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Neurosurgical Treatment of Neuropathic Facial Pain Syndromes

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Abstract

Neurosurgical Methods against Atypical Facial Pain, Neuropathic Pain, and Cluster Headache including Explanation of Mechanism of Functional Neurosurgery. Pain is treated primarily pharmacologically or by physical medicine or behavioural interventions. Conditions refractory to conservative non operative strategies are challenging. If the chosen conservative methods are ineffective, specialists like functional neurosurgeons are consulted for invasive methods. The following article will inform on functional neurosurgical treatments against neuropathic and atypical facial pain. An interdisciplinary approach in complex pain syndromes is mandatory.

Keywords: Atypical Facial Pain; Capsula Interna; Deep Brain Stimulation; Facial Pain; Ganglion Gasseri Stimulation; Implantable Electrodes; Neuromodulation; Neuropathic Facial Pain; Neurostimulator; Neurosurgical Pain Therapy; PAG; Pain; Periaquaeductal Grey; Periventricular Grey; Pulse Generator; PVG; Sensory Thalamic Nuclei; Stereotaxy; Tic Doloureux; Trigeminal Neuralgia

Introduction

Pain is an integral part of endogenous protective reaction to external or internal factors. The goal is to maintain the integrity of the tissue by early detection. In the medical field, pain plays a key role; it can be seen as a specific symptom, e.g. in acute appendicitis. Furthermore, pain can be identified as a chronic disease. In both cases, the need for specific, formal identification as well as specialized therapy exists. According to the world health organization (WHO), pain therapy should treat all forms of pain effectively. It is a well-known fact that this ultimate goal is difficult to reach.

New possibilities of interference with neuronal functions without damaging the organism arose with the development of Neuromodulation over the course of the last 40 years. The main field of action for Neuromodulation is neuropathic pain as well as selected forms of nociceptive pain, which do not correspond to conventional pain therapy according to WHO recommendations. Due to its high level of invasiveness, neurosurgical pain therapy is always considered as the last step in a multimodal therapy setting.

It is not uncommon that patients suffering from major chronic pain never reach this last step, and physicians who treat them often eventually have to accept the untreatable, chronic form of pain. Since pain is almost invisible to others, empathy with these patients is very difficult. Other factors that may complicate adequate treatment of chronic pain are competition between medical disciplines, cultural idiosyncrasies, as well as the feeling of a „personal failure“in case a doctor must admit that a patient suffers from chronic pain. In this article we present an overview of neurosurgical pain therapy for neuropathic facial pain.

Basics

Nociceptive Pain

Pain can be caused by mechanical, thermal, or chemical damage to the tissue. It can be classified as nociceptive, neuropathic, or functional types. In the following section, we briefly describe anatomic and physiological properties of pain sensation and

processing, since these are the basics for neurosurgical pain therapy. Chronification of pain, pain memory, the processing of chronic pain, neurotransmitters, neuromodulators, first messenger and second messenger systems of microglia and astrocytes have been addressed in earlier manuscripts.

In nociceptive pain, stimulus reception occurs in peripheral receptors, i.e. end-bulbs of Krause and Ruffini corpuscles and free nerve endings. Afferent C- and A-delta fibers then transmit the stimulus to the dorsal column of the spinal cord, i.e. nociceptive synapses in the substantia gelatinosa. From there, the signaling pathway follows via ascending spinal cord neurons through the spinothalamic and the spinoreticular tract to the brainstem, on to the thalamus and finally to the cerebral cortex. Studies based on functional imaging (Positron Emission Tomography [PET]) demonstrated that several structural centers perform pain processing and sensation, i.e. thalamus, basal ganglia, mesencephalon, periaqueductal gray, anterior cingular cortex, insula, primary sensory cortex I+II, motor cortex, premotor cortex, supplementary motor cortex, prefrontal cortex, posterior parietal cortex, and cerebellum.

The lateral pain conduction mainly describes sensoric-discriminative aspects of pain processing; the medial system mostly motivational-affective and cognitive-evaluative aspects. Pain memory seems to be contained within the medial system, as well as autonomous and endocrinal reactions. The lateral system conducts signals through the spinothalamic tract and the ventrobasal thalamus to the primary (I) and secondary (II) sensor cortical areas, to the parietal operculum, and the insular cortex. In the medial system, signaling pathways run through the spinothalamic tract and the intralaminar and medial thalamic nuclei to the anterior cingular cortex, the amygdala, hippocampus, and hypothalamus as well as spinoreticular projections to the parabrachial nucleus and coeruleus locus and via spinomesencephalic projections to the periaqueductal gray matter **[1]**.

Neuropathic Pain

Contrary to nociceptive pain, neuropathic pain is caused by direct injury to the nervous system itself by traumatic, inflammatory, or toxic damage to a peripheral nerve, the plexus, the nerve root, or the central nervous system (infarction or intraparenchymal hemorrhage) **[2]**. This damage leads to a loss of information within the central nervous system and is accompanied by a hypesthetic area and burning pain. Damage or dysfunction of nociceptive fibers lead to an abnormal impulse generation or even the complete loss of it, thus creating neuropathic degenerations to the axon, glia tissue, and the surrounding tissue. A decrease in concentration of substance P and calcitonin-generated-peptide as well as an increase of galanine and neuropeptide Y in afferent neurons lead to hyper excitability and ectope neural pacemaker function. Furthermore, changes to the integrity of neural cell membranes take place. Endogenic suppression of pain with descending effects can terminate nociceptive input to the myelon by releasing noradrenalin and serotonin. In patients with chronic pain, the activability of this descending inhibition is reduced. Activation of glial cells caused by injury to a peripheral nerve, inflammation, or a strong pain stimulus promotes hyperalgesy. On the other hand, inhibition of glial cells prevents hyperpathy. Propentofylline may inhibit glial cells and therefore prevents hyperpathia. For further information on this topic, see current basic research of pain physiology.

As mentioned above, neuropathic pain is associated with a loss of information in the central nervous system. The information is conducted in form of electric impulses. The thalamus receives little or no information, electric impulses in the afferent sensory system. Thalamic nuclei involved in pain processing are the ventral postero-lateral nucleus, the ventral postero-medial nucleus, the ventral postero-internal nucleus, the posterior nuclei, and selected inter laminar nuclei. Pain is processed via bursts that are forwarded via sensor and/or nociceptive fibers from the peripheral system to the brain. If this information is missing, a sensory deficit, i.e. hypoesthesia, occurs. In neuropathic pain, the missing information is replaced by dysesthesia, or more commonly, allodynia.

Neurosurgical Therapy

Neuromodulation and Stereotactic Surgery

Neuromodulation can be described as a reversible electrical interference of neural structures. Around year 60 in our time, the Roman physician Scribonius Largus used torpedo fish and electric eels to treat arthritic joint pain and headache **[3]**. After the development of the first cardiac pacemaker in Stockholm in 1958, evaluation of implantable neural stimulators began. Over the last 60 years, persistent stimulation of the spinal cord and the brain has proved to be a viable option for treatment of neuropathic pain. In 1967, Shealy and Mortimer published the first report of subdural spinal cord stimulation for treatment of neuropathic leg pain **[4]**. In the 1960s, Deep Brain Stimulation was developed and performed as an experimental treatment of chronic pain **[5-17]**. Since fully implantable stimulation systems were not available until the 1970s, lesional surgery and lobotomies were performed. In 1974, the first fully implantable, monopolar stimulation electrode became available and in 1981, the first prototype of a full implantable stimulation system was introduced. The battery lifetime of earlier systems was initially limited to a maximum of 6 years; since 2009, rechargeable systems with a more than sufficient lifetime are available. By using stereotactic devices intraoperatively, it is possible to perform minimal-invasive surgery via small trepanations in order to treat movement disorders and psychiatric disorders.

Stereotactic devices are highly sophisticated mechanical instruments that have been developed between 1880 and 1960. In stereotactic surgery, a rigid circular frame is attached directly to the patient's head. Geometric localizer plates that are visible in x ray imaging and computed tomography (CT) or magnetic resonance imaging (MRI) scans are fixed to the frame. The acquired imaging data were transformed to a virtual three-dimensional stereotactic space related to the frame and every single point within the patient's brain can then be addressed by three dimensional Cartesian coordinates x,y,z. For accurate,

minimally-invasive trepanation, an insertion guide is attached to the frame. The cerebral structure that is intended to be treated can then be stimulated by electrodes with different amplitudes and currents. The depth of current distribution can be varied by using increasing currents intensities; thus, unwanted damage to adjacent neural structures can be avoided.

By stimulating cerebral structures before therapeutic sclerotherapy, it is possible to identify functional areas accurately. As mentioned before, field current distribution plays an important role in stereotactic surgery; however, by modulating the frequency, different effects on brain tissue can be evoked.

Low frequency simulations with (1 to 80Hz) cause neuronal activation or excitation; higher frequencies above 100Hz cause blocking or inhibition effects of neuronal activity. As an example, stereotactic treatment of Parkinson's disease is performed by inhibition stimulation of the subthalamic nucleus.

Over the last 30 years, Deep Brain Stimulation has proven to be an effective treatment for movement disorders **[18]**, while lesioning procedures such as neurotomies and amputations have been performed for over 2000 years.

Neuromodulation as treatment for chronic pain has been available for 60 years, turning away from destructive procedures. These surgical procedures can be separated into peripheral and central procedures. Peripheral neurostimulation or spinal cord stimulation are performed by all surgical subgroups such as neurosurgery, anesthesia, general medicine, plastic surgery, vascular surgery, orthopedics, and traumatology. Surgery on the central nervous system itself, especially the brain, should be performed only by specialized and highly experienced neurosurgeons. For unexperienced neurosurgeons, deep brain stimulation and stereotaxis may be too challenging. Therefore, it is recommended to maintain highest quality in neurosurgery the number of neurosurgeons specializing in this area has to be kept at a low level to keep highest experienced surgeons due to limited cases.

Atypical Facial Pain

Neuropathy of the Trigeminus Nerve

Neuropathic pain originating from the trigeminus nerve may be caused by direct trauma to the nerve in its central course, the gasserian ganglion, or to the peripheral branches (orbital nerve, maxillar nerve, mandibular nerve). Trauma may occur by traumatic head injury/traumatic brain injury or by iatrogenic impairment during surgical procedures on the head and face. However, anatomical variances, eg. the Eagle´s syndrome may cause such a state, too **[19]**.

Patients affected initially present dysesthesia and may develop burning pain with dysesthesia and allodynia. Complete disruption of afferent fibers may lead to one of the most painful conditions in humans, analgesia dolorosa. It encompasses a complete loss of sensation together with permanent burning pain and very often with allodynia and dysesthesia. This condition presents an extremely high grade of impairment and is accompanied by a high suicide rate among afflicted patients. Pain medications such as NSAIDs and opioids have only a very limited effect, even when administered in high doses. Even though neuroleptic medication and tricyclic antidepressants such as pregabalin, gabapentine, or amitriptyline may show better results but international guidelines are talking of a desired 30% pain reduction being very little for such a disastrous condition. Very often administration of this medication must be reduced or terminated due to undesired side effects associated with long-term usage. For further information, see literature on conservative treatment of neuropathic pain **[20,21]**. The following section considers surgical treatment of trigeminal neuropathy **[22]**.

Until the 1970s, trigeminal neuropathy was not considered as an entity separate from other neuropathies despite different underlying pathologic conditions. Therefore, treatment options were rhizotomies and tractotomies (medullar, pontine, mesencephalic, and spinothalamic tracts). Morbidity and mortality rates were comparatively high, as was the rate of recurrence. Beginning in 1947, stereotactic mesencephalotomies were introduced. Less invasive methods included thermocoagulation or rhizotomy of the gasserian ganglion with glycerol injections. Prof. William Sweet performed thermocoagulations of the ganglion; he observed that patients already reported pain relief during probative stimulation of the ganglion for proving correct position of the probes **[23]**.

Patients suffering from typical trigeminal neuralgia report zapping pain, usually without loss of sensation **[24]**. The suspected underlying cause is a pathologic contact between nerve and vessels in the trigeminal root entry zone **[43]** or hyperactive trigeminal nuclei (E.W. personal communication with A. Moller), i.e. a short span of the trigeminal nerve before the entrance into the brainstem anatomically related to the CNS (central nerve system) instead of PNS (peripheral nerve system) **[43]**. In this area, the neural sheath consists of more vulnerable and sensible oligodendroglia instead of myelin. Pulsations in a circular section of either the anterior inferior cerebellar artery (AICA) or posterior inferior cerebellar artery (PICA) leads to focal demyelination in the root entry zone and consecutively, electric activity from sensory afferences (e.g. contact, talking, chewing, …) develop into or jumps to nociceptive afferences, thus causing pain. Therapeutic approaches include pharmaceutical means such as carbamazepine; surgical options include microvascular decompression (Jannetta technique), rhizotomy with thermocoagulation or glycerol injection or balloon compression of the gasserian ganglion. Furthermore, radiosurgery with gamma knife techniques can be applied. Complications related to surgery may cause damage to nerve, associated with the onset of permanent pain. As mentioned before, the occurrence of a sensory deficit in conjunction with burning pain is characteristic for trigeminal neuropathy. Here the change in nomenclature is happening. Trigeminal neuralgia changes to trigeminal neuropathy. Prof. Ulrich Steude from Munich University, developed a method for stimulation of the gasserian ganglion in trigeminal neuropathy in the end of the 70ies beginning 80ies **[25-33]**; he reported that 2 out of 3 patients showed an improvement of more than 60% of their

constant burning painful sensations. He described the importance of neural stimulation between the damaged structure (the nerve) and the processing entity (the brain) becoming a fundamental basis in neuromodulation. This anatomical need differs from transcutaneous electric nerve stimulation (TENS) as well as subcutaneous electric stimulation, where stimulation ensues distal to the lesion. Now, 40 years after development of this method, it is rewritten from collegues in atlanta **[34]** additionally verifying the effectiveness of percutaneous trigeminal nerve stimulation for facial pain **[35]**. In 2018 a small series of 12 patients showed that a stimulation of the upper cervical spinal cord at the cranio cervical junction is able to reduce more than 50% of pain-intensity according to the numeric analog scale. This methods sounds promising but requires further clinical trials **[36]**.

The following case reports demonstrate the historic development in therapy of neuropathic facial pain over the course of the last 50 years. This timespan was chosen deliberately, since the revolution in imaging took place in the 1970s with the advent of computer-tomography, leading to revolutionary new techniques in neurosurgery.

Description of the implantation of electrodes into the gasserian ganglion in an 18-year-old female suffering from pharmacoresistant neuropathic facial pain after extraction of a wisdom tooth.

The following section gives a detailed description of gasserian ganglion stimulation, first described by Prof. U. Steude. Patient treated with this method initially receive a testing electrode implanted through the foramen ovale directly adjacent to the gasserian ganglion. Similar to thermocoagulation of the ganglion, surgery takes place under short lasting general anesthesia without intubation utilizing a nasal wendel tube. In a stationary setting, the effect of this stimulation is tested over the course of a few days. A positive effect is achieved when the painful area is covered by tingling sensations caused by stimulation and the pain should be reduced by at least 60%. Four weeks later, the definitive implantation of a stimulation electrode is performed. For definite implantation, a monopolar electrode containing contacts on the tip of the probe is used and connected to the neurostimulator being placed in upper chest infraclavicular of patients. Several aspects during the intervention are crucial for a good therapeutic effect. First of all, proper positioning of the patient must be ensured. The patient's head should be reclined and the jaw facing the surgeon directly. Thus, the foramen ovale lies in a straight line to the surgeon and its entire diameter is available for the insertion probe. Tangential insertion of the probe in the foramen may not be successful since the insertion probe requires an 18G needle. The next step is to disinfect the skin, starting at the corner of the patient's mouth. Due to the positioning, the eyes may be affected by the agents used for that. This should be avoided by all means since the patient is awake for a short time after insertion of the puncture cannula and she or he may not tolerate this irritation, possibly aborting the intervention. The insertion of the probe should not be performed too low in relation of the corner of the mouth or to the horizontal extension of the lips, which may lead to displacement of the electrode on opening the mouth. If such misplacement has occurred, the electrode may be dislocated distally by the opening of the foramen ovale; thus, dysesthetic sensations caused by stimulation may be transferred into areas that are primarily not affected by pain. In one of our cases, a patient was treated successfully with stimulation but her frequent usage of chewing gum led to deterioration of the positive stimulation effect due to increase the distance between skin and gasserian ganglion by chewing. Therefore, no electrode should be placed lower as the corner of the two lips. It would be better to perform the puncture slightly above that line.

The ideal trajectory follows a straight line to the pupil at frontal view until crossing at halfway point of an imaginary line between external acoustic meatus and lateral canthus. Puncture too far laterally may lead the probe into the foramen spinosum and may cause puncture of the medial meningeal artery. A hematoma in the cheek may occur.

After correct placement of the probe within the foramen ovale, the mandrin is replaced by a stimulation electrode, monopolar or quadripolar with bullet tip type are preferred to only ring type electrodes. Then, an external stimulation device is set to zero amps and a rectangular impulse at 2 Hz is selected. Stimulation intensity is increased gradually until rhythmic contractions of the patient's mouth, i.e. chewing movements, are observed. A flush within the stimulated trigeminal areas may occur, especially at a frequency of 50 Hz. It is imported to instruct the patient now to keep his head still. For definite testing, intensity is reduced once again to zero and is then increased very slowly. Then, the patient is asked where he senses paresthesia, i.e. jaw, cheek, ala of the nose, forehead, or around the eye. According to the stimulated area, the position of the electrode is corrected. When sufficient stimulation has been reached, the testing electrode is removed and replaced by a permanent electrode, either for further testing or for definite stimulation. For replacement of the testing electrode with the permanent electrode, the cannula for puncture is still in place of the oval foramen; caution is required while removing the cannula in order not to remove the electrode. Lateral fluoroscopy is recommended for verification of correct placement of the electrode. The electrode should be fixated to the skin by small stitches and steri-strips for the test trial and subcutaneously by small incision of 3 to 4 mm in the site of skin puncture for permanent implantation. The patient is transferred to the ward and receives instructions for the test stimulation. Different stimulation settings should be tried over the course of a few days in order to find the best result. In our experience, definite implantation of a stimulating electrode and the pace maker should not be performed immediately after the testing phase. Due to the percutaneous channeling of the electrode, bacterial contamination of the operating area must be avoided. Bacteria may ascend by 0,3mm per day; the tunneling of test electrodes on the face should only be performed over the course of a few centimeters, while definite electrodes may be tunneled percutaneously over a longer distance. Therefore, in a test setting, the risk of wound infections is not low but could be avoided by test trial duration limited to 5 days. The electrode

will be removed just by opening the suture and pulling out of the test electrode without any need of anesthesia. Furthermore, due to time pressure when the patient awaits the definite implantation, expectations regarding the therapeutic effect may be interpreted erroneously and placebo-like effects may occur. Therefore, we recommend implantation of the definite system at least 4 weeks after the testing phase.

Implantation of the definite system is performed similar to the testing system. An additional skin incision must be made with a thin non-absorbable suture loop; puncture of the foramen ovale is then performed in the same way as in the test stimulation, and the suture is then tightened for fixation. The electrode is then tunneled subcutaneously to the jaw angle and via connectors to the ipsilateral infraclavicular area. There, the neurostimulator is inserted subcutaneously and connected to the electrode. The stimulator is programmed percutaneously in the same manner as SCS or DBS stimulation systems. Out-patient follow-ups should occur every 3 months initially, and then once a year.

Stereotactic Implantation of Electrodes into Basal Ganglia

This chapter explains central modulation of neural structures. Stimulation of certain areas of the sensory thalamus (ventral posterior nucleus of thalamus) as well as the posterior limb of the internal capsula according to the method developed by the senior author in 2012. The stimulation of other structures of the pain-processing areas described previously may reduce but not eliminate neuropathic facial pain. If an additional nociceptive component exists, stimulation of the periaqueductal or periventricular gray may lead to release of endogenous opioid peptides.

A meta-analysis performed by the European society of functional neurosurgery in 2007 **[37]** demonstrated, that deep brain stimulation in pharmacological resistant pain syndromes achieved better results against nociceptive pain (63%) than against neuropathic pain (47%). This demonstrates poor outcome by stereotactic surgery in comparison to the treatment of movement disorders. The meta-analysis showed that stimulation of the anatomically largest target area, the periaqueductal grey, had better results than stimulation of the smaller target structures.

For the senior author it was a clear mathematic calculation reaching almost 50% in effectivity means having gained only 50% of the structures needed to be implantated to get better results. He estimated that the sensory thalamic region is 50% of the afferent fibers on their way to the cortex the consciousness of humans. By fiber tracking utilizing Brain Lab AG (Munich, Germany) navigation system vector vision he identified a fiber separation into thalamic fibers and fibers direct passing to the cortex. According to the observation he made he draw the conclusion to implant two electrodes per cerebral hemispheres reaching equal good results as in deep brain stimulation in movement disorders surgery. The next step was to reintroduce the posterior limb of the capsula interna as a complete new target area in deep brain stimulation. The combination of stimulating both the sensory thalamus and the dorsal limb of the capsula interna was resulting in a complete reduction of neuropathic facial pain, even with analgesia dolorosa. It is also possible to achieve satisfying results in treatment for allodynia, hyperpathia, and dysesthesia. If an additional nociceptive component of pain exists, it is possible to stimulate the periventricular or periaqueductal grey and therefore activate inhibiting descending fiber tracts and release of endogenic opioidpeptides. In conclusion, we were able to develop and improve stereotactic surgery in neurosurgical pain therapy over the course of the last 25 years; since 2012 until today we are able to eliminate pain entirely in patients suffering from the severest forms of chronic severe neuropathic pain conditions.

Case Report

In 2005, a 56-year old female suffered from thalamic hemorrhage, accompanied by left hemiparesis. The patient was treated neurologically in a peripheral hospital. After resorption of the intracerebral hematoma, the paresis regressed gradually and adequate mobilization was achieved. Afterwards, the patient began to suffer from strong pain on the left body side accompanied by hemihypesthesia; on the left hand, she suffered from highly intensive burning pain as well as a decrease of motoric function due to increased tonicity. The typical pain medication as well as neuroleptic medication was barely sufficient. In 2006, the patient was admitted to our department. Conventional MRI showed a decrease of signal intensity in the pyramidal tract around the resorbed hematoma. fMRI as well as 3D reconstructions were also performed for planning purposes. In accordance with the patient, the following strategy was laid out: as a first step, we decided on stimulation of the motocortex due to its non-invasiveness. If this should prove to be insufficient, we would perform Deep Brain Stimulation of the sensory thalamus and the periventricular gray. As the ultimate measure, in case of non-responsiveness to the first two alternatives, intracerebral intraventricular opioid therapy would be performed.

Therefore, in 2006, a Resume Round electrode by Medtronic Inc., Mineapolis, USA with eight contacts was implanted. We used neuronavigation (frameless stereotaxy) which allowed for projection of the central sulcus and functional motor areas of the mouth, the hand, and the leg gained by functional magnetic resonance tomography onto the patient's skin and to the dura after craniotomy. Referencing of the preoperatively performed imaging was accomplished by electrophysiological tests for the central sulcus, as well as motorically evoked potentials for the area of the hand. In order to guarantee rigid contact, the stimulation electrode was sutured to the dura. The cables were laid through 2 small burr holes, the cables were tunneled subcutaneously on to the infraclavicular region and there they were connected to the pacemaker. Programming was performed while the patient remained on the ward; after 12 days, the stitches were removed and patient was discharged. The patient described an improvement in pain sensation from 8-10 on the visual analogue scale (VAS) initially to VAS 4 postoperatively. Follow-ups were after 3 months, 6 months, and 12 months, then on demand. We achieved a significant reduction of the pain and

an improvement in quality of life, nevertheless, the patient never became entirely pain-free. In 2007, the pain medication was reduced gradually without increase of pain. In 2008, the pain became more violent again and increased to VAS 6-7; in 2009, the effect of the stimulation was lost entirely. Percutaneous testing confirmed that the stimulation system was still functioning. Therefore, it was decided that further planning for step 2 of the previously laid-out strategy had to be performed. A new MRI scan was scheduled; therefore, the entire system had to be removed surgically. Intraoperatively it became evident that calcified scar tissue had appeared between the electrode and the dura. Thus, transdural transmission of electricity and therefore the therapeutical effect of motor cortex stimulation had been hampered. By the end of 2009, we implanted 2 electrodes directly into the sensory thalamus (right ventral posterolateral nucleus) and into the periventricular gray. Pain was once again reduced to VAS 4. In early 2010, an additional electrode was implanted into the posterior limb of the right internal capsula. Thereby, pain was further reduced. In 2012, several episodes lasting from 3-5 days with reduced therapeutic effect occurred. Similar to medication break, we performed a pause in stimulation for several months while increasing pain medication. The initial results were promising, but after a few weeks pain was increased once again. The stimulating system was then coupled with intensity modulation system we had developed ourselves. The stimulation is now done in a cyclic manner; 10 seconds of stimulation with increasing current intensity by ramp time of 6 seconds are followed by a pause lasting 10 seconds (50Hz, 240µsec, 2.4V). The patient is now satisfied with the results; quality of life is described as acceptable and better than in the year before. Certain suicidal tendencies that existed previous to the change of stimulation to intensity modulation and absent.

This complex case report documents the importance and effectiveness of creative and interdisciplinary work. Together we can handle even the most difficult aspects of painful conditions and can significantly improve the quality of life in the affected patients.

Epidural Motocortexstimulation

Epidural stimulation of the motocortex **[37-40]** has been abandoned by our group after 5 years of application. All of our patients reported a significantly diminished effect or even a loss of effect after two years or more. Even with a reduction of pain up to 30-60%, the persisting pain was still reported as unacceptable after a certain time of reduced pain state by forgetting the pain in its previous intensity. A recent review from 2020 showed a reduction of 46.5% for trigeminal neuropathic pain **[41]** in motor cortex stimulation patients.

In the early stages of the therapy, an increased intensity of stimulation led to increased muscular tone in the associated areas; therefore, we concluded that the positioning of the electrodes on the motocortex was correct. Nevertheless, the pain reduction decreased continuously after one year. After more than two years of stimulation and confirmed integrity of the stimulation system, proved by correct resistances within the system, positive effects could not be reproduced. Revision surgery was performed in a few patients; in two cases, we found thickening of the dura, and in one patient a calcified layer between dura and electrodes. In our hypothesis, these alterations are due to a shift in tissue pH causing of precipitation of calcium, by high current density. This biochemical reaction can be observed in all applications of external electrical fields applied to human tissue over long time periods, i.e. plate electrodes in spinal cord stimulation as well as in stimulator pockets, cable course or cardiac pacemakers. Around the source of electric current, i.e. the electrode, a tough, crude coating is formed; this fibrotic or even calcified coating leads to isolation of the electric current in terms of an endogenous defense reaction. These observations led to abandoning of epidural motocortex stimulation in favor of deep brain stimulation for neurosurgical pain therapy.

Cluster Headache

Case Report

A 24 year old female patient, mother of a one-and-a-half-year old daughter, developed left-sided headache, pain in the left eye and orbita, accompanied by flush of the left eye, lacrymation, and nasal secretion. Initially, the patient ignored the symptoms due to her preoccupation with her young child. The patient treated the pain with NSAIDs; the effect, however, was limited and the level of suffering rose. The number of pain attacks increased up to 15 per day and the patient noticed that the pain medication was no longer effective. The patient intermittently reported pain up to VAS 10. Only sumatriptan injections, administered by her general practitioner, were effective enough to relieve the pain. After admission to the neurological department, she was treated with oxygen inhalations with up to 10 liters per minute and further injections of sumatriptan. Due to the known side effects of sumatriptan, especially increased fatigue, family stress increased.

Eight years ago, we implanted a 4-contact electrode into the dorsal hypothalamus; the cable system was tunneled subcutaneously to the left clavicle and connected to a stimulator programmed and recharged percutaneously via induction. With this therapy, the patient is almost entirely pain-free. Without activity, the patient reports no pain; only under physical exercise she experienced anticipation of a typical pain attack; the pain itself, however, fails to appear. Pain medication, especially sumatriptan, is no longer needed.

Currently, we are working on the optimization of the generator program in order to eliminate the last remaining symptoms. In this patient, all four electrode contacts were polarized negative, while the generator casing was polarized positive, hence a bipolar stimulation was achieved. The impulse bandwidth, i.e. the penetration depth, is set to 300µV, the frequency to 130 Hz, and the intensity to 6 V. The generator must be recharged percutaneously once a week. The patient is highly satisfied with the result and describes her quality of life as high.

Etiology and Therapy of Cluster Headache

The following section describes the etiology as well as neurosurgical therapy of cluster headache that has proven not to respond to pain medication **[42]**. This painful facial condition is described as one of the most affecting pain syndromes. It always occurs unilaterally on the same side of the face, switches to the contralateral side are not described but we have two cases with bilateral appearance. Van Swieten was the first to perform research on this entity and published his findings in 1745. The current guidelines regarding this topic derive from International Headache Society, including a classification of headache and facial pain syndromes as well as diagnostic criteria. Cluster headache consistently affects the first trigeminal branch, the ophthalmic nerve. Pain is accompanied by vegetative symptoms such as ipsilateral lacrimation, nasal secretion, conjunctival injection, myosis, ptosis, blepharedema, and activation of the parasympathicus. Characteristic attributes are cyclic occurrence of the symptoms, as well as seasonal variations, exact circadian rhythm, and punctuality. Initially it was assumed that inflammatory processes at the sinus cavernosus, afferent veins, or the sympathic plexus around the internal carotid artery cause these symptoms. This theory was supported by the fact that vasodilatation by nitroglycerine causes the onset of pain attacks. On the contrary, the strict one-sidedness as well as the circadian rhythm may be indicative for a central-nervous process. Today, the vascular alterations are assumed to be epiphenomenal of an activation of the trigemino-vagal system.

During attacks of cluster headache, the plasma level of testosterone varies; furthermore, a decreased sensitivity for thyreotropic releasing hormone and a loss of the circadian melatonin rhythm accompanied by nocturnal serum level peaks occurs. These factors support the hypothesis of hypothalamic participation. Circadian processes are known to be controlled by the ventral hypothalamus, i.e. oscillators in the suprachiasmatic nuclei, and furthermore, influences caused by brightness occur via retino-hypothalamic tracts; therefore, it is assumed that the trigger for cluster headache must be located within the hypothalamus or its immediate vicinity. Due to the possibility of provoking the attacks with nitroglycerine and terminating the attacks with sumatriptane, an examination of these phenomena by means of a PET scan was indicated; here a radioactive water molecule with a short half-life period (H_2O^{15}, 7 minutes) was used. Researchers at the Department for clinical neurology and cognitive neurology, Queens Square University Hospital, London, UK were able to reproduce activities typical for facial pain in the anterior cingular cortex bilaterally, the insula, the thalamus, the cerebellar hemispheres, and the vermis cerebelli without any activation of the brainstem as seen in migraine, by using nitroglycerine and sumatriptane. Interestingly, ipsilateral activation of the hypothalamus and the hypothalamic grey in patients affected by cluster headache was detected.

Therefore, it was concluded that Deep Brain Stimulation, similar to treatment of movement disorders, could be a viable therapeutic approach. Always platinum electrodes are used because of less toxicity and never other metal are utilized. The electrode is placed within the active area of the hypothalamus and inhibitory high frequency stimulation is performed.

The outcome of this approach is excellent; hundreds of patients have been treated successfully. A limitation of this method, however, is the fact only few patients suffering from this diagnosis do not respond to classic medication and therefore are eligible for Deep Brain Stimulation.

Neurodestructive Interventions

Destructive surgery such as chordotomy, tractotomy, or exheresis is no longer performed by our study group. These interventions should only be performed in case of extreme pain originating from malignant diseases that do not respond to other therapeutic means and when only a short life expectancy is given. It has been proven that due to the surgical differentiation, even more intense pain may occur.

Physicians who are not specialized in functional neurosurgery and neurosurgical pain therapy may ignore these facts. It can often be observed that, patients who seemingly do not respond to surgical therapy are transferred to psychiatrists; however, it is the responsibility of all specialists in pain management to handle even the most difficult cases and increase the quality of life of our patients.

Case report – Trigeminal Neuralgia/Neuropathy, Deep Brain Stimulation – Novel Therapeutical Concepts, Radiosurgery

The following section describes treatment of a difficult case of failed therapy in chronic trigeminal pain; step-by-step, all therapeutic options had to be considered in order to achieve satisfying pain reduction and quality of life.

In 1999, a female in her thirties started to develop acute, lancinating pain in the second and the third trigeminal branch on the left side. NSAIDs showed no significant effect on both pain intensity and frequency of pain attacks. Administration of carbamazepine at up to 2.5 grams per day as well as high-dosed amitriptyline and pregabaline could reduce the intensity, but the results were still not satisfying. From 2002 onwards, the patient also developed trigeminal pain on the right side. In 2006, after more than 6 years of unsatisfying conservative treatment, microvascular decompression of the “root entry zone” (entry point of the trigeminal nerve in the brainstem) on the left side was performed. Intraoperatively, a loop of the AICA was found to compress the root entry zone; the vessel loop was removed and a Teflon sponge was used as an interponate. Half a year later, the same procedure was performed on the right side. The initial results were good, the patient was pain free. Within one year, however, the symptoms recurred on the left side and then also on the right side. Conservative treatment now showed better results than in the initial treatment of the patient, but the results remained unsatisfying. In 2010, surgical exploration and re-decompression of the right trigeminal nerve was performed; this procedure, however, showed no effect on pain intensity and frequency of pain attacks. Again, conservative treatment

showed no improvement; after interdisciplinary review, a rhizotomy of the trigeminal nerve was considered. By the end of 2012, the patient was still suffering from unbearable chronic pain of neuropathic character accompanied by partial hypoesthesia on the right side of the face and additional intermittent neuralgic pain attacks. Therefore, a selective sensory rhizotomy of the sensory branch of the trigeminal nerve was performed. Postoperatively, the patient described a complete loss of touch and pain sensitivity on the right side of the face. Subjectively, the patient felt a hot, burning form of dysesthesia; small drafts of air or slight touching lead to increase her unbearable pain. Gabapentine, amitriptyline, and pregabaline were administered in the highest dosage possible (side effects as dosing limitation). After removal of the stitches, the patient was discharged. The patient then had to tolerate chronic neuropathic pain with abnormally intensified touch sensitivity and dysesthesia. She could not tolerate air or moderate levels of noise. Bright light, such as reflections in the snow were also unbearable. The additional administration of clomipramine resulted in a slight improvement if the patient could reduce external disturbances.

After rhizotomy on the right side, the patient developed recurring neuralgia on the left side with lancinating pain in the nasolabial sulcus and around the corner of the mouth to the left; high dosage of carbamazepine and other specific medication showed little or no effect. The patient was admitted to the gamma-knife center at the general hospital (AKH) in Vienna; in April 2014, radiosurgery on the left trigeminal nerve was performed. Afterwards, neuropathic pain on the right facial side including the eye was increasing again to a very intense form of analgesia dolorosa; the patient was finally admitted to our department for evaluation of further therapeutic options. We decided on application of our modified therapeutic concept for chronic neuropathic pain, i.e. test stimulation of the sensory thalamus (ventral posterior nucleus of thalamus) and the posterior limb of the capsula interna ipsilateral to the affected side of the face.

In May 2014, an electrode for deep brain stimulation was implanted into the right sensory thalamus and another electrode into the posterior limb of the right capsula interna (in general anaesthesia). The electrodes were temporarily channeled subcutaneously, thus enabling activation through the skin on the head. After the implantation, the patient reported improvement regarding her burning pain sensation; this was seen as the microthalamotomy effect after correct implantation of electrodes. Over the course of the next 3 days, all contacts of the 4-pole platinum electrode were repeatedly test stimulated; the neuropathic, chronic pain sensations as well as the intense, painful touch sensitivity had disappeared. Even the preexisting allodynia had disappeared; the patient was able to touch her face again without pain. In the next step, the definite stimulating system was implanted, and the pulse generator was activated. The stimulation intensity was programmed in way, that the patient was pain free on the right side of the face when she did not move. Under physical strain, the patient still felt a sensation of flush on the right side; this was reported as unpleasant, but not as painful as it was before the implantation of the electrodes. Sometime later, the patient developed a light tingling, i.e. intermittently appearing lancinating pain on the left side of the face. Pharmaceutical treatment improved these sensations; the patient regularly visits our specialized outpatient department for treatment of chronic pain. Currently the patient reports a high quality of life with little to no pain.

This case report demonstrates the value of different surgical treatment modalities of chronic pain syndromes. Limitation of treatment options solely to pharmaceutical means is a common and widespread mistake. Nevertheless, it is important to evaluate invasive therapy options under critical consideration of potential risks and undesired side effects.

The Innsbruck Algorithm of invasive intracerebral pain treatment (W. Eisner)

Preconditions:

- Failure of at least three different conservative therapeutic attempts performed by specialists
- Last surgical intervention over 12 months in the past
- No contraindication against surgery

- Preoperatively:
- Anamnestic definition of the underlying type of pain: neuropathic, nociceptive, or mixed-type
- Stereotactic MRI scan for surgical planning
- Neuropsychological testing
- Administration to our outpatient department
- Neurophysiological exams for quantitative follow-up

- Step Ia: Neuropathic pain
- Implantation of electrodes into the sensory thalamus and the posterior limb of the capsula interna in general anesthesia

- Step Ib: Nociceptive pain or mixed-type
- Implantation of electrodes into the sensory thalamus, the posterior limb of the capsula interna and into the periventricular/periaquaeductal grey

- Step II: After failure of Step I, after removal of test electrodes
- Revision surgery in combined local anesthesia and intravenous sedation analgesia, 5-channel-semimacrostimulation via preexisting burr holes while the patient is awake, reevaluation of the individual functionality of the selected target area

- Step III: After failure of Step II, continuing unbearable pain, all pain types
- Implantation of electrodes into the anterior cingulate cortex bilaterally

- Step IV: After failure of Step III or in addition to Step III, all pain types

- Intracerebral intraventricular administration of morphine after positive testing via port system with implanted pump

Special Notes on Neuromodulation

Deep Brain Stimulation has been performed by our study group in Munich as well as in Innsbruck since the early 1990s. No severe complications have been observed in our patient population. We have treated over 1000 patients; more than 100,000 patients have been treated worldwide. DBS can be regarded as a safe and clinically reliable method. The low number of surgeons performing this method is caused by its complexity.

One special focus should include the consequent avoiding of bacterial infections such as pneumonia or urinal tract infections since ascending infections of the implants are common. Prophylactic antibiotics should be administered long enough in order to prevent the need of implant removal and therefore continuing pain.

Conclusion

Cases similar to those we described here can be found in numerous medical facilities, hospitals as well as ambulatory offices. We intend to demonstrate alternate "exit strategies" in seemingly desperate cases of chronic pain. Furthermore, we plea for understanding, that ups and downs of therapeutic results should not be accounted as failures of others instantly. Rather, we intend to achieve a form of relief for other participating entities with potential benefit for the patient. In Austria, we intend to achieve complete documentation of all therapeutic interventions described in this manuscript and we plea for consequent teaching in neurosurgical pain therapy. Facial pain must be regarded as an interdisciplinary entity; it encompasses odontology, maxillofacial surgery, neurology, anesthesiology, and neurosurgery.

List of abbreviations

WHO	:	World Health Organization
PET	:	Positron Emission Tomography
CT	:	Computer Tomography
MRI	:	Magnetic Resonance Imaging
AICA	:	Anterior Inferior Cerebellar Artery
PICA	:	Posterior Inferior Cerebellar Artery
TENS	:	Transcutaneous Electric Nerve Stimulation
VAS	:	Visual Analogue Scale

Conflict of Interest

Univ.-Prof. Dr. Wilhelm Eisner is trainer and instructor at the "International Young Neurosurgeons Training Program" by Medtronic™ and lecturing for abbot. Other authors have declared that no competing interests exist.

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