgery. In this case, the SCA penetrated and compressed the nerve (correctly identified preoperatively on MRTA) but fistulated directly into a distended pulsatile petrosal vein (misclassified as a 2nd artery on MRA) but which also compressed the nerve. Even armed with this information, we do not believe that we could have made this distinction preoperatively, considering MRA detects rapidly flowing blood (almost exclusively arterial) and slow flowing venous blood becomes saturated, which accounts for the misclassification in this case as the vein was “arterialised”. Persistence of a primitive trigeminal artery was confirmed surgically in both cases in which this was suspected from the MR images and provided useful information for the neurosurgeon because of the potentially confusing anatomy. Our findings speak to the robustness of the technique[77].

Features thought to be highly specific for TGN (nerve distortion, nerve grooving and double compression), mirroring findings reported by the neurosurgeon during MVD, were present in many instances, bringing us to the question of significant versus non-significant compression[16, 22, 26, 77-79, 81, 89, 91, 93, 95, 128, 138, 141].

Significance of Neurovascular Compression

The issue of what constitutes significant vascular compression has never been

satisfactorily resolved. Although neurovascular contact/compression is not specific for TGN, being present in 3-12% of autopsy cases at the REZ and 8% of our 114 control nerves, some findings such as distortion and grooving of the nerve and double compression have been reported from the surgical and autopsy literature as being limited to TGN patients only, as was also our experience[16, 22, 26, 78, 79, 81, 89, 91, 93, 95, 128, 138, 141].

Distortion/grooving of the nerve has been reported in 20-75% of patients from the surgical literature and has not been reported from autopsy studies in controls. In support of reported surgical findings, we found distortion or deviation of the nerve in 31% of symptomatic patients (vs. 0% in controls) ($p<0.01$) and grooving of the nerve in 26% (vs. 0% of controls) on MRTA[1, 77, 142] ($p<0.01$). Operative demonstration of nerve grooving or distortion in surgical series of TGN is correlated with a favorable outcome, presumably as it denotes more serious degrees of vessel-nerve conflict. However, identification of grooving of the nerve at surgery may require additional brainstem manipulation (it is located on the medial side of the nerve, potentially hidden from the neurosurgeon by the nerve itself) and is not a finding that is always pursued. Once posterior fossa exploration has been planned, the decision to perform MVD of any offending vessel has obviously already been taken and its identification may be an extravagant luxury. This highly significant observation of grooving is easily identified on MRA by an abrupt caliber change in the nerve, best identified on coronal images, at the level of the compression. Also, the finding of nerve distortion may be complicated by alteration of normal relationships during surgical manipulation, but easily identified on MRTA (deviation of the nerve from its normally arrow-straight course). Thus, the surgeon can be

armed with knowledge preoperatively that increases the significance of NVC disclosed at surgery and can confidently propose MVD to the patient and a greater likelihood of cure.

“Double compression” i.e. compression of the nerve between two vessels, was present in 17% of TGN cases (0% of controls) although we believe it is likely that 2-vessel contact will ultimately be shown to be present in a small number of controls[1]. We contend that demonstration of double compression is also a highly important factor for the operating neurosurgeon, as forearmed with this knowledge, the neurosurgeon will search for and decompress a 2nd vessel before concluding the operation. In this respect we highlight the findings in the single patient in group 3 who had unsuccessful response to previous decompression of the SCA, only to have complete relief following decompression of the AICA identified on MRTA but which was overlooked at the time of the previous operation[77].

Overall however, in the vast majority of cases of TGN, the findings of NVC (single vessel contact without nerve grooving or distortion) were indistinguishable from those seen in the “positive” control group[1]. Nonetheless, we propose that, given the absence of definitive criteria distinguishing “significant” from “incidental” compression in most patients, the finding of NVC in a patient with TGN must be assumed to be significant, even in the absence of nerve distortion, grooving, or compression by two vessels, pending additional data correlating MR imaging appearance with operative outcome (see later under functional Imaging in TGN).

Significance of venous compression:

Venous compression was identified in a minority of patients in our study but suffice

it to say that pre-pontine veins can be easily identified *provided* post-contrast MRA is performed[1, 77]. We misclassified some veins as arteries although with additional experience we believe this should be less[77]. We admit that our data set was incomplete as few of our patients had post-gadolinium MRA and the venous relationships were not clarified in most patients and not at all in controls. Therefore, a comprehensive study employing post-gadolinium imaging or other MRI method to detect venous contacts in controls would undoubtedly increase the number of asymptomatic contacts. This should be addressed in a future MRI study.

Notwithstanding, a few points about venous compression are notable. It is less common, surgical results for venous MVD are less compelling and, in terms of the pathogenesis of the disease it is less clear how venous compression by veins with intravascular pressures close to 0 mm Hg could induce a tiny focus of demyelination within the nerve[78]. Its significance therefore remains contested, particularly in light of theories of causation[85].

Evidence supporting or refuting NVC as cause of TGN in instances where NVC might be expected to be absent:

1. Multiple sclerosis – This will be discussed in detail below
2. Charcot Marie Tooth and two pediatric patients with TGN. Our experience with Charcot Marie Tooth syndrome and two paediatric patients with TGN is largely anecdotal but included for completeness.

The thorny issue of TGN in MS: Plaques expected, NVC is not

The well-known association between MS and TGN has been established over many decades[3, 18, 34, 39, 40, 114, 115, 143, 144]. Conventional wisdom is that

trigeminal neuralgia in patients with multiple sclerosis is due to a demyelinating plaque affecting the trigeminal nociceptive pathway[39, 144]. Many review articles and book chapters on the subject show conventional T2W images demonstrating plaques either close to the REZ or along the trigeminal pathways and it has been widely assumed that these plaques were responsible for the genesis of TGN.

Although Jannetta has suggested that the pain of trigeminal neuralgia in patients with multiple sclerosis is milder than that seen in the idiopathic group, this is not our experience, and all patients in the our study (Group 4) had severe symptoms refractory to drug treatment[71, 78, 144]. Therefore, our TGN/MS cohort was indistinguishable from TGN not associated with other causes.

Post-mortem examination of the brain has been performed in a small number of patients with trigeminal neuralgia and multiple sclerosis. In most reported cases, histological evaluation revealed demyelination affecting the pons at the root entry zone, however, in none of these studies was the possibility of NVC entertained[15, 34, 39, 144]. It appears that as the association between MS and TGN is so well known amongst practitioners active in the field, the mantra that “MS causes TGN” has taken hold and the possibility of NVC has not been raised[145]. For instance, Brisman states that microvascular decompression is contraindicated in patients with trigeminal neuralgia associated with multiple sclerosis and even Jannetta, who popularised microvascular decompression, agreed with this statement[15, 34]. Of note, Lazar and Kirkpatrick reported the demonstration of a plaque affecting the trigeminal nerve at the root entry zone in a patient with multiple sclerosis, in whom a vessel was seen to compress the nerve at operation but this vessel was dismissed as unimportant and the fact that demyelination was demonstrated histologically in a

nerve biopsy was regarded as evidence to refute the relevance of the vessel[144].

We question this assertion, as demyelination is a non-specific response to injury and has been reported in biopsies taken from the root entry zone in patients with trigeminal neuralgia who did not have multiple sclerosis. Furthermore, in our cohort, post-mortem examination of the pons disclosed demyelinating plaques bilaterally affecting the root entry zone in one patient (patient #5) who experienced immediate pain relief after decompression of two vessels compressing the right trigeminal nerve[2, 113].

At the time of our study, the neurovascular relations of the trigeminal nerve had not previously been studied in patients with multiple sclerosis and the possibility that vascular compression might be responsible had been summarily dismissed by most authors or not considered. Patients with associated neurological conditions such as multiple sclerosis may be disadvantaged owing to the tendency to attribute all neurological symptoms to the underlying disease without consideration of potential coexistent pathology such as tumour or neurovascular compression.

In our TGN/MS cohort which comprised five unilateral cases and 2 bilateral cases for a total of 9 instances of TGN, all patients had been referred to a pain institute with a special interest in trigeminal neuralgia[113]. Although the criticism could potentially be levied that our cohort is not representative of the overall population of patients with multiple sclerosis and trigeminal neuralgia, we believe this is not the case.

Considering the rarity of MS (prevalence is less than 1:1000 in the general population) and the rarity of TGN in that condition (1-9% depending on the cohort and diagnostic criteria), we believe that this study is representative of a huge MS

population[2, 146]. Regardless of potential criticisms of selection bias, the finding of a potentially treatable cause in seven instances is notable. In only one of the nine cases (a patient with unilateral symptoms) was a demyelinating plaque shown to affect the trigeminal nerve root entry zone on the symptomatic side. In three of four patients with unilateral trigeminal neuralgia, vascular compression of the nerve was present at the REZ, and an epidermoid tumour was present and causative in the fourth. In two patients with bilateral trigeminal neuralgia, vascular compression was identified on both sides in one patient and on one side only in the other patient.

Whereas most researchers would accept that response to microvascular decompression remains the ultimate test of the significance of vascular compression, the majority of our patients did not have surgery. However, we propose that NVC of the nerve is indeed the cause of TGN in the majority of patients with MS and that this must be excluded before assuming that MS *per se* is responsible.

Despite advances in both MRI and laboratory technology, the diagnosis of multiple sclerosis remains a clinical one, and most clinicians should remain extremely reluctant to forward a diagnosis of multiple sclerosis without firm clinical evidence. Although the diagnosis hinges upon demonstration of white matter hyperintensities (“plaques”) is a typical distribution and with a particular morphology, most white matter hyperintensities are non-specific and there is a considerable “grey-area”[147]. Poser et al and later McDonald et al have developed criteria to aid the clinician in coming to the correct diagnosis[143, 148]. The presence of abnormalities referable to multiple lesions within the CNS, separated both in time and space, with

evidence of remissions, strongly favours a diagnosis of multiple sclerosis. In a patient with one CNS abnormality and coexistent trigeminal neuralgia, it seems reasonable to attribute both to the same underlying pathological process. However, we emphasise that trigeminal neuralgia can only be used as corroborative evidence to support a diagnosis of multiple sclerosis if secondary causes such as vascular compressions and tumours have first been excluded.

Charcot Marie Tooth Syndrome

We examined one patient with Charcot Marie Tooth syndrome and bilateral TGN. Although our experience with this condition is entirely anecdotal (both sides were positive for NVC), we simply mention it to highlight another “neurological” disease where it should *not* be assumed that TGN is secondary to the underlying neurological disorder as is often the case[77, 149]. We merely reiterate the point that NVC is present and the causative in the majority of patients with TGN regardless of the presence of another disease which might explain it. In other words *TGN is a separate disease with a specific cause (NVC) in the vast majority of cases.*

TGN in a paediatric population (2 cases, both with NVC)

TGN is hardly, if at all acknowledged in most paediatric texts, although there are sporadic reports of idiopathic TGN occurring in childhood[33, 149].

We encountered two children with severe typical trigeminal neuralgia, both of whom had been rendered effectively moribund by their symptoms. In each case delayed diagnosis and consequently delayed initiation of appropriate treatment

served to exacerbate the distress of both children and their families. Because of the poor acceptance of TGN in the paediatric population, many alternative diagnostic possibilities and treatments were explored before accepting TGN as the diagnosis in our first case, despite the fact that his pain, hyperaesthesia, and difficulty with facial hygiene were typical of the presentation of TGN in later life. We identified NVC on MRA in this case and our experience heightened our awareness of neurovascular compression as a possible cause of symptoms in a second child who presented later with similar symptoms and in whom NVC was also identified which allowed earlier neurosurgical intervention and ultimate cure.

There is no doubt that both children experienced much more severe symptoms than most adult patients with TN. It is discouraging that although neurovascular compression was confirmed at surgery in both children, neither child responded quickly to surgery and repeated procedures were necessary to achieve symptom control[33, 77].

There are a number of possible explanations for the poor response to surgery. For example, multiple poor prognostic factors for a good surgical outcome such as severe symptoms, prolonged duration of pain, venous compression, and a younger age at presentation were all present in both patients. Additionally, the neurovascular relations shown by MR angiography (MRA) may not correspond well to what is seen at craniotomy, as manipulation of the brain stem, especially within the relatively “tight” posterior fossa of children may alter neurovascular relations, resulting in difficult identification of the critical compressing vessels even in expert hands. This

may have been the situation in our 2nd case, where the vessel deforming the nerve on MRA was not appreciated but another vessel, remote from the nerve on MRA, was found to be in close relation to the nerve at craniotomy. Also, the process of revascularisation, which results in recrudescence of symptoms owing to new vein formation may be more aggressive in children. Lastly, it is postulated that it is not the compression of the nerve *per se* but the resultant focus of demyelination that causes the typical neuralgic pain in TGN and it is possible that the regenerative process in the nerves of children, when myelination is not yet complete, may be different and may account for their delayed response to surgery[33, 77, 150].

Summary of findings in groups 1-4

We demonstrated the presence of NVC in the majority of patients with TGN and confirmed absence of NVC in the majority of controls (without TGN), which had high statistical significance ($p < 0.01$). We also confirmed (to our initial surprise) that NVC was present in the majority of patients with TGN associated with MS, bilaterally in a patient with Charcot Marie Tooth and bilateral TGN and in 2 children with severe unilateral TGN. Essentially, our findings suggest that NVC is responsible for the majority of cases of TGN regardless of association.

Microvascular Decompression (MVD): History of the Microvascular Decompression technique

Before the introduction of microvascular decompression, the common treatment of recalcitrant trigeminal neuralgia was sectioning of the trigeminal nerve, surgical

rhizotomy[22, 26]. The main disadvantage was sensory loss[118]. Frasier improved the operation by making only a partial section, saving the ophthalmic branch to avoid corneal keratitis as a complication. However, eliminating the sensory function of a nerve which provides such an important function in protecting the face from noxious stimuli, is a radical step and one which cannot be reversed.

While the observation that blood vessels found in close contact with the roots of the trigeminal nerve might be causative of TGN by Dandy, it was not until 1960 that James Gardner of the Cleveland Clinic suggested that moving the vessel away from the nerve by interposing a small pledget of inert material (e.g. Ivalon) between it and the nerve could be curative[118, 151]. In his first paper on trigeminal neuralgia Gardner observed an “anomalous” artery found lying against the nerve and reported that the pain was completely relieved after separating this vessel from the nerve roots by interposition of a piece of sponge. This was the first reported microvascular decompression procedure without simultaneous sectioning of part of the nerve root. Almost 50 years after he first described it, Gardner’s simple method is still in use in many surgical centers all over the world, with minimal modifications[118]. Gardner exploited Walter Dandy’s retro-mastoid approach to the posterior fossa, to gain safe access to the cerebellopontine angle but introduced a major improvement by using the binocular microscope to assist these operations[118].

The microvascular decompression operation is remarkable in several ways. It is non-destructive and highly effective[122]. When done by experienced surgeons, the success rate is approximately 80% but with some added sophistication can be as high as 95%. The microvascular decompression operation is therefore an attractive treatment that has many advantages over other treatments for trigeminal

neuralgia[8, 22, 26, 78, 79, 81, 89, 91-94, 96, 103].

Importance of demonstration of NVC in TGN (motivation for the thesis)?

It is now clear that NVC is present in the majority of patients with TGN (and in a minority of controls). In a nutshell, surgical separation of a compressing artery from the nerve in patients with TGN, by interposition of a small inert spacer, via a retro-mastoid approach to the posterior fossa by a neurosurgeon, is curative in the majority of patients without damage to the nerve, a technique called Microvascular Decompression (MVD). Not only is this treatment effective, but it gives permanent and more lasting relief in more patients than any other treatment.

However, MVD is but one of many treatments for TGN, and historically was only used for severe cases where other treatments failed, despite the fact that NVC was assumed to be present in the majority of cases. To frame the place of MVD in management, especially in the light of the ability to demonstrate NVC preoperatively, the other treatments will now be discussed.

Drug treatment and non-drug (Destructive versus non-destructive techniques) treatments of TGN:

At the time of this study, MVD was exploratory and treatments were by and large given in the following order:

1. Drug treatment (carbamazepine/Phenytoin/Baclofen)[57, 100, 132]
2. Interventional procedure with either a destructive procedure (Gasserian ganglion ablation with glycerol or radiofrequency ablation or balloon ablation) [18, 24, 25,

27, 57, 125, 126, 152-154]

3. Microvascular decompression: the only non neuro-destructive intervention.

Assessing the efficacy of treatment of TGN is complicated by the fact that spontaneous remissions are common and that most patients with trigeminal neuralgia respond to drug treatment and percutaneous procedures on the ganglion, at least initially, even those with vascular compression, highlighting the fact that cure of pain can be achieved by interruption of the pain pathway at one of many sites. As eventually there is a poor response to both drug treatment and percutaneous ablative procedures in patients with trigeminal neuralgia including those with multiple sclerosis, it is important to identify NVC to offer definitive treatment to the patient at some timepoint. The reluctance to proceed to MVD without exploring all other options should now be mitigated by the ability to demonstrate NVC preoperatively with MRA. This is especially important as MVD is the treatment with the greatest likelihood of long-term success, however it must be noted that but the longer the duration of symptoms, the less likelihood of cure with MVD.

Drug treatment

The fact that spontaneous, protracted remissions occur in trigeminal neuralgia (at least one such remission lasting at least six months, or more was noted by Rushton and McDonald in 50% of their patients), gives rise to confusion about the value of serially administering treatments[42].

Drug treatment for trigeminal neuralgia is effective in the majority of patients, at

least initially. It came into its own with the observation of Bergouignan on the effect of phenytoin, and of Blom et al on the even more effective use of carbamazepine[98, 155-157]. More recently Fromm et al reported on the value of Baclofen as a secondary agent.

In an early appraisal of carbamazepine (143 patients followed for 16 years), Taylor reported that 69% had complete or acceptable pain relief, 25% had inadequate relief and 6% has drug intolerance leading to withdrawal[100, 101]. Carbamazepine is so consistently effective, at least initially, that if doses of 600-800mg/day are tolerated but give no relief, the diagnosis of trigeminal neuralgia should be in doubt. Some of the patients also required phenytoin, amitriptyline or diazepam. Only 13% of all patients had late resistance to the drug, with recurrence in 2 months to 10 years (average 4 years), for a total treatment failure rate of 44%[100, 101].

However, these drugs can have serious side effects. Fatal cases of aplastic anemia have been reported with carbamazepine along with severe liver function abnormalities. A major deterrent to long term use of carbamazepine has been the insidious development of both mental and physical “sluggishness”, which may be so gradual that the patient and family wrongly attribute it to normal aging. Long term use of carbamazepine can also cause inappropriate secretion of vasopressin. There is also an interaction with warfarin, the half-life of which is markedly shortened placing patients at risk for recurrent thrombosis. Also, patients with multiple sclerosis are often more susceptible to the toxic effect of all 3 drugs for trigeminal neuralgia and are therefore more likely to need some type of surgical intervention[100, 101].

Percutaneous treatments (interventions through the foramen ovale):

The trigeminal ganglion can be accessed via the foramen ovale (which transmits the mandibular division of the trigeminal nerve) under radiological guidance with introduction of a radio frequency probe, hollow needle or inflatable balloon to cause a thermal or chemical lesion (by injection of glycerol) or pressure damage by inflation of a micro-balloon, a process referred to as *percutaneous rhizotomy*[18-22, 24, 27, 28, 57, 89, 90, 135, 136].

Ablation of the trigeminal/Gasserian ganglion by radiofrequency heating or glycerol injection or balloon compression (Percutaneous Rhizotomy):

Tactile and kinesthetic fibers within the trigeminal nerve are more heavily myelinated than those transmitting pain sensation (which are lightly myelinated or sometimes not myelinated at all), therefore small graded increments of radiofrequency heating or metered instillation of tiny amounts of pure glycerin (glycerol) which is neurotoxic, selectively destroys the pain producing fibers whilst leaving tactile and kinesthetic fibers intact for a best result[18, 19, 21, 24, 27, 28].

Producing analgesia or severe hypoalgesia to pinprick in the areas of the trigger zone for pain may give lasting relief. There are few contraindications to the procedure which can be performed as a day case and there are few complications (and only a tiny number of reported deaths) from the procedure[24].

After the initial lesion is induced, completely pain relief is the rule, and there is little neurological deficit. Corneal anesthesia leading to ulceration can occur in 2-5%.

Dysesthesia in the denervated area represents the most serious complication which

may occur in up to 2% of patients, despite preservation of touch sensation. Because of the unpleasantness of dysaesthesia for the patient, experienced operators emphasize that lesions should be limited in order to minimize its incidence, despite the increase in recurrence rate that this approach entails. Failure to access the foramen ovale may prevent a lesion from being induced, however, this is rare with imaging guidance (in rare instances where the foramen ovale cannot be traversed, sectioning of the nerve - surgical rhizotomy – gives the same effect).

Initial failure rates of 5-10% and long-term recurrence in approximately 50% between 3 and 8 years are reported although a repeat procedure, either early or late, gives relief as effective as the first procedure[23, 24, 27, 57].

Open Surgical Rhizotomy

Open rhizotomy requires posterior fossa exploration and is sometime performed in association with MVD or on its own when NVC of the trigeminal nerve is absent. As this is a neuro-destructive procedure it is not a first line treatment[26].

Pathophysiology of TGN

The pathophysiological processes underlying trigeminal neuralgia remain an enigma. It is known that compression, distortion, or stretching of the trigeminal nerve by a slow growing tumour, aberrant vessels, or vascular malformations, can cause typical trigeminal neuralgia[18, 34-37, 53, 85, 114]. Intrinsic brain lesions such as syringobulbia, brain stem infarcts and, most commonly multiple sclerosis, may also cause trigeminal neuralgia[38, 40, 113, 114]. The most plausible hypothesis regarding pathophysiology, which explains the fact that both extrinsic and intrinsic brain lesions may produce typical trigeminal neuralgia as well as the paroxysmal nature of the pain, is that trigeminal neuralgia had a peripheral cause and a central

pathogenesis[57, 85]. Fromm et al have postulated that chronic irritation of the peripheral nerve leads both to ectopic action potentials within the nerve and failure of segmental inhibition in the trigeminal nucleus. This theory explains the origin of pain in the case of tumours and aberrant vessels compressing the nerve, when ectopic action potentials generated in the nerve would presumably be responsible, and also the cause of pain in patients with intrinsic brain lesions such as multiple sclerosis when a plaque would lead to increased activity within the trigeminal nucleus[53, 85, 86]. Regardless of which of these mechanisms operates, episodic activation of the trigeminal neurons may result in paroxysms of pain whenever these bursts of activity exceed the threshold for activation of pain neurons in the trigemino-thalamic tract. To satisfactorily explain the unexpectedly high incidence of vascular compression of the nerve in patients with trigeminal neuralgia and multiple sclerosis, we wish to extend this theory further. Given the occurrence of trigeminal neuralgia in about 1-2% of patients with multiple sclerosis, and that trigeminal neuralgia is encountered in only 0.01% of the general population in whom an 8-15% incidence of vascular contact with the nerve is expected, we postulate that vascular compression is more likely to cause trigeminal neuralgia in patients with multiple sclerosis than it is in the population without this condition, because of underlying hyperexcitability in the trigeminal nucleus or nerve caused by MS[113]. This same argument may explain the higher incidence of bilateral trigeminal neuralgia in patients with multiple sclerosis, and perhaps also the earlier onset. Another factor could be the accelerated brain atrophy over controls seen in patients with longstanding MS, in whom brain sagging might lead to increased nerve-vessel contacts[3, 26, 40, 117, 124]. It also satisfactorily explains the cause of symptoms in

a patient we have recently encountered with bilateral trigeminal neuralgia associated with Charcot-Marie-Tooth syndrome, in whom bilateral NVC was present and successfully treated with bilateral microvascular decompression which effected cure on both sides after failure of all other treatments[77, 149]. In such cases an intrinsic neurological abnormality is assumed to form the basis for the provocation of trigeminal neuralgia by neurovascular compression.

Significance of our studies and major outcomes

Following our studies, there can be little doubt that severe “idiopathic” TGN is a misnomer and that the majority of cases are secondary to NVC of the trigeminal nerve by a vessel impacted within the axilla, usually a caudally looking superior cerebellar artery, a cranially looping anterior inferior cerebellar artery, a large (petrosal) vein, or some combination of these three vessels[1, 77]. Our anatomical study clearly dispels the notion that NVC of the trigeminal nerve in asymptomatic controls is a common entity, and furthermore has confirmed that there are findings that are highly specific for TGN such as distortion of the nerve, grooving of the nerve and double compression. Because of the small number of subjects who had gadolinium contrast agent injection to demonstrate the nerves, we were unable to clarify the normal venous relationships in the control group[1].

Our research further demonstrates that “secondary” causes of TGN such as MS, are associated with NVC in the majority of cases[113]. Although this flies in the face of conventional wisdom that for decades has accepted that the cause of TGN in MS was a demyelinating plaque, our surprising results provide support for the notion that TGN is caused by NVC in the majority of cases, although susceptibility to NVC is increased by coexistent neurological disorders such as MS[7, 57, 84]. This finding is consistent with theories of genesis of TGN which propose a peripheral (NVC) cause and a central pathogenesis (plaques increasing sensitivity to the effects of NVC and increased sensitivity of the central nuclei to ephaptic discharge), and we propose a similar effect in the single patient with Charcot Marie Tooth syndrome who was afflicted with TGN.

Our observations of NVC in two paediatric patients again hammers home our mantra that TGN is caused by NVC of the trigeminal nerve in the majority of cases, regardless of association with other neurological conditions, thus accounting for the positive studies in MS, Charcot Marie Tooth syndrome and in paediatric patients[33]. In this respect, we also highlight a single case from our operative study where a patient had recurrent pain despite MVD of the SCA previously but in whom a second compressing vessel (the AICA) was successfully decompressed at re-look exploration following demonstration of continued NVC by this artery by MRA[1, 77].

Lastly, we propose that high resolution imaging with MRA or successor high resolution techniques in the future will alter the way in which MVD is perceived, as once NVC is confirmed, physicians and surgeons involved in the management of TGN can broach the subject of MVD, the most effective treatment and one which is extremely safe, with patients in the usual case where drug treatment and percutaneous interventions fail[1, 76, 77, 113, 142]. This will be of particular relevance in “vulnerable” groups in whom the risks of surgery and anaesthesia in the presence of definitive demonstration of NVC by MRA might be acceptable, but not in the absence of MRA as the risks of surgery which could be associated with negative exploration may be deemed to be too high.

In summary

1. We have confirmed without reasonable doubt, the hitherto theory, unproven since 1934, that NVC is the cause of “idiopathic” TGN in the majority of patients[1].
2. We have shown that NVC can be reliably demonstrated by MRA, using a commercially available 3D TOF MRA sequence[1, 77].
3. We propose that, in patient with severe facial pain consistent with TGN, the default position should be that it is caused by NVC of the trigeminal nerve, until this possibility is excluded by details MRA/V, as presented in this thesis[1, 77, 113].
4. NVC is probably the cause of TGN in the majority of patients with neurological syndromes associated with TGN, such as multiple sclerosis, the underlying disorder serving to increase susceptibility to NVC that ultimately culminates in TGN[33, 113]. Essentially, we contend that NVC is responsible for the majority of cases of TGN regardless of association with other neurological syndromes, across all age groups[33, 113].
5. MVD, an effective and safe procedure, can be confidently offered to patients with TGN in whom NVC is demonstrated, eliminating the risk of negative and therefore unnecessary posterior fossa exploration in patients without NVC.
6. NVC in symptomatic (TGN) patients is indistinguishable from that in some controls (those without TGN), however, features such as grooving and distortion of the nerve and compression by two arteries appears to be highly specific for TGN[1, 77].

Potential reclassification of TGN based on NVC identified by MRA

Perhaps a more practical approach to TGN would be to categorize patients on the basis of presence or absence of NVC on MRA.

Although this would raise questions as to the significance of NVC, those with NVC could be subcategorized as

- Those with distortion or grooving of the nerve and those with double vascular compression.
- A further condition “NVC within the axilla (REZ)” could also be applied.

Patients with facial pain and NVC by an artery with grooving/distortion/double compression could be classified as having a “classic” form of TGN and treatment algorithm would have MVD firmly in mind from the start (even if the patient had MS).

Those with NVC but without grooving/distortion/double compression could be classified as having a separative form of TGN (“tentative”).

Those with venous NVC would be classified separately with a view to MVD with a more guarded prognosis.

Those without NVC would not enter a surgical (MVD) pathway.

Although this may fly in the face of conventional wisdom regarding clinical subclassification of TGN, it would give the clinician a clearer overview of the role of the many effective (at least initially) treatments, stratify patient into different treatment arms and allow consideration of the possibility of surgical MVD early in the course when appropriate.

Limitations of the study:

We admit that there are some limitations to the study. Although our patients were carefully pre-selected for the study on the basis of exclusion of other underlying causes (in the largest groups - 1 and 2), all of whom who were referred through a highly specialized pain clinic and in whom other treatments had failed, this highly selective group might not be representative of the wider group of patients with TGN, and certainly is not representative of the wider population with facial pain for which there are many causes. Therefore, indiscriminate application of this test to a large population of patients with facial pain could probably result in many false positives ("random" NVC in patients who have facial pain and not trigeminal neuralgia in the first place), although this risk would be mitigated by use of clinical criteria. Like all tests, the findings must be couched in terms of the clinical scenario. We emphasize strongly therefore, that the test has been developed in and validated for patients who have been referred through a specialist pain management pathway and our results are not generalizable to the wider cohort of patients with facial pain[1, 77].

A certain amount of expertise is required to perform multiplanar reformats although we contend that this should be available in all imaging departments, especially those with expertise in neuroimaging[1].

We have noticed that with the passage of time since the performance of our study, with every iteration of the standard MRA technique introduced into clinical practice, that the trigeminal nerves appear less conspicuous. This is entirely predictable as

the aim of MRA for its common indication of demonstration of aneurysms or intravascular stenosis, is to generate highest possible signal within the arteries and to eliminate, as much as possible, the background signal (including the nerves), to ensure best quality MIPs[107, 108, 110-112, 140, 158, 159]. Therefore, although the MRA technique we employed was a largely unmodified clinical MRA sequence introduced into clinical practice to evaluate intracranial aneurysms and vascular patency and stenosis in the mid 1990s, MRA sequences nowadays need to be modified to “restore” some background signal although this is easily implemented by sequence optimization by experienced MR practitioners (radiographers, physicists and radiologists).

Follow-up studies since 1996 with special reference to diagnostic MRI/MRA

Other imaging approaches to detection of NVC in TGN:

Since our first study, detailing findings on MRA in patients compared to controls and our 2nd study reporting accuracy compared to surgical findings, several other authors have reported similar findings, some exploiting a different technique of high-resolution T2W imaging using a “balanced technique” which demonstrates the nerves as low signal structures suspended within the high signal CSF[63, 160-180] at a multitude of field strengths[168, 170, 181]. Functional imaging has also been investigated along with, most recently, ultra-high definition tractography of the trigeminal nerve at 7.0T. The point is that, once we demonstrated that NVC was efficiently clarified with high resolution MRA, other researchers exploited additional

MR approaches and have come to the same conclusion[63, 161, 165-173, 177-180, 182-188].

Balanced sequences

A family of sequences collectively referred to as “*balanced acquisitions*” are steady-state coherent sequences (the net gradient-induced dephasing over a repetition time is zero) in which *balanced gradients* are used along all three axes[63]. Images generate high resolution and heavy T2 weighting (under certain conditions) – image contrast is dependent on the ratio of T2:T1 - but in terms of MR appearance are the opposite of the type of MRA images (FISP) produced in this thesis. Essentially vessels appear as signal voids and brain parenchyma and cranial nerves appear as low intermediate to low signal structures suspended in the CSF, although their signal is notably higher than the signal void of vessels. Isotropic sub millimetre resolution (like MRA) is possible which allows reconstruction of images in orthogonal planes without loss of resolution.

Examples include **True FISP** (fast inflow with steady-state precession, Siemens), **FIESTA** (Fast Imaging Employing Steady-sTate Acquisition, General Electric) and **Balanced-FFE** (Fast Field Echo – Philips Medical Systems) respectively. **CISS** (Constructive Interference in Steady State, Siemens), a variant of these sequences is a modification of TrueFISP, exploits a strong T2-weighted 3D gradient echo technique which produces high resolution isotropic images[189, 190]. In essence it is a pair of True FISP sequences each acquired with differing regimes of alternating the phase of the excitation pulses produces very strong T2 weighting but are affected by dark phase dispersion bands as a result of patient induced magnetic field

inhomogeneities and exaggerated by the relatively long TR used. The banding artefact is eliminated by combining the different excitation pulse regimes in the two sequences which results in elimination of banding. The only downside is that image combination is performed automatically after data collection, adding a small amount of time to the reconstruction process. The main advantages of these sequences is that because of their exquisite spatial and contrast resolution, most authorities believe they completely remove the requirement to inject gadolinium contrast agent to identify acoustic neuromas, but the same properties that allow tiny tumours on the vestibulocochlear (8th) cranial nerve (which are much smaller than the trigeminal nerves) also makes them an ideal candidate for depiction of NVC.

The vessels are also demonstrated as low signal structures or “signal voids” (i.e. lower than the nerves). Although there are pros and cons to either black-blood or white-blood techniques, a significant drawback of the black-blood technique is that arteries cannot be differentiated from veins under many circumstances. Nonetheless, demonstration of NVC has been achieved with a high degree of success.

Functional imaging in TGN

Computational Fluid Dynamics - Wall Shear Stress and WSS ratio

Computational fluid dynamics (CFD) is a numerical analysis method used to solve problems involving flowing fluids. Advances in MRI and CFD have made it possible to simulate blood flow patterns in anatomically realistic models, with extension to the clinical arena e.g. for analysis of ascending aortic pathology and intracranial aneurysms[191].

Yamada et al analyzed the hemodynamic features of the offending artery at sites of neurovascular compression (NVC) using a sophisticated technique called computational fluid dynamics (CFD). They evaluated 23 patients who underwent microvascular decompression (MVD) for TGN and generated a 3D surface model of the trigeminal nerve region from preoperative magnetic resonance imaging (MRI), and implemented CFD analysis of the target artery.

They calculated wall shear stress (WSS), one of the distinctive parameters obtained from CFD simulation, which expresses the force per unit area exerted by the wall on the fluid in a direction on the local tangent plane. In the case of TGN, this indicates hemodynamic stress inflicted upon the REZ caused by the blood flow within the offending artery. They also determined WSS ratio (WSSR) by dividing the WSS at the NVC by the mean WSS of the target.

The mean WSSR of the arterial NVC group was significantly higher than that of the control group (but no significant intergroup differences in other parameters measured such as velocity and pressure). They proposed elevated WSSR, which

indicates elevated WSS at the sites of NVC, as a unique parameter of arterial compression that may contribute to understanding of TGN and the significance of neurovascular conflicts.

Diffusion Tensor Imaging in TGN

In an approach that greatly expands the role of MR in TGN, and which serves to determine the damage produced by NVC rather than simply visualising NVC, several authors focussed their efforts towards exploitation of sophisticated functional imaging techniques to determine the significance of neurovascular conflicts by measuring parameters such as fractional anisotropy (FA) and apparent diffusion coefficient (ADC) which offer unique insights into the disease[185, 192-196]. Moon et al have exploited tractography to enhance understanding of central mechanisms in TGN on an experimental 7.0Tesla MRI system which generates hitherto unknown resolution[181].

Fractional anisotropy (FA)

Fractional anisotropy (FA) is a metric (value between zero and one) that describes the degree of diffusion in the three orthogonal directions. A value of zero means that diffusion is isotropic, i.e. it is unrestricted (or equally restricted) in all directions. A value of one means that diffusion occurs only along one axis and is fully restricted along all other directions. FA is a measure extracted from diffusion tensor images that reflects fibre density, axonal diameter and myelination, all of which are thought to be disrupted in TGN patients with NVC.

Apparent diffusion coefficient (ADC)

Diffusion Weighted Imaging (DWI) detects the random motion of water molecules, the extent of which is influenced by tissue cellular density and intact cell membranes. This is quantitatively assessed by applying different b-values (via changing gradient amplitude in multiple short acquisitions), which allow calculation of the apparent diffusion coefficient (ADC) value. Diffusion weighted imaging (DWI), is as an indispensable tool in the examination of altered brain structure[193, 195, 196].

Functional MRI exploiting DTI and DWI in TGN

Several articles on DTI in TGN caused by NVC reported a significant decrease in FA values and one found a significant increase in ADC values in the affected nerves. Liu et al. studied 16 consecutive patients with classical TN with DTI at 3.0T and demonstrated that FA was significantly lower on the affected side, while radial diffusivity (RD) and mean diffusivity (MD) were significantly higher in the affected side compared to the unaffected side[194]. Lummel investigated 12 patients with TGN caused by NVC, 12 patients with TGN caused by multiple sclerosis, and 12 normal control subjects with DTI[193]. The authors found that FA was significantly lower on the affected side (vs. unaffected side) in patients with TGN secondary to TGN compared to normal control subjects. Lutz et al. in a large cohort of 81 patients with NVC who underwent MVD reported significantly lower FA values within the vulnerable zone of the affected TGN compared with the contralateral side.

Lutz et al, acknowledging that high-resolution MRI with steady-state sequences and MR angiography (MRA) as the gold standard for detecting neurovascular

conflicts and secondary causes of TN, performed functional imaging to determine whether there was objective, quantifiable data regarding structural changes in the nerve in 81 patients with a 13year mean duration of symptoms[193]. They exploited Diffusion tensor imaging (DTI) to provide detailed analysis of white matter integrity by measuring fractional anisotropy (FA) and apparent diffusion co-efficient (ADC) values in a large patient cohort that underwent surgery for proven NVC and correlated findings with clinical and anatomical parameters. They reported that DTI reveals alterations in FA within the REZ of the trigeminal nerve in patients with NVC which indicate changes in microstructural integrity associated with NVC in TGN. These findings were independent of the duration of symptoms, the severity of compression, and the type (artery/vein) of the offending vessel, and were present even early in the course of the disease. The authors proposed that this might reflect alternating demyelination and remyelination (i.e., a “remodelling” of the myelin sheaths rather than a constant decline in myelination). They reported pathological changes in DTI indices in both arterial and venous contacts/compression, which strongly supports the hypothesis that both arteries and veins can cause TGN and might therefore be equally eligible for consideration for MVD. Crucially, asymptomatic control nerves with neurovascular contact on MRI also showed no significant change in FA values, which raises the tantalising prospect that this test could assess the significance of neurovascular conflicts.

However, Fujiwara did not find significant differences between the absolute FA and ADC values for symptomatic versus unaffected sides or between the absolute FA and ADC values in patients with classical TN versus control subjects[197].

These highly sophisticated aforementioned studies (with the exception of Fujiwara) provide direct evidence *in-vivo* of pathological changes such as axonopathy, axonal loss, demyelination, and residual myelin debris as demonstrated in histological studies of trigeminal fascicles collected from patients with NVC near the REZ. The restricted diffusion in the REZ of affected nerves indicates axonal loss and focal demyelination. Reduced anisotropy could result from removal of highly aligned cellular structures such as axons or from focal endo-neural injury resulting directly from NVC. These findings lend support to the theory of focal demyelination of the sensory axons at the site of the NVC and that ephaptic short circuits are responsible for neuralgia, as hypothesized by Gardner. Demyelinated nerve fibers are also known to be sensitive to even subtle deformation, in theory compression by a pulsatile vessel which could potentially initiate axonal impulses that spread ephaptically within the REZ.

One group used DTI to investigate TGN at baseline and 4 years after MVD. After MVD, the reduction in FA persisted, but initially reduced ADC normalized in the affected nerves, suggesting an improvement in conduction sensitivity and reduction of edema in the trigeminal root following MVD[195]. The re-establishment of diffusion could well be the reason for pain relief after MVD. From a management perspective, DTI metrics could ultimately be shown to provide an effective biomarker for confirmation of the significance of NVC found

on imaging and the likelihood that MVD would be successful, thus adding a functional element to the already highly effective methods for detecting NVC but which is often indistinguishable from the pattern seen in controls.

It is true that trying to infer microscopic processes from MR images (which have relatively crude resolution) is fraught with potential problems. Nonetheless, DTI and DWI are widely accepted as valid functional MRI techniques for a variety of applications. Notwithstanding, the many limitations of DTI such as partial volume effect (the small size of the root that is bathed in cerebrospinal fluid may confound DTI measurements), motion artefacts and magnetic susceptibility effects (secondary to large discontinuities in bulk magnetic susceptibility at tissue-air interfaces around the mastoid and petrous bones, producing local magnetic field gradients) that could degrade and distort DTI, nonetheless, differences in the FA values have been a consistent finding in all published studies on NVC in TGN (although the published data regarding value of ADC values is inconsistent, with reports of no significant differences, increased and decreased ADC values).

Future horizons

There is no doubt nowadays that “idiopathic” TGN is caused by NVC of the nerve at the REZ by a looping vessel in the majority of cases. MRA and other MRI techniques will continue to improve in respect of their ability to clarify neurovascular conflicts, however, improvements will bring incremental benefit only. It should be possible in

the near future to perform time-resolved, ECG triggered high resolution dynamic imaging of the artery at the REZ with a sufficient temporal resolution to visualise compression of the nerve at different phases of the cardiac cycle.

Much more importantly, functional imaging will deliver measurable physiological information regarding the extent of damage to the nerve prior to and following surgery and may allow prognostication.

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