Teaching Course 15

The “difficult to treat” headache patient - Level 3

Refractory trigeminal neuralgia

Giorgio Cruccu
Rome, Italy

Email: giorgio.cruccu@uniroma1.it
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Background.
Trigeminal Neuralgia (TN) is a unique neuropathic facial pain condition, characterized by unilateral paroxysmal pain in the distribution territory of one or more divisions of the trigeminal nerve, triggered by innocuous stimuli. Patients with atypical trigeminal neuralgia also suffer from concomitant continuous pain, i.e. a background pain between the paroxysmal attacks.

The most recent classifications (Cruccu et al. 2016; Headache Classification Committee of the International Headache Society 2018), which are going to be reflected in the imminent International Classification of Diseases 11 (ICD-11) distinguish three etiological categories of TN: classical TN (caused by neurovascular compression causing morpho-logical changes to the trigeminal root), idiopathic TN (no cause can be found), and secondary TN (caused by major neurological disease, e.g. multiple sclerosis or cerebellopontine angle tumours (Table).

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<th>Table</th>
<th>Definition and classification of trigeminal neuralgia (TN)</th>
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<td>Definition</td>
<td>TN is orofacial pain restricted to one or more divisions of the trigeminal nerve. With the exception of TN caused by multiple sclerosis, the pain affects one side of the face. It is abrupt in onset and typically lasts only a few seconds (2 minutes at maximum). Patients may report their pain as arising spontaneously but these pain paroxysms can always be triggered by innocuous mechanical stimuli or movements. Patients usually do not experience pain between paroxysms. If they do report additional continuous pain, in the same distribution and in the same periods as the paroxysmal pain, they are considered to have TN with continuous pain.</td>
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<tr>
<td>Classification</td>
<td>TN is classified in 3 etiologic categories. Idiopathic TN occurs without apparent cause. Classical TN is caused by vascular compression of the trigeminal nerve root. Secondary TN is the consequence of a major neurologic disease, e.g., a tumor of the cerebellopontine angle or multiple sclerosis. Either phenotype (with purely paroxysmal pain or with additional continuous pain) may occur with any of the 3 categories.</td>
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(From Cruccu et al. Neurology 2016; 87:220-8)
Pathophysiology. One aspect of pathophysiology is fully agreed, being supported by established neurophysiologic, neuroimaging, and histologic evidence (relevant references can be found in Cruccu 2017). Both in classic and secondary trigeminal neuralgia, the primary mechanism is focal demyelination of primary afferents near the entry (extraaxial or intraaxial) of the trigeminal root into the pons. Some investigators believe this area represents a locus minoris resistentiae (a site of lower resistance or higher susceptibility to damage) because it is the site where Schwann cells are substituted by oligodendroglia in providing the myelin sheath (Cruccu et al. 1990).

A second pathophysiologic step, admittedly more debatable, is that the damaged primary afferents, in the area of focal demyelination, become a source of ectopic generation of impulses. Demyelinated axons become hyperexcitable. Spontaneously, or because of a local direct mechanical stimulus such as the artery pulsation, ectopic activity is generated. The concept of ephaptic transmission (cross talk) from close, healthy nerve fibers, and the generation of high frequency discharges, is supported by evidence in animal models of focal demyelination of the trigeminal root. Although secondary changes of excitability and grey matter thickness are induced in the central nervous system—as in any other type of chronic pain—they are by no means necessary to develop typical TN.

Voltage-gated, frequency-dependent sodium channel blockers are the ideal candidates for dampening the high-frequency discharge that is perceived as an electric shock or stabbing pain. This is well documented by recordings from trigeminal ganglion neurons before and after vixotrigine (Figure 1).

Indeed, according to main neurological guidelines (Cruccu et al. 2008) this class of drugs, in particular oxcarbazepine (OXC) and carbamazepine (CBZ), are first line. The authors’ first choice is oxcarbazepine because of its better tolerability (Attal et al. 2010; Di Stefano et al. 2014). If the patient reaches the dosages adequate for most patients (1200 mg/d to 1500 mg/d) without achieving the desired pain relief (ie, she or he is one of the rare cases of a real nonresponder), no other drug will be enough. Hence surgery, being extremely efficacious in trigeminal neuralgia, should be proposed.
Refractory trigeminal neuralgia.

A real non-responder to OXC/CBZ is so rare in classical TN, that finding one must pose the problem of a possible misdiagnosis and warrant neuroimaging, neurophysiological, and genetic investigations. Aside from responders and non-responders, however, a third type of patient exists who requires the due consideration (see Treatment Algorithm, page 7). Some patients cannot take either of the two choice drugs because of specific contraindications (most frequently cardiac conduction problems or severe arrhythmias). Some other patients encounter serious side effects and allergic dermatitis, which, unfortunately, tend to be cross-reactive (i.e., the patients who had the allergic reaction to one of the two drugs cannot be switched to the other) or, in the case of CBZ, a fall in blood elements (white cells, red cells, or platelets) rarely reaching aplastic anemia. Indeed, patients on CBZ must undergo a complete blood count every 3 to 4 months. Both drugs may cause sodium depletion. Both drugs, being antiepileptic drugs, induce central nervous system (CNS) depression, presenting as somnolence, confusion, or imbalance. These central side effects, which are far more frequent with CBZ than OXC (Figure 2) (Di Stefano et al. 2014), may prevent patients from maintaining adequate doses. Hence, in this third group of patients, who are neither responders nor non-responders, other drugs can be tried. In this case, the AAN/EFNS guidelines (2008) suggest trying other pharmacologic options as monotherapy or add-on medications. In particular, analysis of the evidence-based trials led to the following suggestions: lamotrigine, baclofen, and pimozide. Unfortunately, neither baclofen nor pimozide represent a valid alternative. Only lamotrigine, used as add-on, and thus allowing the reduction of
OXC/CBZ to dosages that the patient can bear, may help (Zakrzewska et al. 1997).

Often, this third group of patients is eventually referred for surgery. Many patients, however, may not accept surgery that easily. We believe that in those patients who do not want to undergo any kind of surgical intervention, botulinum toxin injections of the trigger areas should be tried, particularly because a new drug, vixotrigine, will soon be available.

**Vixotrigine.**

A new voltage- and frequency-dependent sodium channel blocker, has been discovered that has selectivity for the sodium channel 1.7 (Nav1.7) subtype (Morriset et al. 2013). Nav1.7 is a major sodium receptor in the nociceptive system, but no Nav1.7 receptors exist in the brain. This absence of brain Nav1.7 receptors promises to prevent any side effects associated with depression of CNS excitability. Nav1.7 has been validated as a key pain target by human genetic linkage, as gain of function mutations are linked to a severe chronic pain syndrome, whereas loss of function mutations leads to the inability to feel pain. Furthermore, its efficacy and extreme tolerability has already been proved in patients in a phase-2 trial. Zakrzewska and colleagues (2017) have now demonstrated that vixotrigine can inhibit the firing of trigeminal neurons, adding further mechanistic support to the potential of this new molecule (Figure 1). Two big phase-3 trials are expected to begin in June 2018, one in Europe and one in the US.
**Botulinum toxin.**

The amount of published evidence about the efficacy of botulinum toxin injections is growing day by day, and the safety profile is very high. Reportedly, the pain relief lasts several months, and the main side effect is a transient weakness of the facial muscles in the injected area.

A systematic review (Morra 2016) identified 4 RCT, on 178 patients, testing the effect of BTX-A in patients with TN [Wu et al, 2012, Zhang et al, 2014; Zúñiga 2013; Shehata 2013]. The dosage used varies from 25 U to 100 U and the number of injections (subcutaneous or intradermal) from one to twenty. The overall effect favored BTX-A versus placebo in terms of proportion of responders; paroxysms frequency per day was significantly lower for BTX-A group. The duration of effect was relatively long (at least 3 months). Adverse events included transient facial weakness, edema and hematoma at the site of injection. Despite these encouraging findings, future studies assessing the optimal dose, duration of the therapeutic efficacy, adverse events, the time and indications for repeat injection are required.

Naturally, botulinum toxin injections should be performed by neurologists experienced in botulinum toxin injections for other established indications.

**Trigeminal neuralgia with concomitant continuous pain.**

No clinical trials assessing pharmacological treatment of background pain in atypical TN have been conducted. Different studies clearly demonstrated that concomitant continuous pain is associated with poorer medical and surgical outcome, i.e. the number of non-responders is higher in this TN phenotype (Obermann et al, 2008; Sandell and Eide, 2008; Zhang et al, 2013). Recently, in a prospective study totalling 158 patients
with typical and atypical TN, the prevalence of responders to sodium channel blockers was lower in the group with also concomitant continuous pain (Maarbjergerg 2014). On the basis of these data, constant pain is considered a predictor of poor treatment response. No study has assessed the drug effect in reducing constant and paroxysmal pain intensity separately. Because CBZ and OXC are extremely efficacious in increasing the refractory period of action potentials, they act on the high frequency discharges that characterize the paroxysms of TN. Naturally, in patients with also background pain mediated by other pathophysiological mechanisms, a monotherapy with sodium channel blockers may not be sufficient to control pain. Future RCTs assessing gabapentinoids and antidepressants as add-on treatment in patients with atypical TN are required.

Although botulinum toxin A is expectedly efficacious on constant pain, no study has so far assessed its differential effect in a patient with typical (purely paroxysmal) and atypical TN (with concomitant continuous pain).
Treatment algorithm for TN

- **OXC or CBZ**
  - **RESPONDER**
  - **NON RESPONDER**
    - cannot take OXC/CBZ because of contraindications or cannot reach full dosage because of side effects
      - second-line drugs (possibly in add-on)
        - **RESPONDER**
          - must be taught to self-adapt dosage to current severity of neuralgia
            - if an important adverse event occurs (such as aplastic anemia, sodium depletion or allergic dermatitis) try BoTox or send for surgery
        - **NON RESPONDER**
          - depending on the patient's attitude may try BoTox
            - SURGERY
              - can physically stand craniotomy and MRI demonstrated a significant neurovascular compression: microvascular decompression; if not: gamma knife or percutaneous ganglion lesions
References


