Global Year Against HEADACHE
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Neuromodulation in Primary Headaches

Definition

Neuromodulatory approaches can be divided into invasive procedures (peripheral nerve stimulation, vagal nerve stimulation, cervical spinal cord stimulation, and hypothalamic deep brain stimulation) and noninvasive procedures (transcutaneous electrical nerve stimulation [TENS] and transcranial magnetic and direct current stimulation).

The underlying principle is a modulation of neuronal structures that are directly or indirectly involved in detection or transmission of painful stimuli or in the processing of this information in the brain. This approach comprises a direct modulation of brain structures involved in the generation of attacks (deep brain stimulation of the hypothalamus in cluster headache), modulation of inhibitory antinociceptive pathways (occipital nerve stimulation), modulation of cortical excitability (transcranial magnetic and direct current stimulation), and direct inhibitory effects at the level of the peripheral neuron or the spinal cord (TENS).

Patient Selection

While noninvasive techniques can be used widely, patients scheduled for invasive approaches should be selected carefully, since these techniques are still experimental and harbor potential hazards. Based on previously published consensus criteria for the definition of refractory chronic cluster headache (CCH) and chronic migraine, patients undergoing implantation of an invasive neuromodulatory approach should satisfy the following criteria:

- The headache should be chronic and should have lasted for 2 years.
- Established prophylactic drugs should have been tried without success (or were either not tolerated or contraindicated) in a sufficient dose for a sufficiently long period as monotherapy or combination therapy. In CCH, at least verapamil, topiramate, and lithium and in chronic migraine at least beta blockers, calcium antagonists, and anticonvulsants should have been tried.
- Medication overuse should have been ruled out.
- In unilateral headache, attacks should always be on the same side (side-locked) if a unilateral device such as hypothalamic deep brain stimulation is scheduled.
- A symptomatic origin has been ruled out by a cerebral MRI scan with MR angiography of the intracranial vessels.

Patients should be treated only by an interdisciplinary team that includes an experienced headache specialist, a neurosurgeon, and others (such as a psychologist). Postprocedural care is mandatory after implantation, including optimization of stimulator settings.

Noninvasive Techniques

Transcranial Magnetic Stimulation (TMS)

- TMS transiently modulates the excitability of the brain.
- A magnetic field induces electrical impulses in a small area within the cortex of the brain.
- Single pulses (sTMS) were superior to sham stimulation of the visual cortex in acute migraine with aura, with a higher rate of patients being pain-free after 2 hours in one study. Studies on repetitive TMS as a prophylactic treatment of migraine showed ambiguous results.

Transcranial Direct Current Stimulation (tDCS)

- tDCS modulates cortical excitability depending on the polarity of the stimulation and is less focal than TMS.
- Cathodal tDCS of the visual cortex reduced migraine intensity and attack duration, but not frequency.

Transcutaneous Electrical Nerve Stimulation (TENS)

- Effects are conveyed by electrical stimulation of the skin within a painful area with varying intensity and frequency. Stimulation of nerve fibers sensitive to touch is thought to modulate neurons transmitting nociceptive stimuli at the level of the spinal cord.
- Despite some positive small studies, meta-analyses have failed to provide convincing evidence that TENS is effective in primary headaches.

Invasive Techniques

Deep Brain Stimulation (DBS)

- Electrodes are surgically implanted directly into the target structure in the brain, such as the posterior hypothalamus in cluster headache and other trigemino-autonomic headaches.
- Hypothalamic DBS has so far been used to treat more than 58 patients with CCH, 3 patients with SUNCT (short-lasting unilateral neuralgiform headache with conjunctival injection and tearing), and one with chronic paroxysmal hemicrania. It was effective in more than 50% of the patients (defined as at least 50% reduction in headache frequency). The only double-blind placebo-controlled study did not substantiate a significant effect but did so in the subsequent open phase.
- Potential side effects are limited in most cases and include infection of the electrode tip or lead, syncope, and double vision. In 3% of patients, intracerebral bleeding was described, which in one case was fatal. DBS has not been tried in migraine.

Occipital Nerve Stimulation (ONS)

- Electrodes are subcutaneously implanted close to the great occipital nerve, which innervates the back of the head. An impulse generator containing the batteries is connected to the electrodes via a cable and implanted subcutaneously above the pectoral or gluteal muscle. To avoid a side-shift in unilateral headaches, electrodes should always be implanted bilaterally.
- ONS has been used in more than 60 patients with chronic cluster headache. More than 50% reported improvement (defined as a more than 50% reduction of headache). Sustained benefit was found in one study with 14 patients: 11 patients improved by at least 90% over a mean period of 3 years. In chronic migraine, two studies, one with 51 patients and the other with 125 patients, yielded ambiguous results. Small series with good efficacy have been published in hemicrania continua, SUNCT, and occipital neuralgia.
- Side effects of ONS are generally mild. A mild feeling of paresthesia (tingling, pricking, or numbness) at the site of stimulation is inherent in the method and is essential for a good outcome. Lead migration, battery depletion, and local infection are common problems.

Sphenopalatine Ganglion Stimulation (SPGS)

- A microstimulator is surgically placed below the cheekbone with the electrode tip close to the sphenopalatine ganglion. It is driven by an external controller via an induced current. In previous studies, electrodes were placed percutaneously into the ganglion and powered externally.
- The microstimulator is currently being used in an ongoing trial to test its efficacy in aborting attacks in CCH. Preliminary effects are promising, with an improvement of 80% or more in 5 of 7 patients. External SPGS aborted 11 out of 18 spontaneous and induced cluster headache attacks. In chronic migraine, external SPGS had a pain-relieving effect in 5 out of 10 patients.
- Side effects were generally mild and transient. Temporary numbness in V2 was reported most frequently, and neuropathic pain occurred in one patient.

Other Neuromodulatory Approaches

- Vagal nerve stimulation: There are only anecdotal reports of its efficacy in CCH and migraine.
- High cervical spinal cord stimulation: In a case series of seven patients with CCH, spinal cord stimulation decreased attack frequency in all patients. However, five patients required lead revision due to dislocation or breakage.
- Supraorbital nerve stimulation: There are anecdotal reports of efficacy in migraine and cluster headache. Combined stimulation of the supraorbital and the occipital nerve could be more effective.

Conclusion

- Neuromodulatory approaches are a promising add-on to our therapeutic armamentarium in refractory headache.
- Invasive approaches should be considered only in refractory patients with chronic conditions after careful selection.
- Although experience is still limited, occipital nerve stimulation should be considered in chronic cluster headache and—to a limited extent—in hemicrania continua, chronic migraine, and occipital neuralgia. In CCH and in SUNCT syndrome, hypothalamic deep brain stimulation can be tried as an alternative. Sphenopalatine ganglion stimulation is promising, but it requires further proof of efficacy.
- Noninvasive approaches are preferable, but due to a lack of solid studies and technical limitations, their

implementation in routine clinical practice is problematic.

References

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