Chapter 128

Central Pain in the Face and Head

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CENTRAL PAIN IN THE FACE AND HEAD

International Headache Society (IHS) code and diagnosis:

13.18.1 Central causes of facial pain
13.18.1 Anesthesia dolorosa (+ code to specify cause)
13.18.2 Central poststroke pain
13.18.3 Facial pain attributed to multiple sclerosis
13.18.4 Persistent idiopathic facial pain
13.18.5 Burning mouth syndrome
13.19 Other centrally mediated facial pain (+ code to specify etiology)

Note that diagnosis with IHS codes 13.18.1, 13.18.4, and 13.18.5 may have peripheral causes.

World Health Organization (WHO) code and diagnosis: G 44.810 or G44.847. Central causes of facial pain.

Short description: *Central pain*: The International Association for the Study of Pain (IASP) has defined central pain as pain caused by a lesion or dysfunction in the central nervous system (CNS) (26). Thus, peripherally induced pain with central mechanisms is not central pain, even if the central mechanisms are prominent. Central pain is usually constant and spontaneous, but evoked and paroxysmal pain occur in a minority of patients.

Other terms: *Thalamic pain* is often used in a general sense for all central pain. *Pseudothalamic pain* is then sometimes used for central pain caused by extrathalamic lesions. *Central poststroke pain* in the revised International Classification for Headache Disorders (ICHD-II: 13.18.2) denotes central pain resulting from a cerebrovascular lesion (CVL) affecting the "quintothalamic pathway or thalamus." *Dysesthetic pain* sometimes refers to central pain with a predominantly dysesthetic character, but such pain can have either central or peripheral causes.

Anesthesia dolorosa denotes pain in a region with decreased sensibility after lesions in the CNS or peripheral nervous system (PNS). The term *deafferentation pain* is used for similar conditions, but it is more commonly used in patients with lesions of spinal nerves.

EPIDEMIOLOGY

The prevalence of central pain varies depending on the underlying disorder (Tables 128-1 and 128-2) (7,29). In the absence of large scale epidemiologic studies, only estimates of central pain prevalence can be quoted.

In the only prospective epidemiologic study of central pain, 191 patients with central poststroke pain (CPSP) were followed for 12 months after stroke onset (1). Sixteen (8.4%) developed central pain, an unexpectedly high incidence. Among patients with somatosensory deficits (42% of all stroke patients), the incidence of central pain was 18%. These data contrast with figures obtained from a retrospective study of 63 patients with brainstem infarcts (24): central pain was reported in 44%, CPSP in 25%.

In two studies of central poststroke pain, 33% of 27 patients and 37% of 111 patients had facial pain, respectively, in addition to pain at other sites (9,23). In a mixed material of 73 patients with "central pain of brain origin," 11% had facial pain (30).

In a recent study of 364 patients with multiple sclerosis (MS), a prevalence of 27.5% was found (A. Österberg and J. Boivie, in preparation). This includes 4.9% who had trigeminal neuralgia, which in this context is considered to be a central pain condition because it is caused by an inflammatory lesion located in the CNS (Tables 128-1 and 128-2).

Brain tumors and traumatic brain injuries seldom cause central pain (25,30).

About 3% of patients with spinal anterolateral cordotomy develop late-onset central pain, usually of a

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TABLE 128-1 Causes of Central Pain

Vascular lesions in the brain and spinal cord
Infarct
Hemorrhage
Vascular malformation
Multiple sclerosis
Traumatic spinal cord injury
Cordotomy
Traumatic brain injury
Syringomyelia and syringobulbia
Tumors
Abscesses
Inflammatory diseases other than multiple sclerosis
Myelitis caused by viruses, syphilis
Epilepsy
Parkinson disease (?)

dysesthetic nature (19,25,30). On the other hand, mesencephalic and pontine tractotomies might carry an even higher risk of central pain (29).

GENETICS

Systematic genetic studies of central pain have not been conducted; nevertheless, a genetic predisposition is suspected. In humans, similar lesions lead to central pain with some people, but not in others. In rats, experimental nerve lesions cause neuropathic pain in some strains, but not in others (15).

ETIOLOGY AND PATHOPHYSIOLOGY

Table 128-1 lists diseases and lesions commonly associated with central pain. These include rapidly developing lesions such as parenchymal hemorrhage and the slowly developing inflammatory demyelinating lesions of MS. The incidence of central pain differs in different diseases, suggesting that differences in the lesions are important factors. Unfortunately, little is known about these factors at the cellular level, including what happens to transmitter receptors.

Lesion location is an important factor in the genesis of central pain. Central pain develops with lesions of the spino- and quintothalamic pathways (i.e., pathways that are most important for the sensibility of pain and temperature) (4,8,32,38), including the thalamocortical projections (5,7,9,29). Also, a central pain-causing lesion can be located at any level of these pathways along the neuraxis, from the origin of the spinal trigeminal nucleus or the spinal dorsal horn to the cerebral cortex (10).

The first central pain condition to be described in detail was the thalamic pain of Dejerine and Roussy (14). It was viewed as one component of the thalamic syndrome. The thalamic syndrome is usually caused by a thalamic infarction or hemorrhage (18), but in many cases the lesion causing thalamic pain extends considerably laterally to the thalamus. Also, relatively recent data suggest that central pain develops in about 17% of patients with thalamic stroke only if the ventroposterior region is involved (8,23).

Thalamic involvement is not necessary for CPSP. Recent computed tomography (CT) and magnetic resonance imaging (MRI) studies indicate that at most about half of stroke patients with central pain have lesions involving the thalamus (10,23). Both supra- and infrathalamic lesions, including cortical lesions, can cause central pain. For instance, there is good evidence that lesions involving the parietal cortex and the insular and adjacent perisylvian cortex can produce loss of pain and temperature sensibility (4). Brainstem strokes of the Wallenberg type (i.e., infarctions in the region of the posterior inferior cerebellar artery [PICA]) are well known to cause central pain in some patients. In one study, such lesions were present in 8 of 27 consecutive patients with CPSP (23). The risk of developing central pain may be higher with brainstem lesions affecting the quintothalamic pathways than with suprathalamic lesions (24).

Neurosurgical lesions of the quintothalamic tract for the treatment of intractable head pain show that lesions of this pathway in the pons and midbrain can lead to central pain (19,28). Some of these patients develop central pain with a dysesthetic quality several months after the operation.

In stroke patients with central pain, pain occurs independently of nonsensory symptoms (Table 128-3) (7,9,10, 23,29). Quantitative sensory tests reveal abnormal temperature and pain sensitivity in all patients, and normal thresholds to touch, vibration, and kinesthesia in many (6).

Other causes of central pain include syringobulbia and MS. Syringobulbia causes central pain by virtue of involvement of the trigeminal nucleus (3). Central pain is common in MS, but a clear reason for its genesis remains

TABLE 128-2 Estimated Prevalences of Major Disorders with Central Pain in the United States (Population Around 280 Million)

Disease	*Total # of patients*	*Patients with CP*	*% patients with CP*
Spinal cord injury	252,000	76,000	30
Multiple sclerosis	168,000	46,000	27.5
Stroke	2,240,000	188,000	8.4
Epilepsy	1,800,000	55,000	2.8
Parkinson disease	560,000	56,000	10

From Andersen et al. (1), Bonica (8), and A Österberg & J Boivie (from a study of central pain in multiple sclerosis, in preparation).

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TABLE 128-3 Diagnostic Criteria for Central Pain

History of disease in the brain or spinal cord
Laboratory examinations showing CNS disease, including x-ray, MRI, and CSF assays
Pain starting after the onset of CNS disease; onset of pain often delayed
Pain with a regional distribution, rather than corresponding to individual nerves
Pain quality compatible with central pain: mostly burning, aching, pricking, lacerating, or lancinating; often more than one quality
Sensory abnormality, including abnormal sensibility to temperature and pain, and commonly hyperesthesia and dysesthesia
Nonsensory symptoms and signs may or may not be present

CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

obscure (6). It is hypothesized that the location of the demyelinating lesion is a crucial factor in the development of pain.

Two general pathophysiologic processes have been hypothesized as possible causes of central pain: (1) an "irritative lesion" hypothesis implying that hyperactive cells at or adjacent to the lesion site produce increased activity in otherwise normal nociceptive pathways (14); and (2) a "denervation or hypersensitivity" hypothesis suggesting that neurons remote from the lesion, but within nociceptive processing pathways, become hyperactive and hypersensitive because they have lost normal synaptic inputs (20). These hypothetical mechanisms are not mutually exclusive. Both may participate, to varying degrees, in the pathophysiology of central pain in different patients.

Head and Holmes hypothesized that pathways mediating tactile sensations normally exert a tonic inhibitory influence on a separate population of pain-mediating neurons (20), and that central pain is produced when inhibition is removed by a lesion in the lemniscal pathways. Modern research has shown, however, that lesions in the lemniscal pathways are not necessary for central pain to appear (5,6).

Craig has presented a new view of the thalamic disinhibition hypothesis, which is based on results from experimental studies in cats and monkeys (12). The hypothesis states that "central pain is due to the disruption of thermosensory integration and the loss of cold inhibition of burning pain" (12). This disruption would be caused by a lesion along the spinothalamic projections to the thalamus, which are activated by cold receptors and delivered to tonically inhibit nociceptive thalamocortical neurons.

Experimental studies of neuropathic pain induced in rodents by lesions of the spinal cord and peripheral nerves indicate that excitatory amino acids, particularly glutamate and its effects on the N-methyl D-aspartate (NMDA) receptors, play an important role in the development of hyperactive and hyperexcitable neuron pools in the CNS (33). Recently, Willoch and colleagues used an opioid ligand to estimate the degree of resting availability of opioid receptors in 12 healthy control subjects and 5 patients with hemibody CPSP due to single thalamic, midbrain, or cortical lesions (34). Despite the focality of the lesion, there was a striking loss of opioid receptor availability in the midbrain periventricular gray and throughout much of the hemisphere contralateral to the pain. The results argue against a focal effect at the lesion site, or a direct or transsynaptic degenerative process. Overall, the observations suggest that there is a reduction or downregulation of the opioid receptors, resulting in reduced effectiveness of endogenous, opioid-mediated analgesic mechanisms (36). Thus, a single lesion within the spino–thalamo–cortical pathways can produce a functionally and neurochemically specific, yet anatomically extensive, deficit (10).

CLINICAL FEATURES

The clinical presentation of patients with central pain is quite variable, sometimes raising difficulties in making a diagnosis. Some patients experience intense pain with severe motor and sensory symptoms, while others have only mild pain and minor neurologic symptoms. Also, the character and location of the pain varies from one patient to the next. Thus, the diagnosis of central pain rests on the total clinical picture, in which history, symptoms, and signs indicate a disease process in the CNS, and with pain the characteristics of which are compatible with central pain. General diagnostic criteria for central pain are suggested in Table 128-3. Central poststroke pain can be considered the prototype of central pain syndromes because its characteristics, apart from pain location, seem to be shared by central pain with other diseases (6,7,9,10,23,29).

Central poststroke pain is usually lateralized and includes the face in approximately 33 to 50% of all patients. In some patients with brainstem strokes the pain is ipsilateral to the lesion in the face and contralateral in the rest of the body. A study of sufferers of brainstem infarcts and central pain indicated that all eight patients had dissociated sensory loss, that is, severely abnormal sensibility to temperature and pain and normal or almost normal tactile sensibility ipsilaterally in the face and contralaterally in the extremities (7). Only three had facial pain, which in one patient was on the same side as the extremity pain.

The pain quality of central pain is mostly burning, aching, pricking, lacerating, or lancinating. Most patients, however, experience more than one pain quality (17 MacGowan, 1997 #987).

The intensity of central pain varies between patients, from excruciating to low-intensity pain. Even low-intensity pain causes much suffering because of its irritating and unpleasant qualities. Central pain is commonly increased by external and internal stimuli, such as light touch, cold, movements, and emotional distress. It is usually constant,

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TABLE 128-4 Sensory Abnormalities in Central Poststroke Pain

	BS	TH	SE	UI	All
Vibration	1/8	7/9	3/6	0/4	11/27 (40%)
Touch	2/8	8/9	2/6	2/4	14/27 (52%)
Innocuous temp.	8/8	9/9	6/6	4/4	27/27 (100%)
Temp. pain	7/8	9/9	5/6	4/4	25/27 (93%)

Proportion of patients with threshold abnormalities as shown by quantitative sensory tests. Abbreviations show location of cerebrovascular lesion. BS, brainstem; TH, includes thalamus; SE, supratentorial, extrathalamic; UI, location unidentified. From Boivie et al. (7).

but intermittent attacks, spontaneous or evoked, may occur.

The onset of central pain is commonly delayed. In a prospective study of stroke patients it was found that the onset was delayed more than 1 month in 37% of the patients (1). Delays as long as several years have been reported (6). The onset of pain often coincides with the return of some sensibility after a period of deep numbness.

Central pain is a result of CNS disease and, therefore, it should be accompanied by other neurologic symptoms. In one study, the only nonpainful feature common to all patients with CPSP was abnormal somatic sensibility (Fig. 128-1) (23). The most prominent sensory signs in CPSP are abnormal temperature and pain sensibility, dysesthesia, and hyperesthesia (Table 128-4). Quantitative sensory tests showed that all of 27 patients had abnormal thresholds to temperature and pain, while at most half had abnormal thresholds to touch, vibration, and joint movements (7). Such abnormalities may not be appreciated with traditional clinical tests, which are less sensitive (29).

Most patients with central poststroke pain have hyperesthesias, often of a hyperpathic nature, with painful overreactions to touch, cold (i.e., touch and cold allodynia), and pinprick (i.e., hyperalgesia [6,7,10]). These hyperesthesias hamper the patients considerably in their activity. Spontaneous dysesthesias are also common.

Syringobulbia can cause central pain in the face, but this condition has not been specifically studied. Syringobulbia is usually present together with syringomyelia, in which central pain is common (6,18). In 7 of a series of 25 patients with syringomyelia, the syrinx extended into the medulla oblongata (J. Boivie, unpublished observations). Two of these had neck pain that probably formed part of their central pain, but none had facial pain. About half of all patients had central pain. This would appear to be the highest prevalence of central pain reported in any neurologic disease. In this group also, the central pain was accompanied by abnormal temperature and pain sensibility, which is characteristic of syringomyelia.

In patients with MS, over one quarter of them develop central pain, including trigeminal neuralgia in almost 5% (A. Österberg and J. Boivie, in preparation). Nontrigeminal central pain is dominate in the lower and upper extremities (89% and 31%, respectively, of all patients). Four of the 18 patients with trigeminal neuralgia had pain also in the legs. The pain in the extremities was not found to be caused by spasticity. It was almost solely constant pain. MS plaques in the entry zone of the trigeminal nerve in the brainstem have been shown with MRI (6).

PROGNOSIS

Central pain is almost always chronic, commonly lasting for many years and frequently for the rest of the sufferer's life. In stable lesions such as those in stroke, the pain is usually stable and does not change character with time, but in patients with MS, new demyelinating lesions can modify the course of central pain. Central pain can also spontaneously and gradually subside in stroke and MS (22). In a recently reported case with central pain after a thalamic infarct, pain disappeared 7 years later after the patient suffered from a second infarct in the internal capsule, ipsilateral to the old thalamic infarct (27). It is not known whether presently available drug treatments affect the natural course of central pain.

MANAGEMENT

Most current treatment for central pain falls under four categories:

1. Peripheral and central electrical stimulation of the afferent systems to counteract the pathologic brain activity
2. Drugs that reduce CNS hyperactivity, such as carbamazepine, lamotrigine, gabapentin, pregabalin, clonazepam, baclofen, and NMDA antagonists
3. Drugs that enhance the activity of endorphinergic pain–inhibiting systems by influencing the reuptake of serotonin (and noradrenaline), that is, antidepressant drugs
4. Drugs that influence adrenoreceptors, such as the alpha-2-agonist clonidine, and direct opiate receptor agonists

Table 128-5 lists the most common forms of treatment for central pain, although many more are used. Except for a few (e.g., amitriptyline, lamotrigine), treatment for central pain is based on anecdotal observations and consensus opinion instead of Class I evidence (i.e., well-designed randomized controlled trials).

We recommend initiating therapy with transcutaneous electrical nerve stimulation (TENS) before resorting to pharmacologic interventions. Electrical stimulation of the brain, for instance in the ventroposterior thalamic region and internal capsule, has also been tried with varying

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TABLE 128-5 Treatment Modalities for Central Pain

Transcutaneous electrical nerve stimulation (TENS)*
Brain stimulation
Antidepressant drugs*
Antiepileptic drugs*
Opioid analgesics*
Baclofen
Alpha-2-adrenergic agonists (clonidine, tizanidine)
Antiarrhythmic drugs (e.g., intravenous lidocaine*)
Neuroleptic drugs

Asterisk indicates first-choice therapies based on at least one positive randomized controlled trial.

success. However, recent reviews suggest that deep brain stimulation or destructive lesions in the brain should only be considered if other treatments have failed and if the pain is very severe (19,29). Excellent results have been reported following surface stimulation of the motor cortex in central poststroke pain (26,31,35), but the experience with this treatment is still limited.

If TENS is unsuccessful, an antidepressant drug is the next choice. The only drugs so far tested in controlled studies are amitriptyline (CPSP and spinal cord injury) (11,21) and trazodone (central pain after spinal cord injury) (13). Amitriptyline was effective in stroke patients, but not in spinal cord injury patients, who had relatively low drug plasma concentrations. It is widely agreed that antidepressant drugs relieve central pain in many patients, irrespective of the cause, but further controlled trials are needed, notably to evaluate the newer antidepressants. From comparisons with studies on peripheral neuropathic pain one would expect that other tricyclic antidepressants might be as effective as amitriptyline in central pain, but this remains hypothetical. The selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine) appear to have weaker pain-relieving effects than the tricyclic antidepressants in general, and the new antidepressants with mixed serotoninergic and noradrenergic effects have not yet been studied systematically. Undoubtedly, antidepressants are associated with untoward effects in some patients, in particular the elderly. Careful information and frequent follow-up are important management strategies.

In two controlled studies of antiepileptic drugs in the treatment of nonparoxysmal central poststroke pain, 20% of 15 patients responded to carbamazepine in one (21), and 44% of 30 patients responded to lamotrigine in the other (32), whereas no pain relief from lamotrigine or from sodium valproate was found in studies on spinal cord injury pain (15,16). Gabapentin has been increasingly used for nonparoxysmal neuropathic pain, including central pain, with mixed experiences (25), but its use for central pain rests on clinical experience and not on the results from controlled studies.

For paroxysmal central pain, including trigeminal neuralgia, carbamazepine remains the drug of choice.

The role of analgesics in peripheral and central neuropathic pain remains controversial. Expert opinion suggests that a few central pain patients may benefit from analgesics, including opioids (2).

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