FACULTY OF HEALTH SCIENCES
UNIVERSITY OF COPENHAGEN

GLOBAL EXCELLENCE IN HEALTH

Danish
Headache Center

# Trigeminal neuralgia – an update

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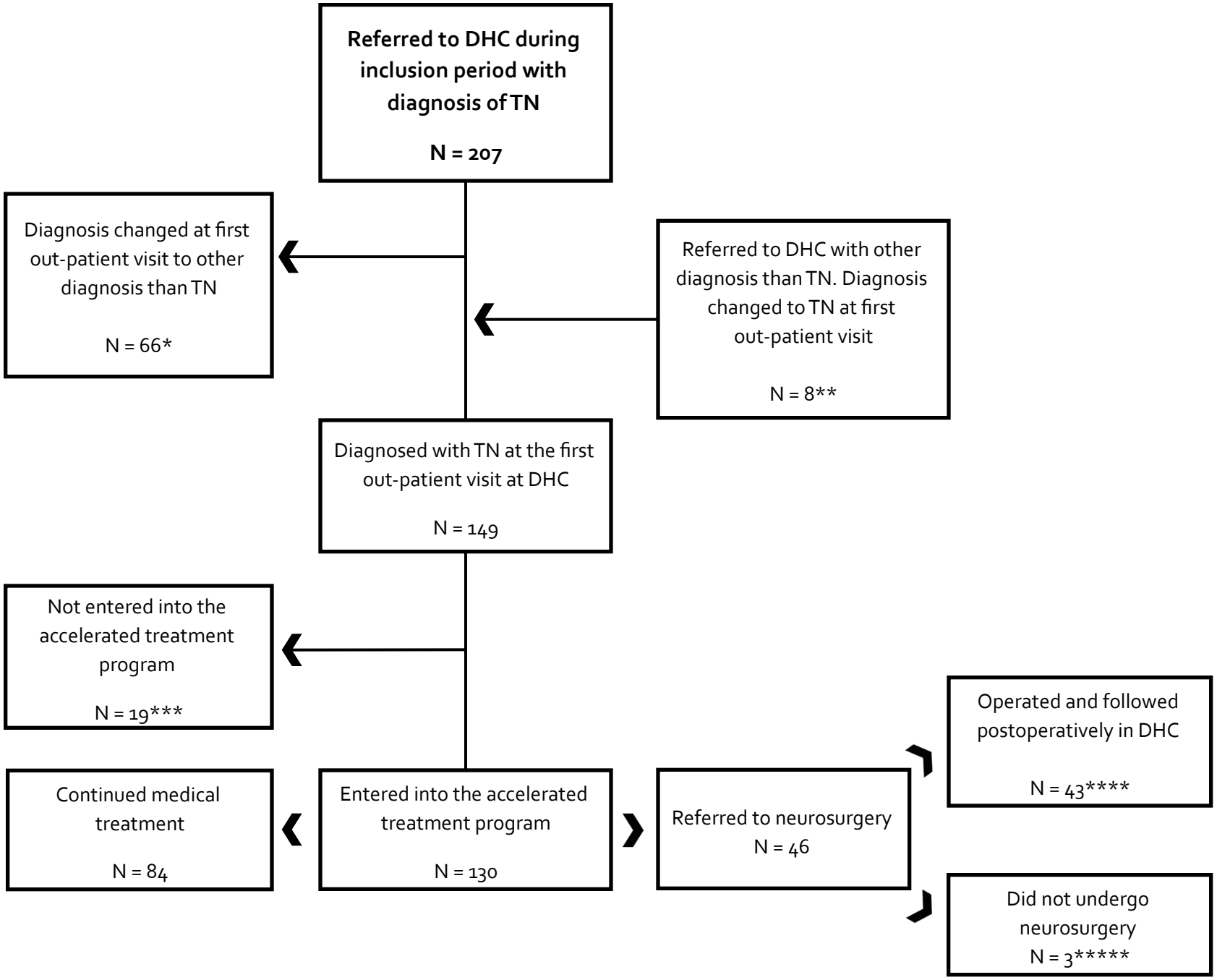
# Disclosures: None

# Trigeminal Neuralgia Center, Danish Headache Center


Referred to DHC during inclusion period with diagnosis of TN
N = 207
Diagnosis changed at first out-patient visit to other diagnosis than TN
N = 66*
Referred to DHC with other diagnosis than TN. Diagnosis changed to TN at first out-patient visit
N = 8**
Diagnosed with TN at the first out-patient visit at DHC
N = 149
Not entered into the accelerated treatment program
N = 19***
Continued medical treatment
N = 84
Entered into the accelerated treatment program
N = 130
Referred to neurosurgery
N = 46
Operated and followed postoperatively in DHC
N = 43****
Did not undergo neurosurgery
N = 3*****

# Trigeminal neuralgia. Management in DHC

All TN patients are referred to DHC

History and clinical examination
Standardized MRI (< 4 weeks)
TN pain diary and calendar
Evaluation of medical treatment

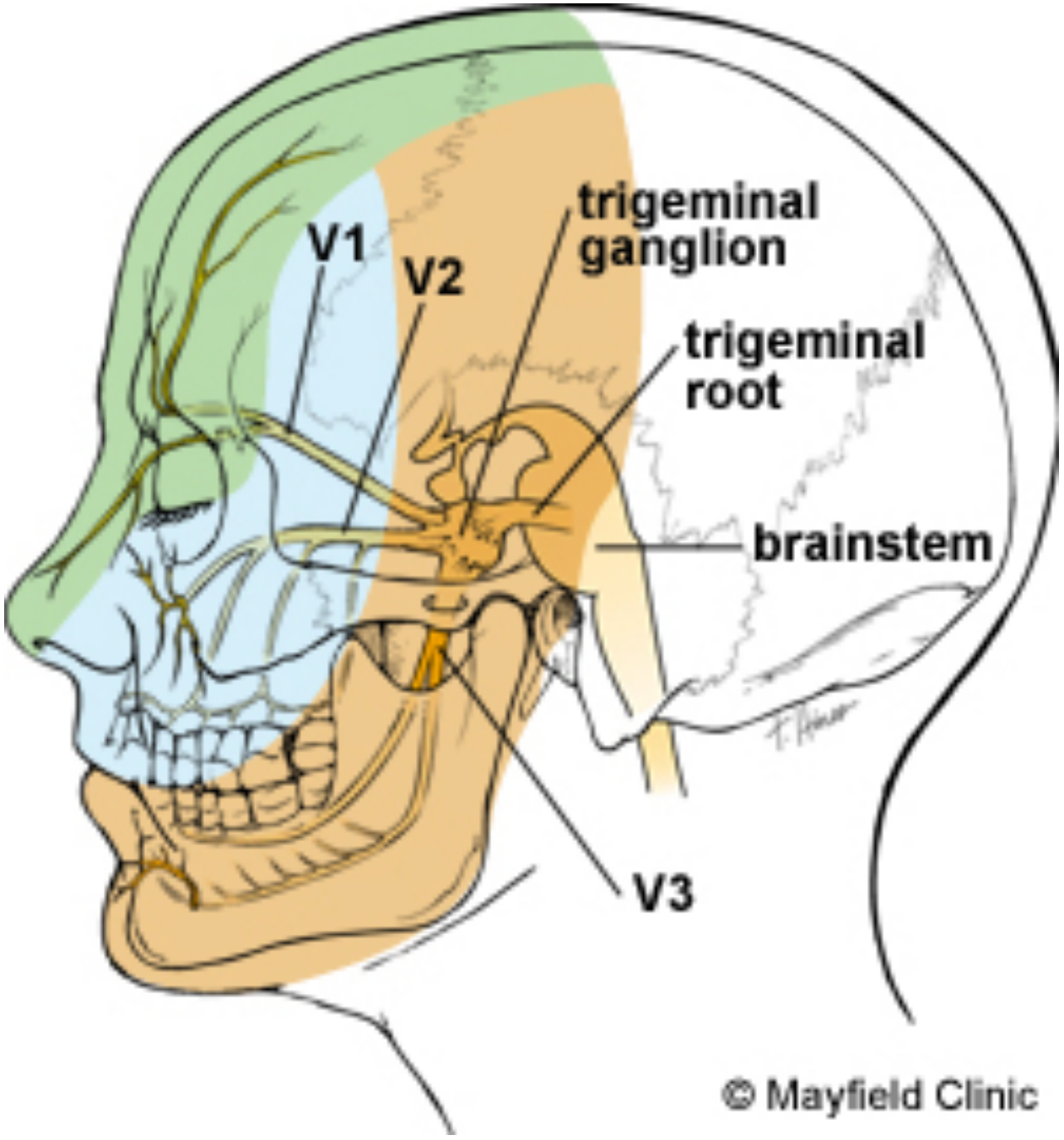
Treated with the following in sufficient doses without effect or with intolerable side effects: CBZ and OXZ monotherapy and best drug in combination with gabapentin

*(each treatment performed in less than 4 weeks)*

**Neurosurgical evaluation at National Hospital**

(MVD or lesion treatment)

All patients are followed with evaluation of efficacy in DHC for at least two years


V1
V2
trigeminal ganglion
trigeminal root
brainstem
V3
© Mayfield Clinic

# Trigeminal neuralgia
## Epidemiology

- Women vs. men: 2:1
- Lifetime prevalence: 0.3%
- Incidence: 4.3 per 100.000

*Katusic, Ann. Neurol. 1991; Mueller, Cephalalgia 2011*

# Clinical characteristics

- Usually a unilateral disorder with intense ultra-short stabbing pains in one or more divisions of the trigeminal nerve
- Usually starts in 2. or 3. division
- Onset usually occurs after 45 years of age
- Pain is often evoked by stimuli such as chewing, washing the face, speech or brushing teeth but also occurs spontaneously

# Clinical characteristics

- Often misinterpreted as pain from teeth or sinuses in the beginning
- Between attacks a dull background pain may persist
- Pains usually remit for variable periods
- Persistent idiopathic facial pain (atypical facial pain) does not have the neuralgiform characteristics seen in TN, but is often a more constant, diffuse pain
- Trigeminal autonomic cephalalgias (TACs) are characterized by autonomic features

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Research Submission

# Trigeminal Neuralgia – A Prospective Systematic Study of Clinical Characteristics in 158 Patients

Stine Maarbjerg, MD; Aydin Gozalov, MD, PhD; Jes Olesen, MD, PhD, ScD; Lars Bendtsen, MD, PhD, ScD

- Average age of onset 53 years
- More prevalent in women (60%) than men (40%)
- Affected solely 2nd and/or 3rd branch in 69%, 1st branch alone in only 4%
- Autonomic symptoms in 31%
- Sensory abnormalities in 29%

*Maarbjerg et al, Headache 2014*

# CASE 1

- *46 year old woman*
- *In 2012, Feb, slow onset of a persistent pain of moderate intensity in V1+2, right side*
- *In 2012, Apr, in addition frequent intense lancinating pain paroxysms in same area triggered by touching and chewing*
- *Any more history needed in order to state the diagnosis?*

# CASE 1, diagnosis

Cephalalgia
An International Journal of Headache

*Additional history:*

- ❑ *Does the pain radiate outside the trigeminal distribution?*
- ❑ *Duration of pain paroxysms?*
- ❑ *Autonomic symptoms? Pronounced or sporadic?*
- ❑ *Trauma to relevant branch prior to pain onset?*
- ❑ *Last dentist check up?*
- ❑ *Other systemic/neurological symptoms?*

TN diagnostic criteria - 13.1.1

ICHD-3 beta

**A.** At least 3attacks of unilateral facial pain fulfilling criteria B and C

**B.** Occurring in trigeminal nerve distribution, no radiation

**C.** Three of the following four characteristics:
1. Lasting max. 2 minutes
2. Severe intensity
3. Electric shock-like, shooting or sharp
4. Precipitated by innocuous stimuli to the affected side of the face

**D.** No clinically evident neurological deficit

**E.** Not better accounted for by another ICHD-3 diagnosis

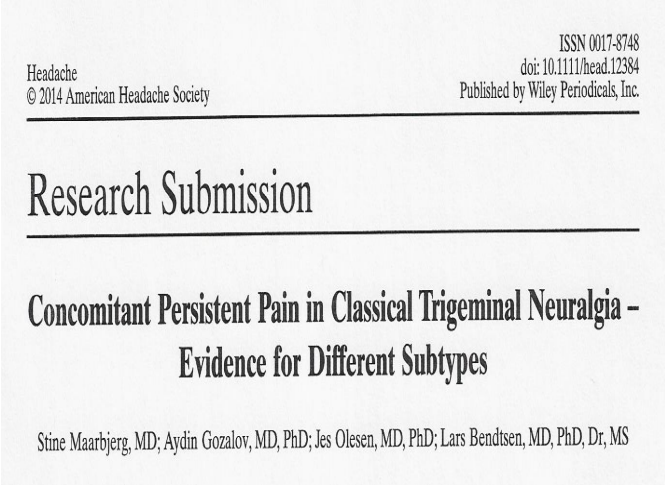
# CASE 1, diagnosis

ICHD-3 beta new subgroups in trigeminal neuralgia:

**13.1.1.1 TN with purely paroxysmal pain**

**13.1.1.2 TN with concomitant persistent pain**

- In 158 TN patients 49% had concomitant persistent pain
- No difference in duration of disease between groups
- Compared with purely paroxysmal pain patients with concomitant pain
  - were more ofte women
  - were 6 years younger
  - had more often sensory abnormalies



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Research Submission

Concomitant Persistent Pain in Classical Trigeminal Neuralgia – Evidence for Different Subtypes

Stine Maarbjerg, MD; Aydin Gozalov, MD, PhD; Jes Olesen, MD, PhD; Lars Bendtsen, MD, PhD, Dr, MS

*Maarbjerg et al, Headache 2014*

## Conclusions

- Concomitant persistent pain is very prevalent
- Not a consequence of paroxysmal pain
- Represents a different disease entity

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
0(0) 1–10

DOI: 10.1177/0333102414542291
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# Field-testing of the ICHD-3 beta diagnostic criteria for classical trigeminal neuralgia

Stine Maarbjerg[1], Morten Togo Sørensen[2], Aydin Gozalov[1], Lars Bendtsen[1] and Jes Olesen[1]

**Table 5.** Proposed modified ICHD-3 diagnostic criteria in trigeminal neuralgia.

A. At least three attacks of unilateral facial pain fulfilling criteria B and C
B. Occurring in one or more divisions of the trigeminal nerve with no radiation beyond the trigeminal distribution
C. Pain has at least three of the following four characteristics:
   1. recurring in paroxysmal attacks lasting from a fraction of a second to 2 minutes[a]
   2. severe intensity[b]
   3. electric shock-like, shooting, stabbing or sharp in quality
   4. precipitated by innocuous stimuli to the affected side of the face
D. At least one of the following
   1. No clinically evident sensory abnormalities at neurological examination
   2. Clinically evident sensory abnormalities at neurological examination but MRI and patient history do not demonstrate structural, systemic or traumatic causes of facial pain[c]
E. Not better accounted for by another ICHD-3 Diagnosis.

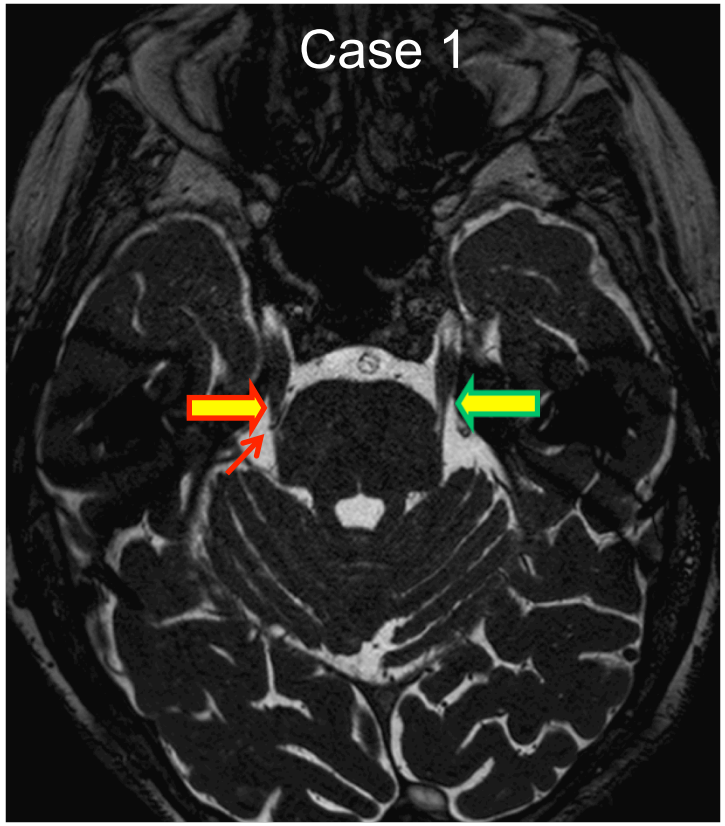
## Conclusions

- ICHD-3 beta no different from ICHD 2 - both lacked sensitivity
- Allowing sensory abnormalities if secondary causes are ruled out greatly increases sensitivity
- This modification is proposed for forthcoming ICHD-3

*Maarbjerg et al, Cephalalgia 2014*

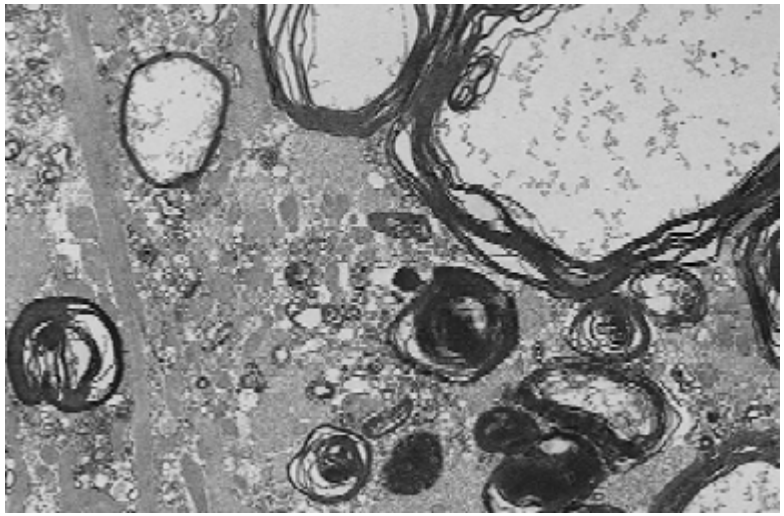
# CASE 1, work-up?

- *Clinical and neurological examination*
- *ECG and laboratory testing*
- *Early MRI*

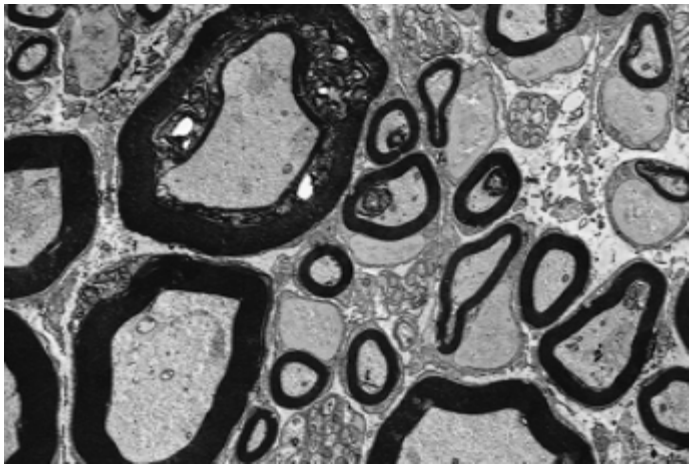


# Pathophysiology – "the ignition hypothesis"

- Demyelinated sensory neurons: hyperexitability and ectopic pacemaker sites
- Neuron-to-neuron cross-excitation due to eroded insulation – amplification and synchronization
- Ephaptic transmission and crossed afterdischarge between non-nociceptive afferents and nociceptive afferents may explain how innocuous sensory stimuli can trigger painful paroxysms



Complete demyelination and loosening of myelin lamellae



Non-injured trigeminal root

*Devor et al. 2002*

# Pathophysiology

- Primary site of damage is peripheral, near root entry zone, possibly because nerve fibres change myelination from Schwann cells to oligodendroglia
- TN can be caused by compression of the trigeminal nerve at the root entry zone, e.g., by vascular contact or tumour
- A demyelinating plaque affecting intrapontine presynaptic primary afferents can cause TN (2-5% of MS patients have TN)

*Cruccu et al, Hand. Clin. Neurol 2011*

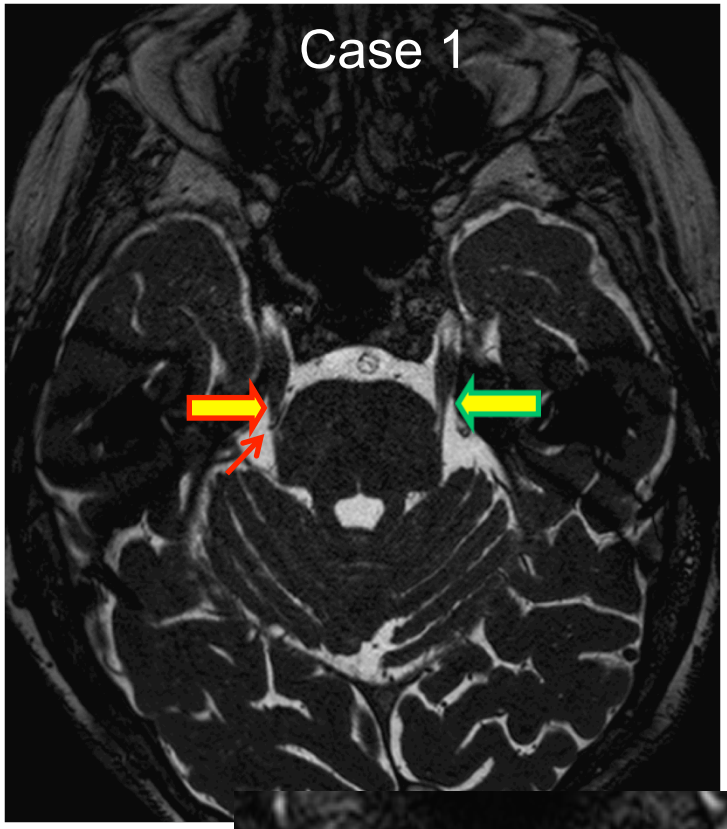
# Etiology

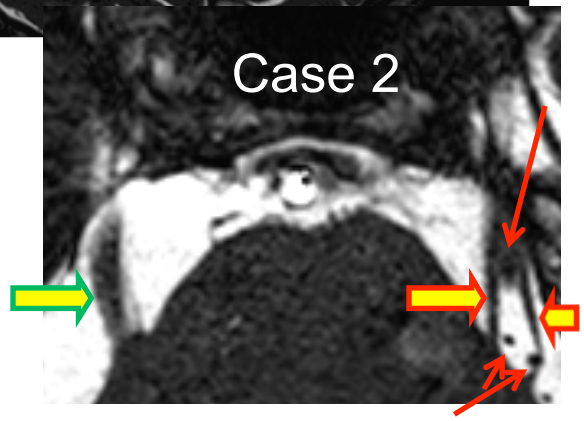
## Prevalence of neurovascular contacts, healthy subjects* and cadavers†

| Study | Any type | Severe |
|---|---|---|
| Klun, 1980† | 32% | 8% |
| Ueda, 1999* | 28% | 1% |
| Ramesh, 2009† | 39% | 11% |
| Peker, 2009* | 88% | NA |

## Prevalence of neurovascular contact, trigeminal neuralgia

| Study | Any type | | Severe | |
|---|---|---|---|---|
| | Sympt. | Asympt. | Sympt. | Asympt. |
| Masur, 1995 | 56% | 39% | 39% | 0% |
| Kuncz, 2005 | 62% | 10% | NA | NA |
| Miller, 2009 | 90% | 60% | 40% | 17% |
| Antonini, 2014 | 88% | 26% | 54% | 3% |



doi:10.1093/brain/awu349 BRAIN 2014: Page 1 of 9 | 1

BRAIN
A JOURNAL OF NEUROLOGY

# Significance of neurovascular contact in classical trigeminal neuralgia

Stine Maarbjerg,[1] Frauke Wolfram,[2] Aydin Gozalov,[1] Jes Olesen[1] and Lars Bendtsen[1]

- First blinded 3.0 Tesla study based in a neurological setting (n=135)
- Neurovascular contact (NVC) was prevalent both on the symptomatic (89%) and asymptomatic (78%) sides
- Severe contact was highly prevalent on symptomatic side (53%) but not on asymptomatic (13%) side
- Severe contact was caused by arteries (98%)

## Conclusions

- Simple NVC is common and often asymptomatic
- Severe NVC is involved in aetiology of TN
- Severe NVC is caused by arteries located in the root entry zone

*Maarbjerg et al, Brain 2015*

Original Article

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# Association between neurovascular contact and clinical characteristics in classical trigeminal neuralgia: A prospective clinical study using 3.0 Tesla MRI

Stine Maarbjerg[1], Frauke Wolfram[2], Aydin Gozalov[1], Jes Olesen[1] and Lars Bendtsen[1]

- Severe neurovascular contact was more prevalent in men (75%) than women (38%)
- No difference between patients with and without severe NVC in age or duration of disease

## Conclusions

- Severe NVC was much more prevalent in men than women
- Women may more often have other disease etiologies contributing to TN
- Severe NVC was not associated with age or duration of disease

*Maarbjerg et al, Cephalalgia 2015*

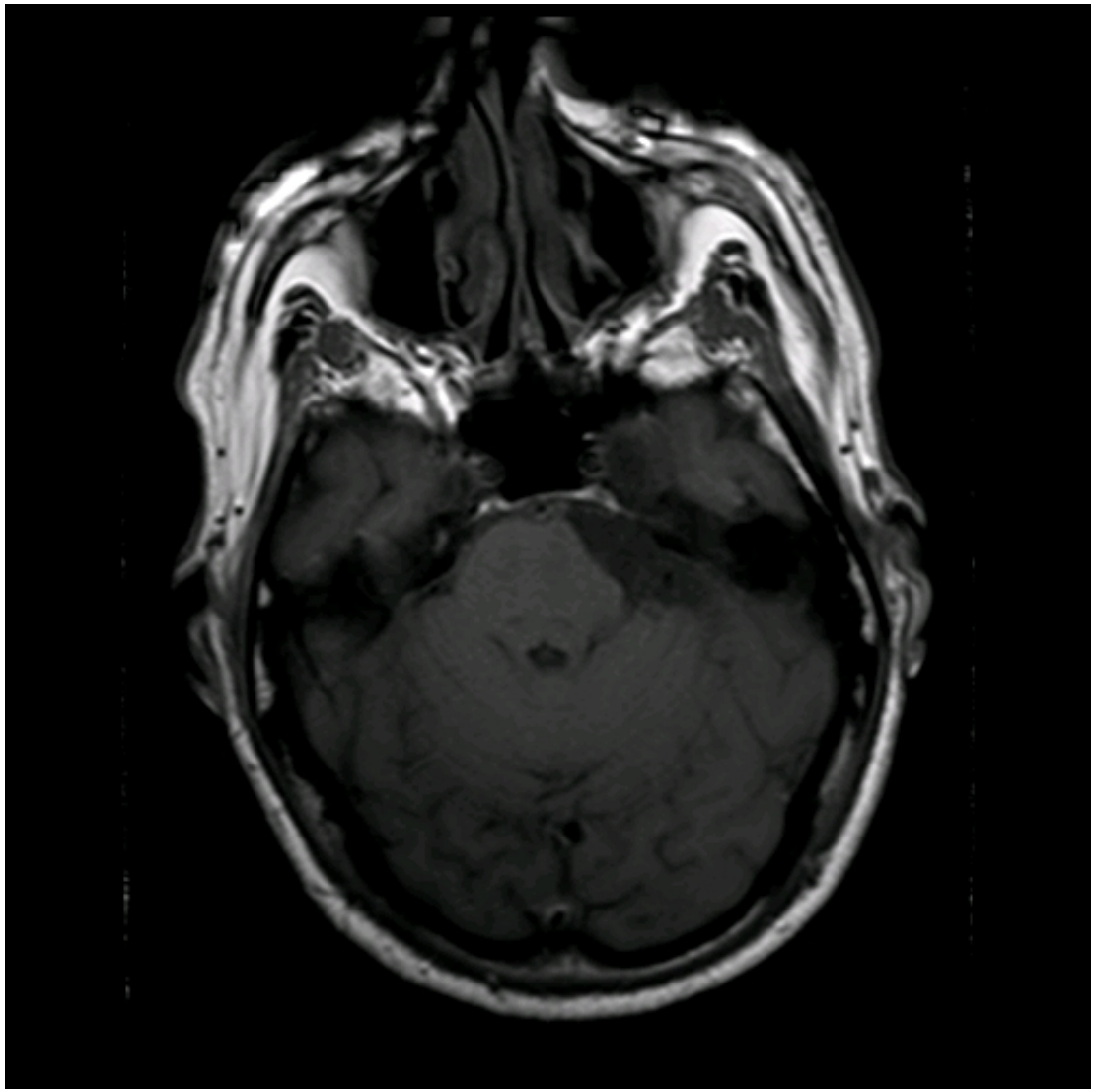
# Diagnosis

- Classical TN may or may not be caused by vascular compression
- Symptomatic TN is caused by a lesion other than vascular compression, e.g., space-occupying process in posterior fossa or multiple sclerosis plaque
- Approximately 15% of TN are symptomatic

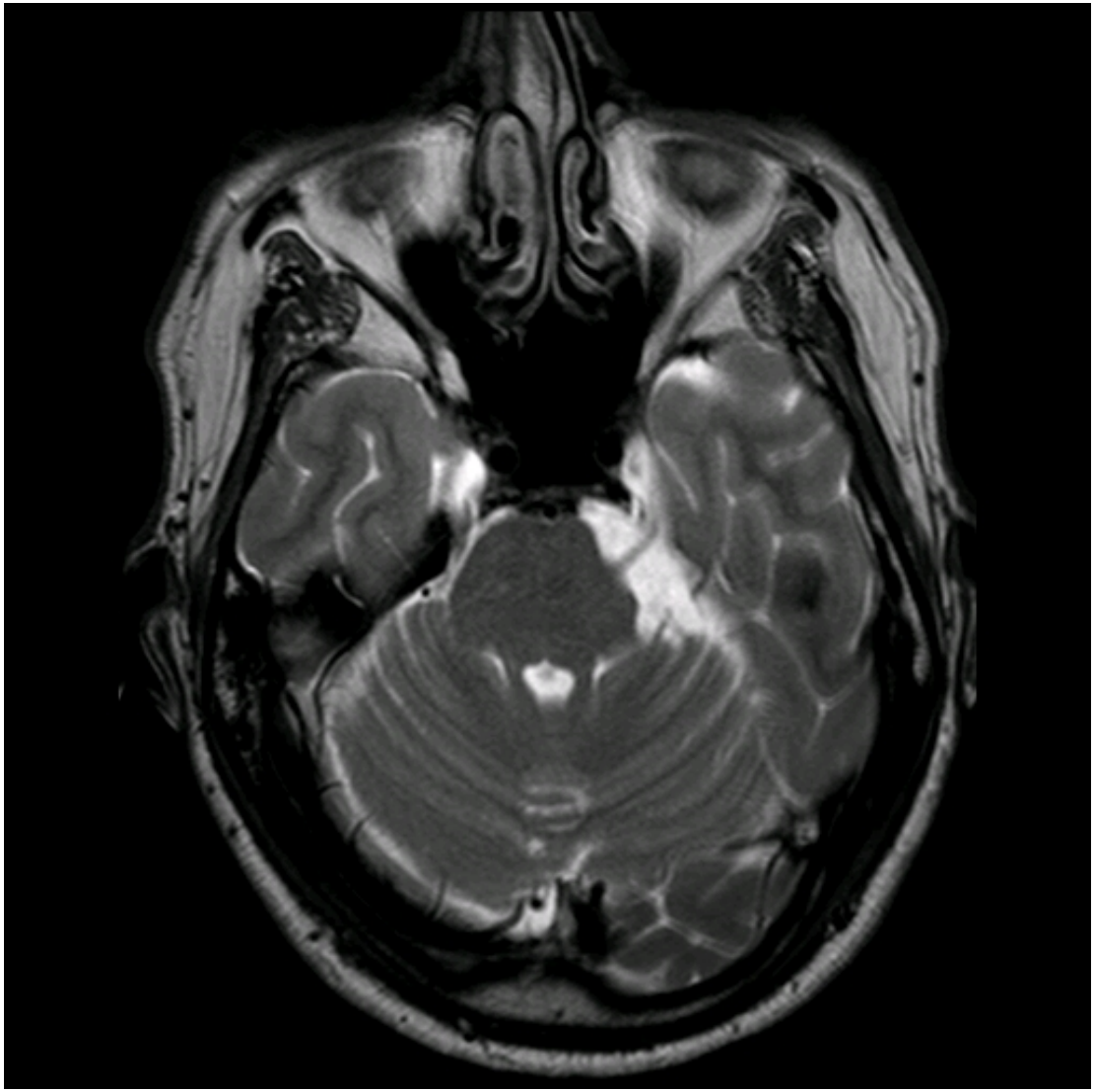
# Diagnosis

- How to differentiate between classical and symptomatic TN?
- Finding of sensory deficits and bilateral pain raises suspicion of symptomatic TN
- Age of onset, involvement of V1 or lacking effect of medications can not be used to differentiate
- Symptomatic TN can not be excluded clinically
- MRI should be performed in all patients

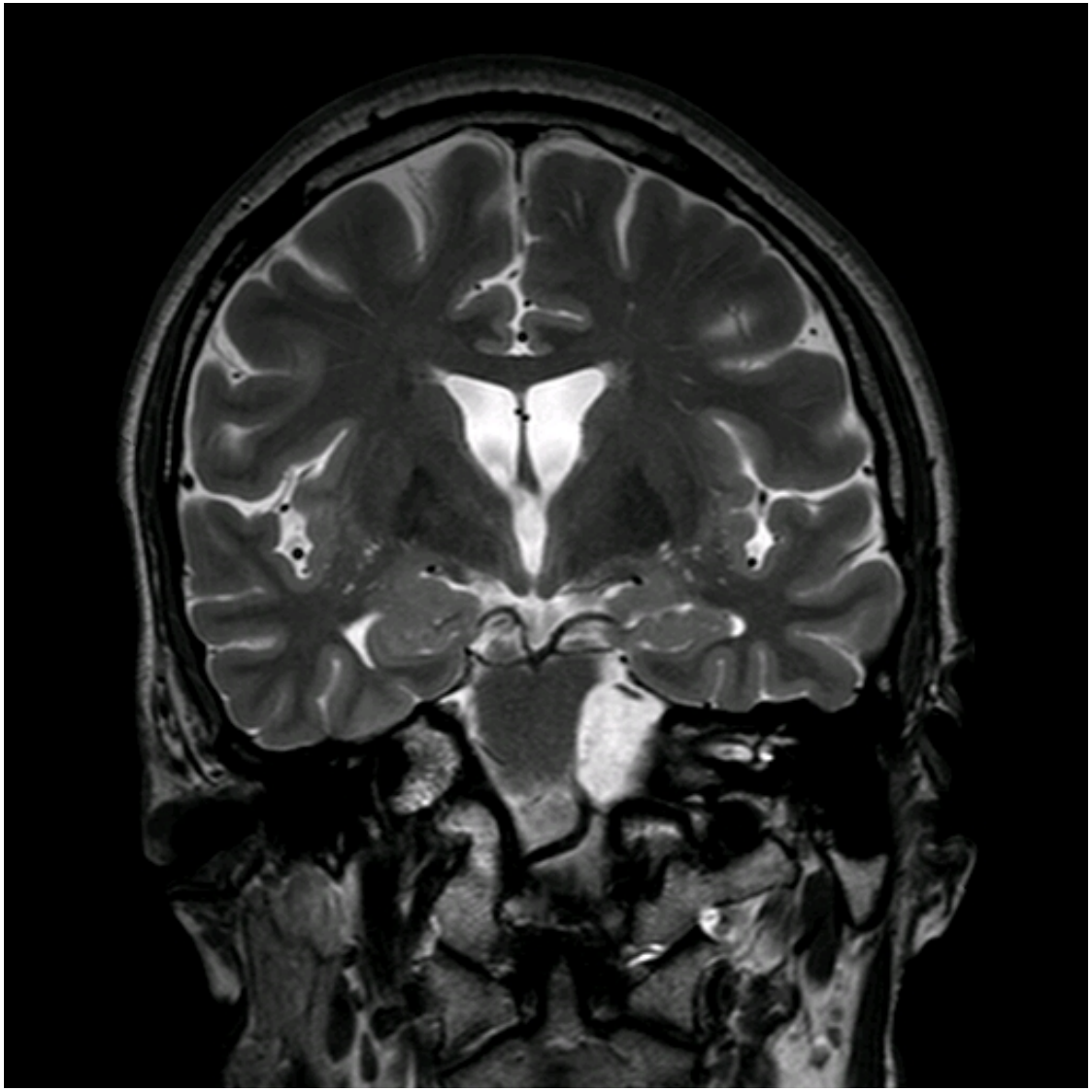
# T1



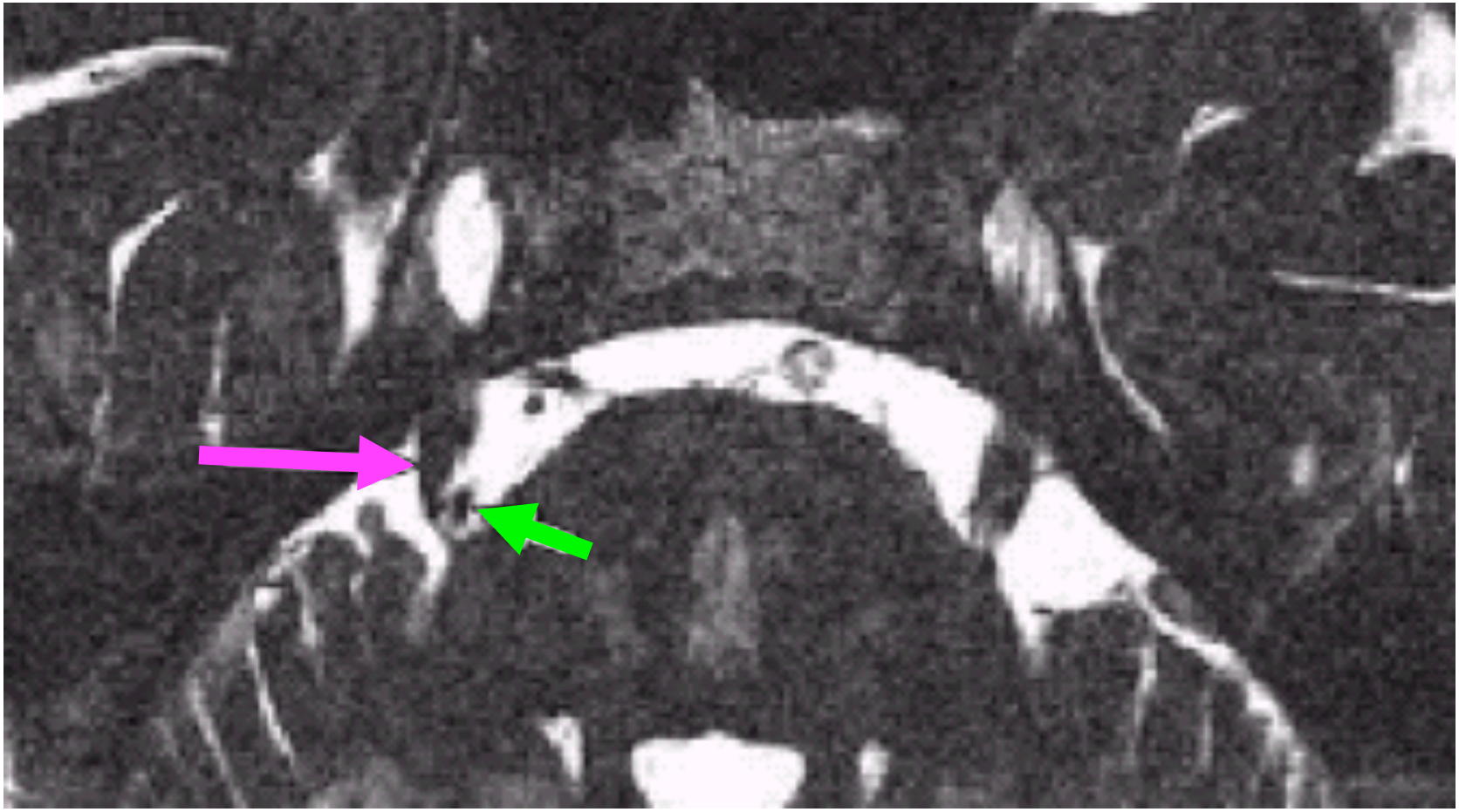
# T2



# T2

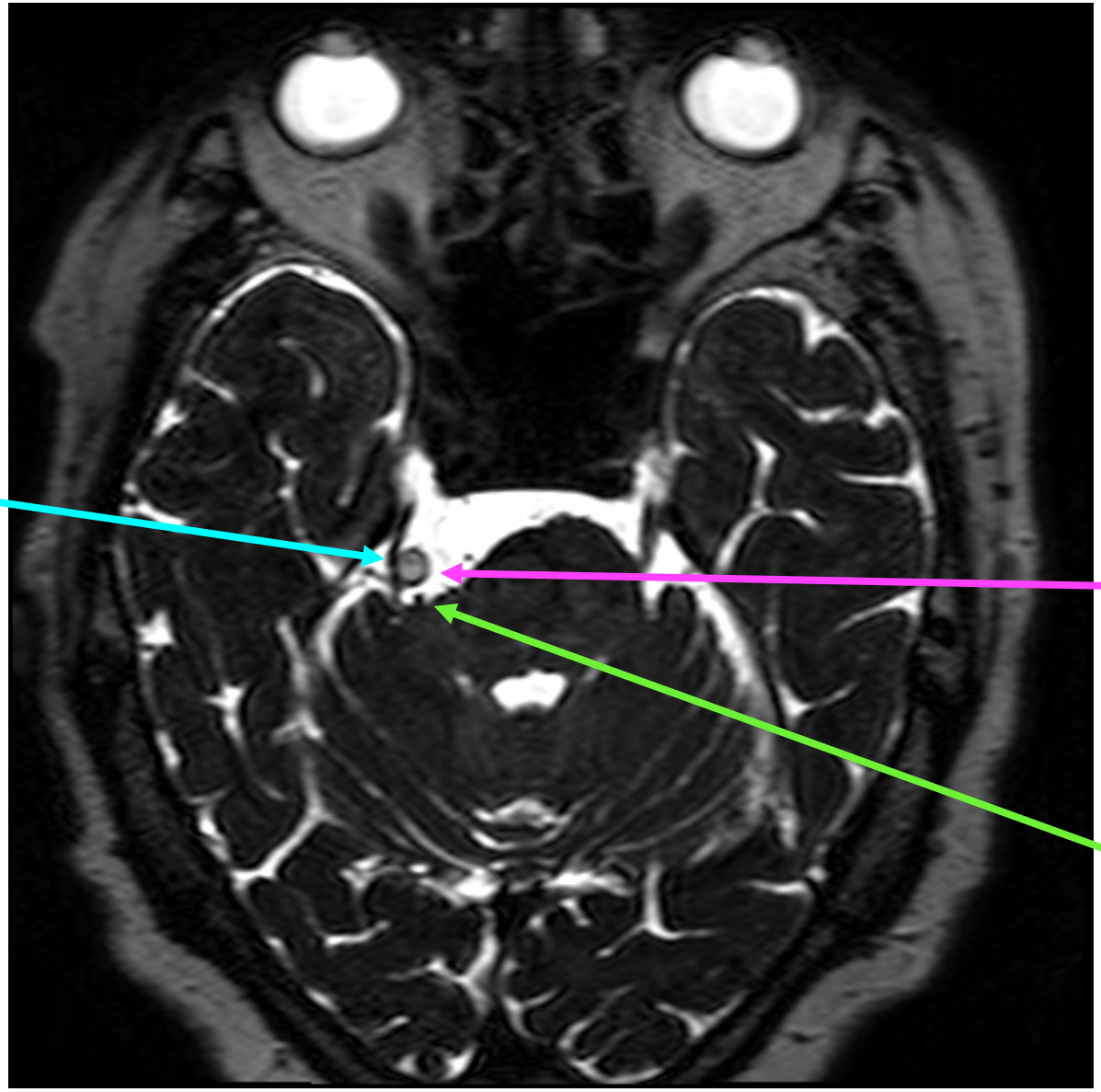


# MRI

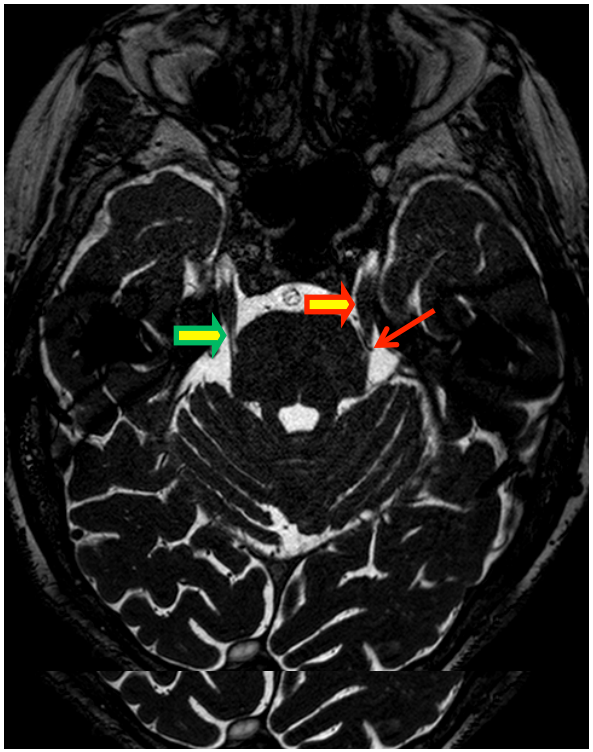


Superior cerebellar artery (**short arrow**) compresses trigeminal nerve (**long arrow**)

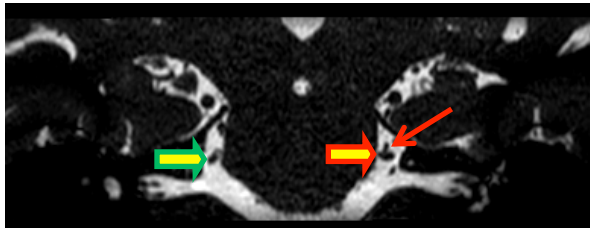
T2 ax


Right trigemi-nal nerve
Left vertebral artery
Right vertebral artery

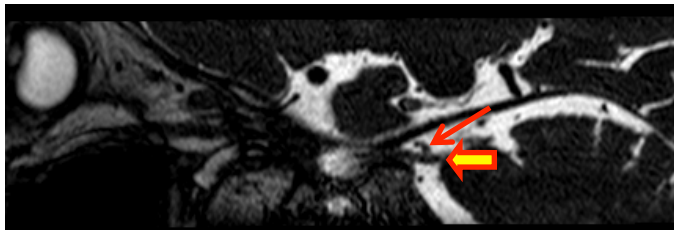
# 3.0 Tesla MRI in trigeminal neuralgia



Axial view
The brainstem is located in the middle



Coronal view of the brainstem



Sagittal view of the brainstem

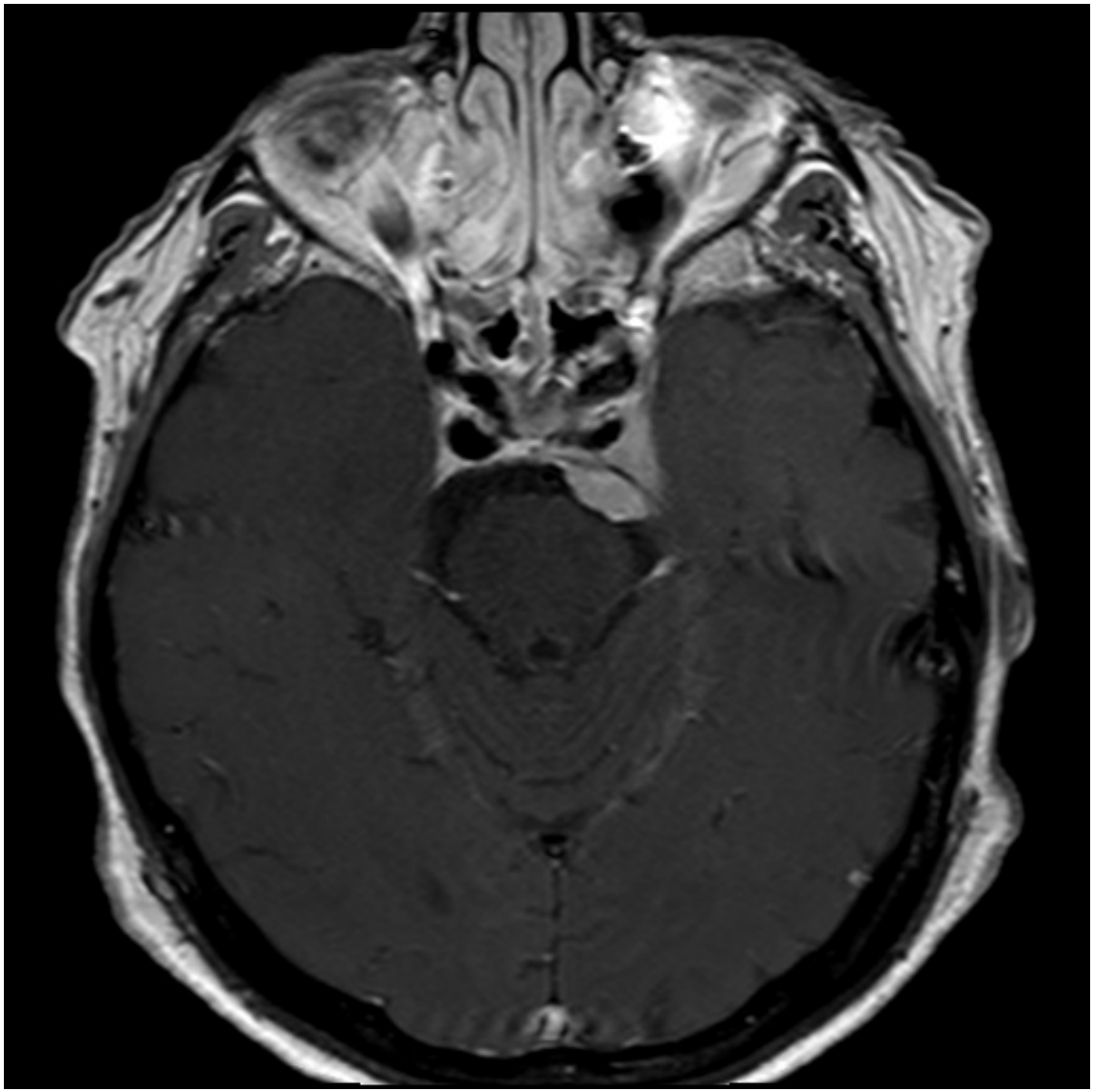
Artery

Affected (painful) left trigeminal nerve

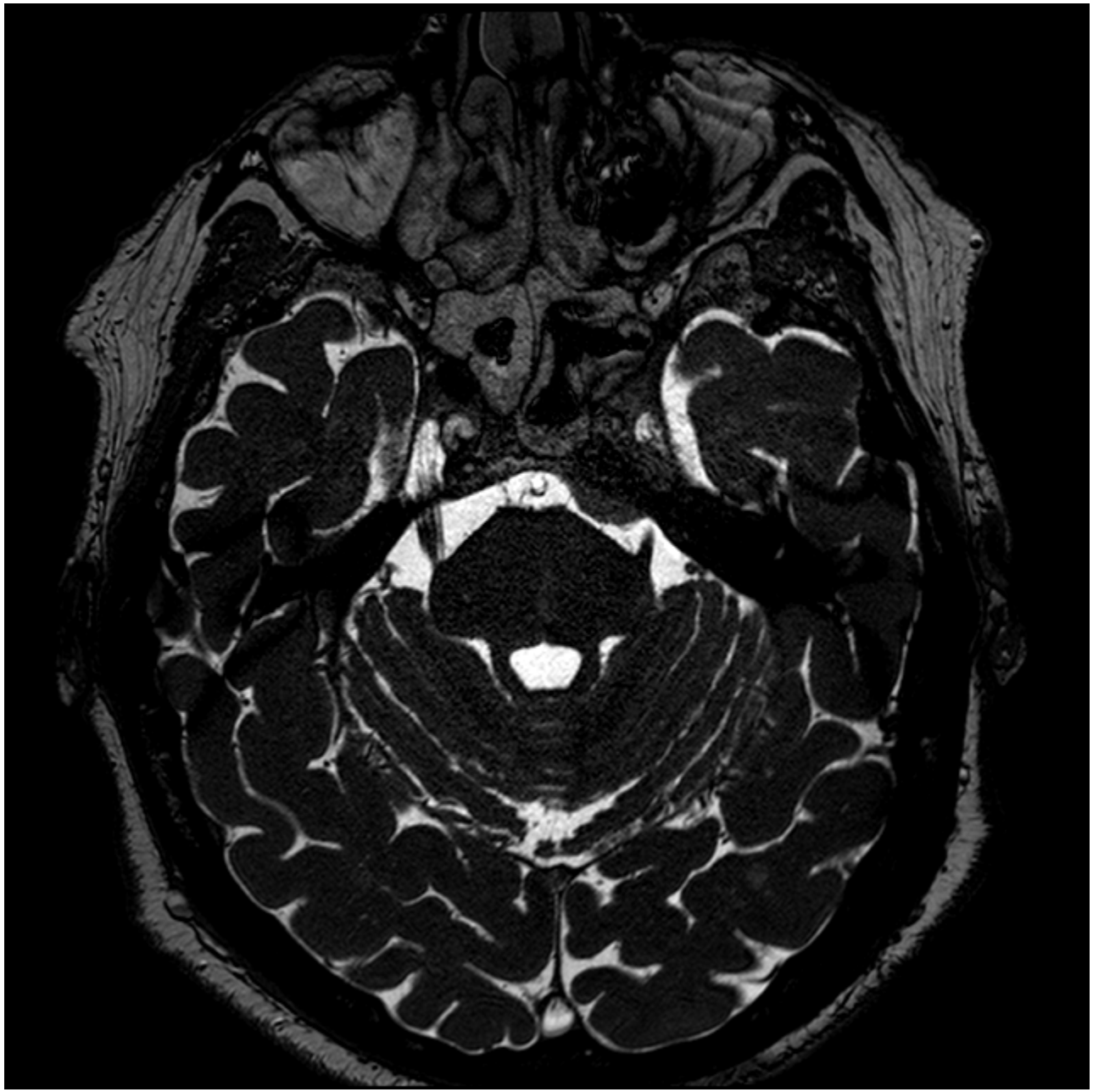
Unaffected (healthy) right trigeminal nerve

Balanced Fast-Field Echo MRI sequence, permission from Wolfram, Maarbjerg and Bendtsen

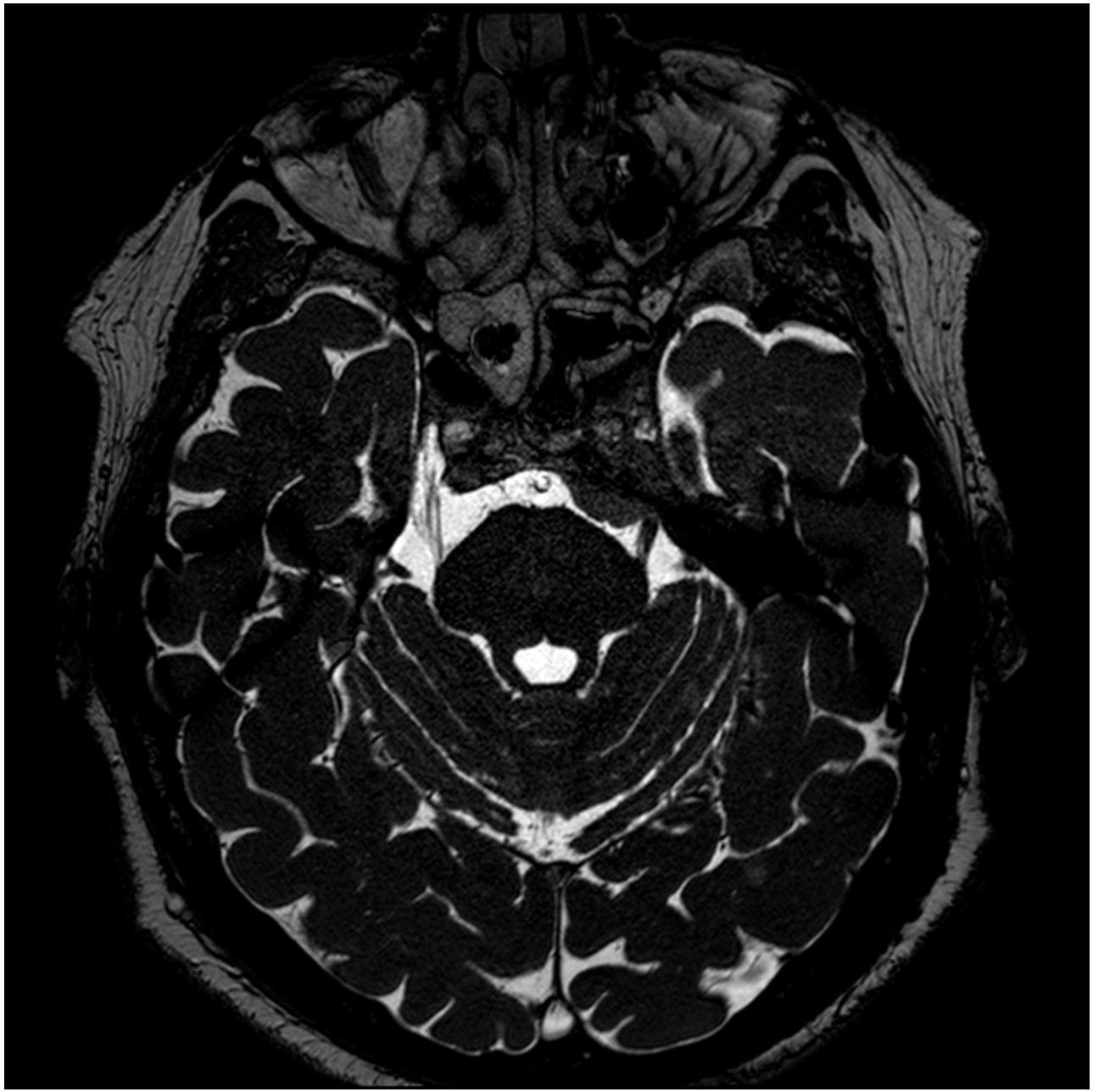
# T1



# T2



# T2



# Acute treatment

- Simple analgesics and opioids usually have no effect
- Severe pain may make it impossible to eat, drink and take medications
- Where acute intervention is needed, infusion of fosphenytoin during admission is usually effective (although no scientific evidence)

# Prophylactic treatment

- Carbamazepine (effective)
  - 60-70% of patients achieve a minimum 50% pain reduction
  - NNT = 1.7
  - NNH = 3.4
  - Typical maintenance dose is 200-1,200 mg daily
- Oxcarbazepine (probably effective)
  - Similar effect to carbamazepine, may be better tolerated
  - Typical maintenance dose is 600-1,800 mg daily

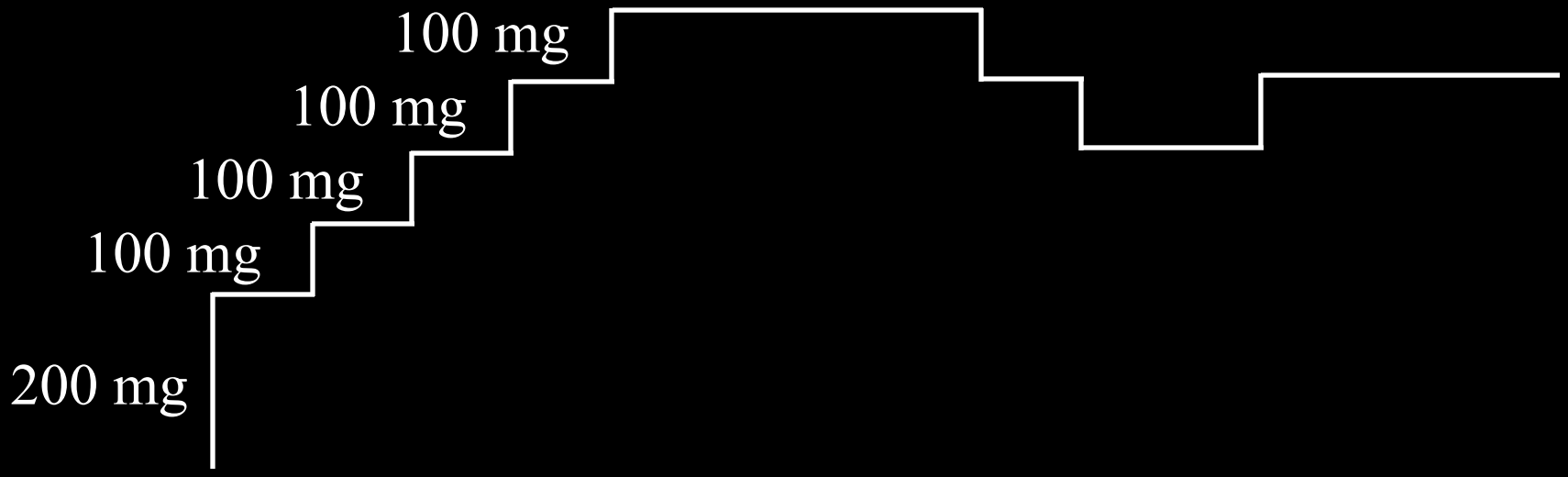
*Cruccu et al, Eur J Neurol 2008*

# Prophylactic treatment

- Gabapentin
- Pregabalin (possibly effective)
- Lamotrigene (possibly effective)
- Baclofen (possibly effective)
- Pimozide (possibly effective)
- Clonazepam
- Valproate
- Combination treatments might be useful

*Cruccu et al, Eur J Neurol 2008; Zakrzewska, Expert Opin Pharmacother 2010*

# Dosage should be adjusted according to severity of TN



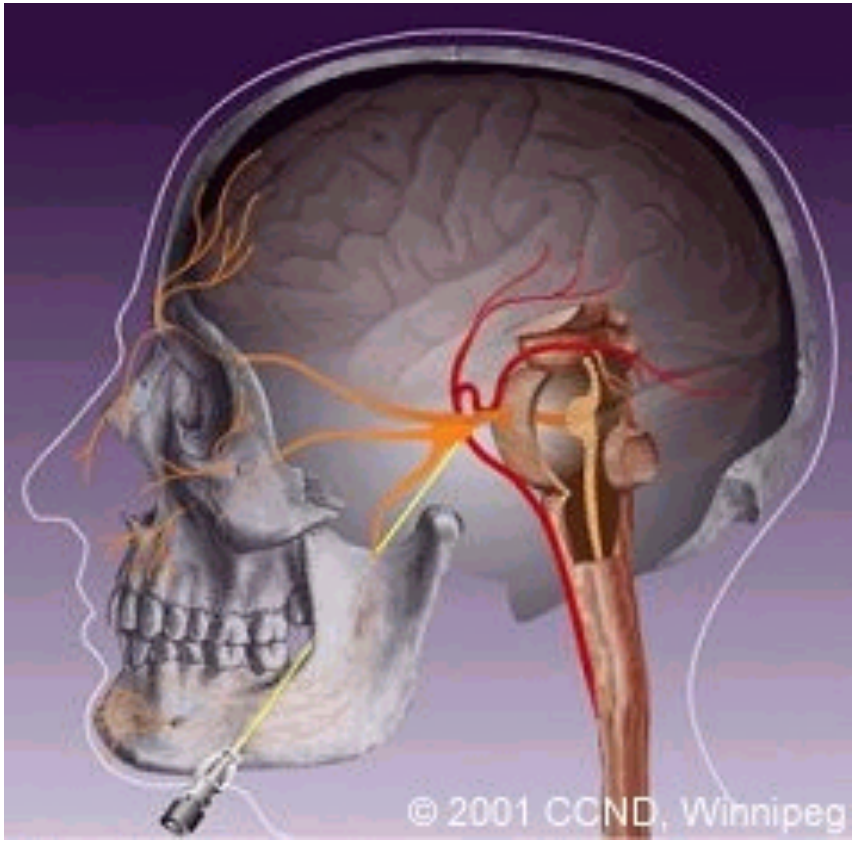

**Carbamazepine**

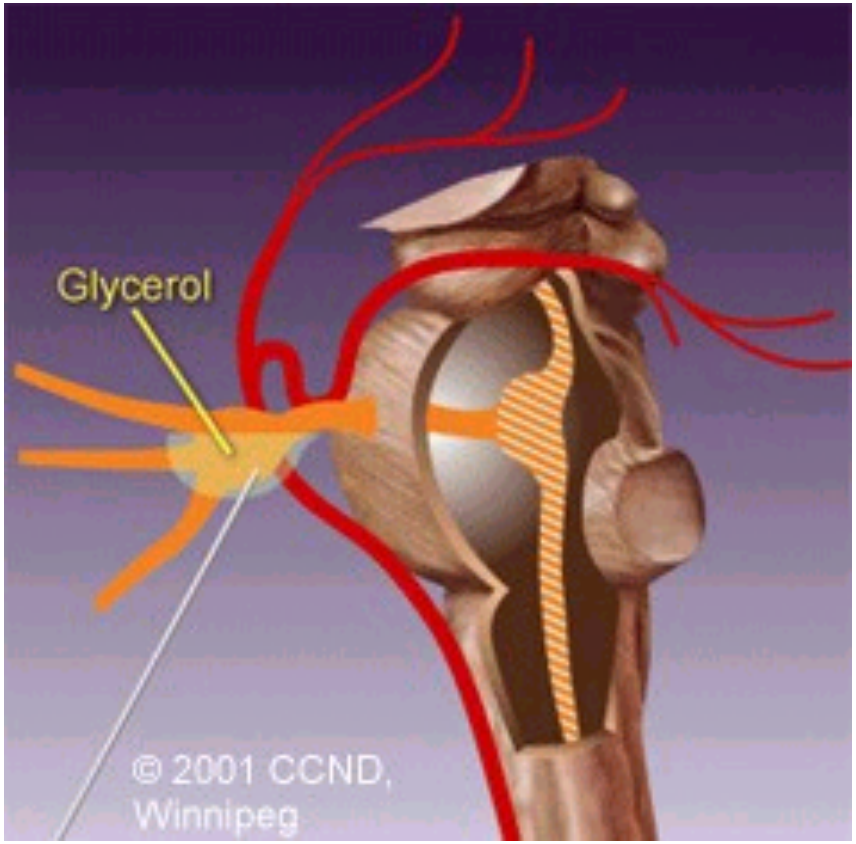
# Surgical treatment

- Should be considered if carbamazepine and oxcarbazepine are not effective or tolerated
- Should be done early to avoid central sensitization?
- 30% of patients in pain centres may need operation
- Peripheral techniques
  - Lidocaine, acupuncture, alcohol injection, cryotherapy, botolinum toxin

*Cruccu et al, Eur J Neurol 2008*

# Percutaneous procedures on the Gasserian ganglion



# Percutaneous procedures on the Gasserian ganglion

- Controlled lesion of trigeminal ganglion or root
  - Chemical (injection of glycerol)
  - Mechanical (inflation of balloon)
  - Thermal (radiofrequency thermocoagulation)
- Efficacy
  - 50% are pain free after 5 years?
- Complications
  - Sensory loss
  - Constant pain (anesthesia dolorosa)
  - Meningitis

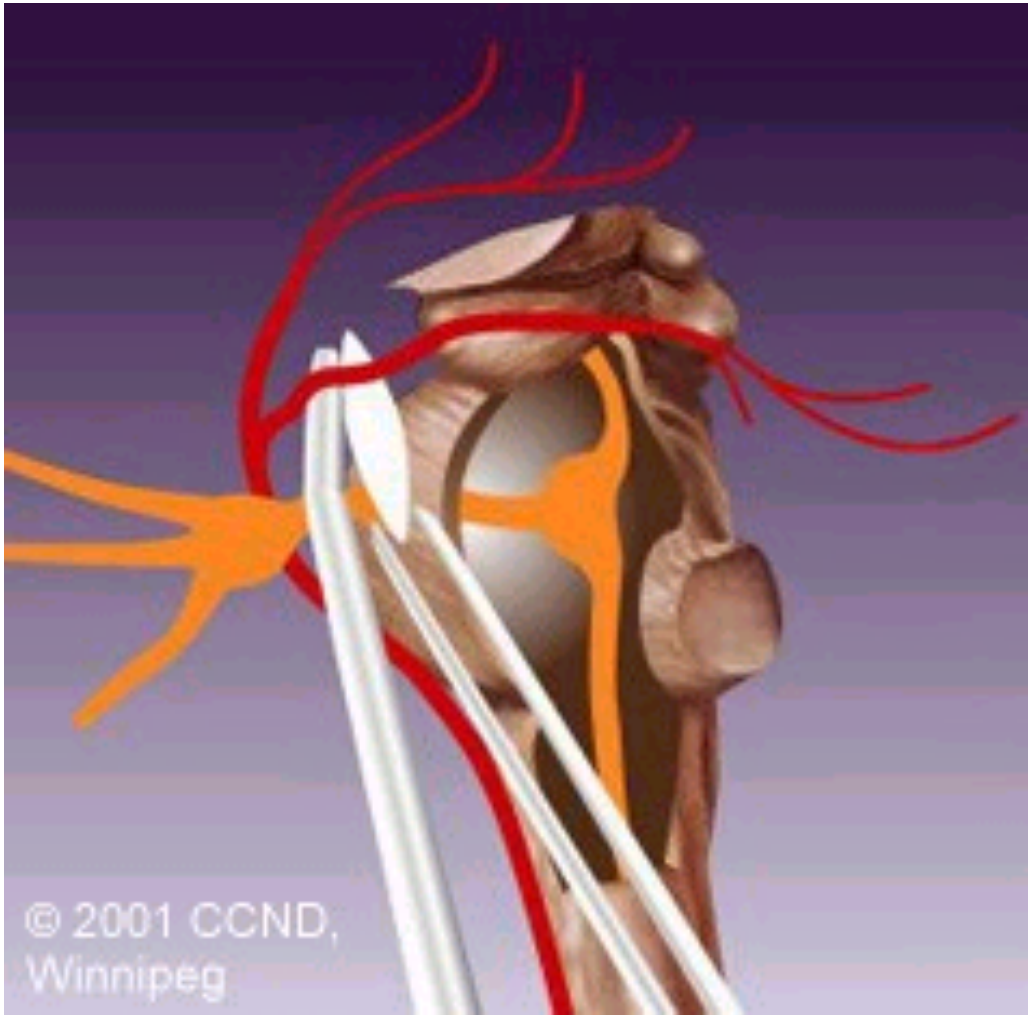
*Cruccu et al, Eur J Neurol 2008*

# Treatments of trigeminal root in posterior fossa

- Gamma knife surgery
  - Focused beam of radiation
  - 52% have effect after 3 years?
- Microvascular decompression
  - Craniotomy
  - Vessels compressing trigeminal nerve are removed

*Cruccu et al, Eur J Neurol 2008*

# Microvascular decompression



# Microvascular decompression

- Efficacy
  - 73% are pain free after 5 years?
- Complications?
  - Aseptic meningitis 11%
  - Sensory loss 7%
  - Ipsilateral hearing loss 10%
  - Mortality 0.2%
  - Morbidity lowest in high volume units

*Cruccu et al, Eur J Neurol 2008*

# Management
## Summary

- Primarily prophylactic pharmacological treatment with anti-epileptics
- Simple analgesics and opioids usually have no effect
- In case of acute aggravation, attacks may be interrupted with fosphenytoin infusion
- Spontaneous remission and aggravation is frequent
- Dosage should be adjusted according to severity of TN

# Management
## Summary

- In case of unsatisfactory effect from medical treatment, surgical therapy should be considered
- Percutaneous procedures on the Gasserian ganglion, gamma knife and microvascular decompression may be considered
- MVD possibly provides longest duration of pain freedom

# Suggestions for further reading

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33, 629–808 (2013).
2. Cruccu, G. et al. AAN-EFNS guidelines on trigeminal neuralgia management. Eur.J.Neurol. 15, 1013–1028 (2008).
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5. Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Trigeminal neuralgia - a prospective systematic study of clinical characteristics in 158 patients. Headache 2014:54(10):1574-1582.
6. Maarbjerg S, Wolfram F, Gozalov A, Olesen J, Bendtsen L. Significance of neurovascular contact in classical trigeminal neuralgia - Neurovascular abnormalities in trigeminal neuralgia. Brain 2015;138(pt2):311-319.
7. Maarbjerg, S., Gozalov, A., Olesen, J. & Bendtsen, L. Concomitant Persistent Pain in Classical Trigeminal Neuralgia - Evidence for Different Subtypes. Headache 54, 1173–1183 (2014).
8. Maarbjerg S, Sørensen MT, Gozalov A, Bendtsen L, Olesen J. Field testing of the ICHD-3 beta diagnostic criteria for classical trigeminal neuralgia. Cephalalgia 2014; 35(4):291-300.
9. Zakrzewska, J. M. & Akram, H. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. Cochrane.Database.Syst.Rev. 1–49 (2011).
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