

Central post-stroke pain: clinical characteristics, pathophysiology, and management

Henriette Klit, Nanna B Finnerup, Troels S Jensen

Central post-stroke pain (CPSP) is a neuropathic pain syndrome that can occur after a cerebrovascular accident. This syndrome is characterised by pain and sensory abnormalities in the body parts that correspond to the brain territory that has been injured by the cerebrovascular lesion. The presence of sensory loss and signs of hypersensitivity in the painful area in patients with CPSP might indicate the dual combination of deafferentation and the subsequent development of neuronal hyperexcitability. The exact prevalence of CPSP is not known, partly owing to the difficulty in distinguishing this syndrome from other pain types that can occur after stroke (such as shoulder pain, painful spasticity, persistent headache, and other musculoskeletal pain conditions). Future prospective studies with clear diagnostic criteria are essential for the proper collection and processing of epidemiological data. Although treatment of CPSP is difficult, the most effective approaches are those that target the increased neuronal hyperexcitability.

Introduction

The concept of central pain was first introduced by Edinger in 1891.¹ 15 years later, in their famous paper “Le syndrome thalamique”,^{2,3} Déjerine and Roussy provided descriptions of central post-stroke pain (CPSP) that have since been widely cited. These researchers described a small series of patients (n=8) with several neurological symptoms and signs ascribed to a lesion in the optic thalamus. The syndrome included “...severe, persistent, paroxysmal, often intolerable, pains on the hemiplegic side, not yielding to any analgesic treatment”. Pathological studies of three of these patients revealed lesions of the thalamus and parts of the posterior limb of the internal capsule. In 1911, Head and Holmes⁴ described in detail the sensory deficits and pain narratives of 24 patients with stroke who had clinical symptoms of lesions of the optic thalamus and central pain. These neurologists noted that the patients often developed pain and hypersensitivity to stimuli during recovery of function. Subsequently, in 1938, Riddoch⁵⁻⁷ provided an extensive presentation of the clinical features of central pain of thalamic and extra-thalamic origin. As central pain also occurs after vascular lesions in parts of the CNS other than the thalamus, and as only a few patients present with the classic “Dejerine and Roussy syndrome”,^{8,9} the term CPSP is now preferred to describe neuropathic pain after stroke.

CPSP belongs to a group of chronic pain disorders that are termed central neuropathic pain (panels 1 and 2)¹⁰⁻¹² because the pain is due to a lesion or dysfunction of the CNS.¹⁰ Because of the difficulty in differentiating this syndrome from other pain conditions associated with CNS disorders, an alternative definition of central neuropathic pain has recently been suggested as “pain arising as a direct consequence of a lesion or disease affecting the central somatosensory system”.¹¹ To complicate matters further, other painful disorders such as headache, painful spasms, contractures, hemiplegic shoulder pain, and other types of musculoskeletal pain can blur the clinical picture of CPSP.

In this Review, we outline the epidemiology, clinical characteristics, mechanisms, and treatment of CPSP, and discuss diagnostic problems of this syndrome.

Post-stroke pain

In 2000, the incidence of stroke in Europe was about 1·1 million per year, and this rate is expected to rise to 1·5 million per year by 2025, owing to an increase in the proportion of elderly people.¹³ Chronic pain after stroke occurs in 11–55% of patients,¹⁴⁻²¹ but the pain is not always associated with stroke¹⁶ (table 1) and pre-existing chronic pain disorders are common in patients who develop post-stroke pain.^{9,16} The most common forms of chronic post-stroke pain are shoulder pain, CPSP, painful spasticity, and tension-type headache.^{15,28,29} Shoulder pain is reported in 30–40% of patients with stroke^{30,31} and has been associated with sensory and motor deficits, subluxation, and a limited passive range of movement.^{30,31} Musculoskeletal pain is often reported in the back and lower limbs, particularly in the knees and hips.²¹ In some cases, patients have more than one type of post-stroke pain.^{15,28} Long-term pain disorders after stroke have been reported to reduce quality of life,^{16,32} affecting mood, sleep, and social functioning.³³

Definition of CPSP

The new proposed grading system for neuropathic pain¹¹ suggests that a diagnosis of definite neuropathic pain requires the presence of pain with a distinct plausible distribution, a history suggestive of a relevant lesion, indication of negative or positive sensory signs within the area, and confirmation of the lesion by a diagnostic test.

At present, the diagnosis of CPSP is one of exclusion, as there are no pathognomonic features of this syndrome. As chronic pain is common in the elderly and post-stroke pain is frequent, many patients will concomitantly present with several types of pain. Many of these patients will fulfil the diagnostic criteria for definite neuropathic pain, despite the pain being of nociceptive origin. In these cases, identifying a central neuropathic element to

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Danish Pain Research Center, Aarhus University Hospital, Denmark (H Klit MD, N B Finnerup MD, T S Jensen MD); and Department of Neurology, Aarhus University Hospital, Denmark (T S Jensen)

Correspondence to: Henriette Klit, Danish Pain Research Center, Aarhus University Hospital, Norrebrogade 44, Building 1A, DK-8000 Aarhus C, Denmark henriette.klit@ki.au.dk

Panel 1: Definition of common pain terms**Pain**

An "...unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"¹⁰

Neuropathic pain

Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system¹¹

Central neuropathic pain

Pain arising as a direct consequence of a lesion or disease affecting the central somatosensory system¹¹

Allodynia

Pain evoked by stimuli that is usually not painful (ie, touch or brush)

Hyperalgesia

An increased response to a stimulus that is normally painful¹⁰

Paraesthesia

An abnormal but non-painful (and not unpleasant) sensation, either spontaneous or evoked

Dysaesthesia

An abnormal unpleasant sensation, either spontaneous or evoked

Aftersensation

A sensory impression that persists after the stimulus has ceased

Central sensitisation

An "...increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input"¹²

the hemiplegic shoulder pain, spasticity, or other musculoskeletal pain might be difficult and, in some cases, several pain types might be present in the same area of the body (figure 1). There are currently no studies to guide us on the differential diagnosis of post-stroke pain. Several authors have described CPSP as a central neuropathic pain syndrome that can occur after a stroke in the body part that corresponds to the cerebrovascular lesion, that is characterised by pain and sensory abnormalities, and where other causes of obvious nociceptive, psychogenic, or peripheral neuropathic origin have been ruled out.^{9,22,34} In our view, the differential diagnosis should be based on the sensory findings, location of the lesion, and specific findings on clinical examination such as increased muscle tone or subluxation of the shoulder.

Epidemiology of CPSP

There are only a few epidemiological studies of CPSP. The prevalence of CPSP in patients with stroke is between 1% and 12% (table 1).^{8,15-28} Development of CPSP is

Panel 2: Common causes of central neuropathic pain

- Ischaemic and haemorrhagic stroke
- Multiple sclerosis
- Spinal cord injury
- Syringomyelia
- Vascular malformations
- Infections (ie, abscess, encephalitis, vasculitis)
- Traumatic brain injury
- Parkinson's disease?

associated with sensory impairment, and, in one study, the prevalence of CPSP was as high as 18% in patients with sensory deficits, compared with 8% in all patients with stroke.^{15,22} Therefore, CPSP does not seem to be a rare disorder and the examination of sensory symptoms (including pain) and signs is an important part of the post-stroke follow-up, particularly in patients who are elderly or who have aphasia.

CPSP occurs after lesions at any level of the somatosensory pathways of the brain, including the medulla, thalamus, and cerebral cortex. Data from several studies indicate that the prevalence of CPSP is dependent on the location of the lesion, and occurrence is particularly high after lateral medullary infarction (or Wallenberg's syndrome) or lesions in the ventroposterior part of the thalamus. In 63 patients with lateral medullary infarction identified both retrospectively and prospectively, 16 developed CPSP.²⁶ In a study of 39 patients with thalamic stroke treated prophylactically with amitriptyline, seven developed CPSP within the first year after stroke with no difference between patients treated with amitriptyline and placebo.²⁵ In 40 patients with thalamic infarcts, only three out of 18 patients with inferolateral thalamic lesions developed CPSP,⁸ of which two presented with a typical Dejerine-Roussy syndrome. There are case reports of subsequent strokes causing both exacerbation and alleviation of existing CPSP.^{35,36}

Age, sex, and side of lesion are not consistent predictors of CPSP.^{9,22,37-39} Age has, for example, been reported to be lower,^{9,38} higher,²³ or the same¹⁵ when comparing stroke patients with and without pain.

Clinical characteristics of CPSP

The clinical characteristics of CPSP resemble those of other central and peripheral neuropathic pain syndromes.⁴⁰⁻⁴² There are no pathognomonic features or uniform signs with regard to onset, presentation, and intensity,⁹ and the characteristics and descriptions of CPSP vary substantially between patients.

CPSP is often described as long-lasting, even life-long, but there are no prospective studies that have documented this. Most studies are based on patients from pain clinics, which might potentially bias results towards more severe and persisting pain.

The pain in CPSP can be spontaneous or evoked. Spontaneous dysaesthesia is common and is reported in up to 85% of patients.³³ On a scale from 0 to 10, the mean intensity of pain varies between 3⁴⁰ and 6.²⁸ In some studies, higher pain intensities have been reported when the lesions were located in the brainstem or thalamus than in other areas;^{9,44} however, in a recent study, the symptoms and severity of CPSP in thalamic versus extrathalamic stroke did not differ.³⁹ The intensity of spontaneous pain often fluctuates and can be increased by internal or external stimuli, such as stress or cold,^{9,38} and alleviated by, for example, rest or distraction.^{9,33} Pain is commonly a great burden to the patient, even when the intensity is low.⁹ Spontaneous ongoing pain is described as “burning”, “aching”, “pricking”, “freezing”, and “squeezing”, whereas intermittent pain is described as “lacerating” or “shooting”.^{9,22,38} Affective descriptions of the pain include “troublesome”, “annoying”, and “tiring”.²⁸ Furthermore, CPSP can reduce quality of life

in patients who have had stroke, compromise rehabilitation,¹⁶ interfere with sleep,³⁹ lead to self-mutilation,²⁶ and even push patients to suicide.⁴⁵

The distribution of pain can range from a small area (eg, the hand) to large areas (eg, to one side of the body). Large areas are the most commonly affected, with or without involvement of the trunk and face.^{9,43} In patients with lateral medullary infarction, the pain can involve one side of the face and the contralateral side of the body or limbs,²⁶ and periorbital pain is frequently reported;⁴⁶ hemibody pain is common in patients with thalamic lesions.⁸

The non-sensory findings depend on the localisation and severity of the cerebrovascular lesion, and there are no universal non-sensory findings in CPSP.⁹ Pain can be localised within the entire area of sensory abnormalities, or within a fraction of this area, and corresponds to the localisation of the vascular lesion.^{9,22,40} A key finding in most, if not all, neuropathic pain

	Time since stroke	Number of patients	Prevalence of all types of pain	Prevalence of CPSP	Comments
Inpatient rehabilitation multicentre prospective study ²¹	Not available	327	Musculoskeletal pain 32.4% (n=106)	4.3% (n=14)	..
Prospective study ²²	12 months	207	..	8% (n=16)	Verified by clinical examination
Stroke register ¹⁸	12 months	253	11% (n=28)
Acute thalamic infarct verified by CT ⁸	Mean 47.5 months (6 months to 9 years)	40	..	8% (n=3) in all patients with thalamic infarct	11% (3 of 27) in patients with sensory dysfunction 17% (3 of 18) in patients with inferolateral infarcts
Questionnaire sent to 1071 elderly individuals (>69 years) ²³	..	72 patients with stroke	..	11% (n=8)	Identified by questionnaire
Stroke unit ¹⁷	3 months	244	55% (n=134)
Stroke register ¹⁶	16 months	297	All pain 21% (n=62) Stroke-associated pain 8% (n=23)	1% (n=4)	Only patients suspected to have CPSP by interviewers were referred to a neurologist
Outpatient clinic, medullary infarcts: (LMI: n=41; MMI: n=14) ²⁴	Mean 21 months	55	..	LMI: body 83% (n=34), face 56% (n=23) MMI: body 71% (n=10), face 7% (n=1)	Residual sensory symptoms, not pain
Out-patient rehabilitation clinic ¹⁵	More than 6 months	107	42% (n=45)	12% (n=13)	..
Prophylaxis study of amitriptyline vs placebo in patients with acute thalamic stroke ²⁵	12 months	39	..	18% (pooled; n=7)	Thalamic strokes only Placebo group 21% (4 of 19) Treatment group 17% (3 of 18)
Stroke registry ¹⁹	12 months	140	All pain 49% (n=68) Stroke-associated pain 21% (n=29)	3% (n=4)	..
Patients with LMI identified retrospectively (n=4) and prospectively (n=9), stroke unit ²⁶	Mean 60 months (2–108 months)	63	..	25% (n=16)	LMI only All patients underwent clinical examination
Severely disabling stroke (Barthel index ≤10), identified by stroke registry and visited at home ²⁰	12 months	122	Shoulder pain 52% (n=64) Other pain 55% (n=67)
Postal questionnaire ²⁷	12 months	119	..	Presumed CPSP 9% (n=11)	CPSP confirmed by clinical examination in 5 of 6 presumed cases (4%)
Inpatient register ²⁸	24 months	288	15% (n=43)	5% (n=15)	Verified by clinical examination and quantitative sensory tests

..=not applicable. CPSP=central post-stroke pain. LMI=lateral medullary infarct (Wallenberg's syndrome). MMI=medial medullary infarct.

Table 1: The prevalence of post-stroke pain and CPSP

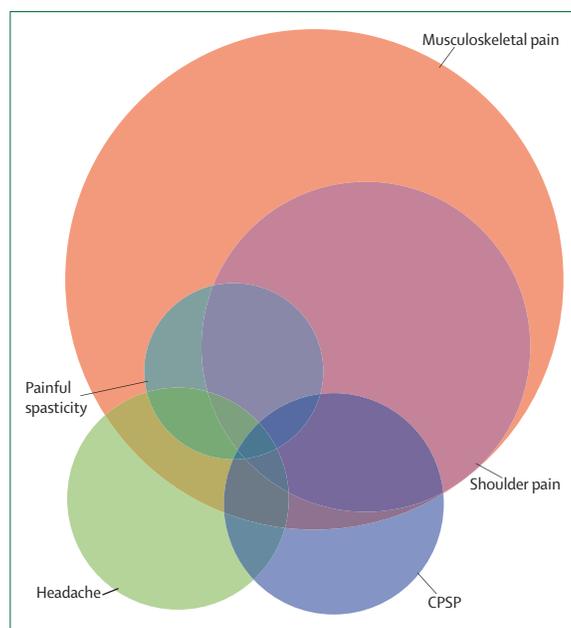


Figure 1: Common types of chronic pain that can occur after stroke
Diagram of the complexity of post-stroke pain. Individual patients can have various combinations of one or several pain types (overlapping areas). The sizes of the circles are approximate to relative frequency (spasticity 7%, headache 10%, CPSP 10%, shoulder pain 20%, musculoskeletal pain 40%). CPSP=central post-stroke pain.

Panel 3: Diagnostic criteria for CPSP

Mandatory criteria for the diagnosis of CPSP

- Pain within an area of the body corresponding to the lesion of the CNS
- History suggestive of a stroke and onset of pain at or after stroke onset
- Confirmation of a CNS lesion by imaging or negative or positive sensory signs confined to the area of the body corresponding to the lesion
- Other causes of pain, such as nociceptive or peripheral neuropathic pain, are excluded or considered highly unlikely

Supportive criteria

- No primary relation to movement, inflammation, or other local tissue damage
- Descriptors such as burning, painful cold, electric shocks, aching, pressing, stinging, and pins and needles, although all pain descriptors can apply
- Allodynia or dysaesthesia to touch or cold

CPSP=central post-stroke pain.

disorders is the combination of sensory hyposensitivity and hypersensitivity in the painful area.⁴⁷ Consistent with this finding, “negative” and “positive” sensory events are characteristic in CPSP and other neuropathic pain syndromes.^{22,40,42,47} Abnormalities in either thermal (particularly cold) or pain (eg, pinprick) sensation are found in more than 90% of patients,^{9,22,38} whereas

sensory loss in other modalities (such as touch and vibration) is less frequent.^{40,43,44}

Positive sensory findings, such as evoked pain, elicited by mechanical or thermal stimuli (particularly cold), are common in CPSP.^{9,22,28,38} In a prospective study of 16 patients with CPSP, allodynia to cold, examined by use of a thermo roll (20°C), a combined thermal and dynamic mechanical stimulus, was found in nine patients; allodynia to touch was found in nine; and dysaesthesia or allodynia to either touch or cold was found in 15 patients on clinical examination.²² Other positive signs, such as aftersensations, radiation of pain, and summation are less common.⁴³

CPSP can develop after both haemorrhagic and ischaemic lesions of the CNS. In one study, four of 13 patients developed CPSP after intracerebral haemorrhage.²⁷ The authors concluded that this high prevalence might be attributed to the frequent involvement of the thalamic region in haemorrhagic lesions.

The time between stroke and pain onset varies, and pain can develop immediately after stroke in some patients and up to years later in others. Onset can be delayed, but development of CPSP within the first few months is most common.⁴⁸ In a prospective study that included 16 patients with CPSP, pain onset occurred within the first month after stroke in ten patients, between 1 and 6 months in three patients, and after 6 months in three patients.²² Any later onset of pain should prompt an examination for other causes, such as a new stroke. Gradual onset of pain is most common.⁹

Diagnostic measures

A definite diagnosis of CPSP is difficult, mainly because of the variable clinical picture, the frequent concurrence of several pain types, and the lack of clear diagnostic criteria for CPSP. The diagnosis should be based on a combination of the history, a clinical and sensory examination, imaging of lesions (CT or MRI), and other clinical measures (panel 3). The history of stroke should be confirmed by imaging (either CT or MRI) to visualise the lesion (type, location, and size) and to exclude other central causes of pain. The history of pain should include details of pain onset, pain quality, presence of dysaesthesia or allodynia, and patients should be asked to indicate the area of pain on a drawing of the body (a pain drawing). The clinical examination should include sensory testing to confirm and map the presence of sensory abnormalities, but also to aid the exclusion of other causes of pain.

Responses to quantitative sensory tests enable detailed sensory testing of controlled and graded physiological stimuli, such as thermal, pressure, pinprick, and vibration stimuli,⁴⁹ and have been used to document common or dissociated sensory findings in CPSP.^{40,43} Abnormalities in somatosensory-evoked and laser-evoked potentials are common in CPSP, but are of limited

diagnostic value.^{39,50,51} Both quantitative sensory tests and neurophysiological examinations might be useful in patients with CPSP in whom a lesion is difficult to verify by imaging, when subtle sensory deficits cannot be confirmed by bedside sensory examination, to rule out other causes of pain (eg, peripheral neuropathy) and to examine underlying mechanisms.^{49,52} However, at present, these diagnostic tests are not routinely used in the clinic because they are time consuming and the equipment is expensive.

Several screening tools for neuropathic pain have been published within the last decade,^{53,54} but their diagnostic value for CPSP has not been clarified. A recent study emphasises that a sensory examination is essential for the sub-classification of pain types.⁵⁵ Pain scales, such as the visual analogue scale and the numeric rating scale, are useful in the evaluation of the pain intensity, but there are no scales developed specifically for CPSP.

Pathophysiology: possible mechanisms

The pathophysiological features of multiple sclerosis, traumatic brain injury, and stroke are obviously different, although the underlying pain mechanisms might not differ substantially. In fact, the clinical characteristics of CPSP resemble those of other central and peripheral neuropathic pain syndromes,^{40–42,45} and different neuropathic pain conditions might have a common or overlapping range of mechanisms. However, even within brain lesions, the underlying pattern of pathophysiological mechanisms could differ depending on the localisation of the lesion in the CNS. Burning pain is more common in patients with lateral medullary infarction than in patients with thalamic infarcts,^{9,26} and descriptions of the pain and aggravating factors are different depending on whether a medullary lesion is located medially or laterally.²⁴ At present, there is little evidence for the association between pain mechanism, localisation and pathology of lesions, clinical manifestations, and treatment response.⁴⁶ Consequently, any proposed explanation of the underlying mechanisms should be based on the clinical characteristics of the disease, such as sensory loss (deafferentation), hypersensitivity (sensitisation and disinhibition), and decreased or increased sensation of temperature and pain (abnormal spinothalamic function; figure 2).^{4,51,56–65}

The sensory processing of temperature and of pinprick occurs via the thalamus by the spinothalamic tract and the spinotrigeminothalamic tracts projecting to the thalamus. The pain system of the brainstem has typically been divided into a lateral and a medial system.^{66–68} The ventral-caudal principal sensory nucleus of the lateral thalamus constitutes part of the “lateral” pain system. This nucleus receives dense spinothalamic tract terminations and projects to the primary somatosensory cortex, the secondary somatosensory cortex, and insula. Data from PET studies indicate that

the primary somatosensory cortex is involved in the sensory-discriminative dimension of pain, the secondary somatosensory cortex in pain intensity, and the insula in thermal and nociceptive information processing. The medial and intralaminar thalamic nuclei also receive spinothalamic tract input and project to the anterior cingulate cortex (the “medial” pain system). The anterior cingulate cortex is consistently activated by noxious stimuli and has been implicated in the affective–emotional aspect of pain.

Central sensitisation

A lesion in the CNS results in both anatomical, neurochemical, excitotoxic, and inflammatory changes, all of which might trigger an increase in neuronal excitability.⁶⁹ Combined with a loss of inhibition and increased facilitation, this increased excitability can result in central sensitisation, which in turn might lead to chronic pain.⁷⁰ This mechanism is supported by the fact that many of the pharmacological drugs available for the treatment of central pain act partly by decreasing neuronal

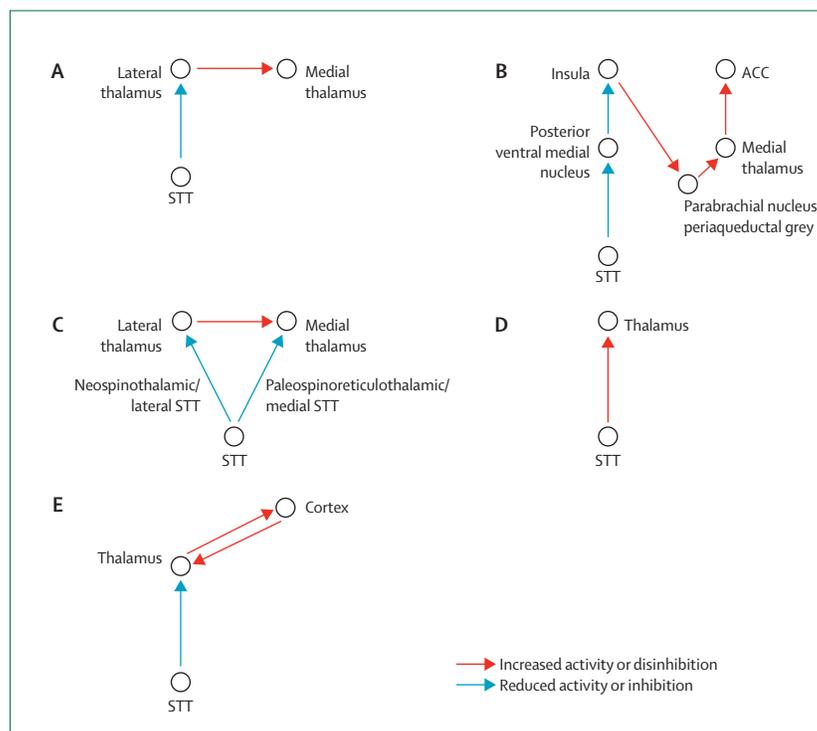


Figure 2: Some proposed mechanisms for central pain

(A) Loss of STT input to the posterior lateral part of the thalamus causes disinhibition of the medial thalamus leading to pain.⁴ (B) The thermosensory disinhibition theory. A lesion in the lateral cool-signalling spinothalamic projections to the thermosensory area of the insula through the posterior part of the ventral medial nucleus causes disinhibition of a medial limbic network involving the parabrachial nucleus and the periaqueductal grey of the brainstem, the medial thalamus, and the ACC.^{56–59} (C) A loss of normal inhibition from the rapidly conducting “neospinothalamic” or lateral STT projections causes disinhibition of the slowly conducting polysynaptic paleospinothalamic or medial STT projections, resulting in pain.^{51,60–62} (D) Deafferentation of ascending pathways to the thalamus might cause central pain due to hyperactive bursting in the thalamus caused by low-threshold calcium spikes.^{63,64} (E) The dynamic reverberation theory. A lesion of the STT causes central pain by creating an imbalance in the normal oscillatory “dialogue” between the cortex and the thalamus.⁶⁵ ACC=anterior cingulate cortex. STT=spinothalamic tract.

hyperexcitability. Spontaneous pain in CPSP might be linked to hyperexcitability or spontaneous discharges in deafferented neurons in the thalamus or cortex.⁴⁰

Alterations in spinothalamic tract function

Disturbances of pain and thermal sensation are common findings in patients with CPSP, and a lesion of the spinothalamic tract might be necessary for this syndrome to develop. Deficits in the function of the spinothalamic tract can be shown with laser-evoked potentials.⁵¹ However, such disturbances are equally common in patients with CNS lesions without pain.^{9,40,71–73} Nevertheless, hypersensitivity to pinprick and thermal stimuli (particularly cold) is more common in patients with stroke with central pain than without central pain,^{22,43} indicating that hyperexcitability and ongoing activity in the spinothalamic tract might be underlying mechanisms.⁷⁴

Disinhibition theories

Input to the CNS is continuously controlled by a fine balance between systems of facilitation and inhibition,^{75–79} including interactions between nuclei of the brainstem (the rostral ventromedial medulla and the periaqueductal grey) and the spinal cord and supraspinal thalamocortical circuits.^{59,65} Imbalance of such equilibria has been proposed to be the underlying mechanism in many theories of central pain, including those that indicate that central pain is a result of a lesion of a lateral system, causing disinhibition of a medial system (figure 2A–C). Head and Holmes suggested in 1911 that central pain was caused by a lesion in the lateral thalamus interrupting the inhibitory pathways, causing disinhibition of the medial thalamus (figure 2A).⁴ A modification of this hypothesis is proposed in the thermosensory disinhibition theory, which states that CPSP results from loss of normal inhibition of pain from cold owing to a lesion. This produces an imbalance between a lateral spinothalamic tract that is involved in signalling cold sensation and a medial spinothalamic tract pain signalling pathway (figure 2B).^{56–59} This theory has been questioned by several authors.^{80–82} Disinhibition of the medially located spinoreticulothalamic or paleospinothalamic pathways, by lesion of the lateral spinothalamic tract, has also been suggested (figure 2C).^{52,60–62} Changes in descending inhibition and facilitation from the rostral ventromedial medulla and the mesencephalic reticular formation of the brainstem might also have a role in maintaining neuropathic pain,⁸³ but this possibility has not been examined in CPSP. In patients with CPSP, ischaemia-induced heterotopic noxious conditioning stimulation did not reduce ongoing and evoked pain despite the ability of patients to activate these systems, suggesting that endogenous descending pain-controlling systems cannot modulate central pain generated in the brain.⁸⁴

Changes in regional cerebral blood flow can be visualised by use of functional MRI, PET, or SPECT (single photon emission computed tomography) techniques. Such

changes have been shown during evoked pain in patients with lateral medullary infarction and CPSP. Increases in regional cerebral blood flow in the thalamus, somatosensory areas, inferior parietal, anterior insula, and medial prefrontal cortices were found during stimulation of allodynic areas. In healthy individuals, there is an increase in activity in the anterior cingulate cortex associated with noxious stimuli, but this response is not seen during allodynia. These studies indicate that plastic changes of the somatosensory and pain pathways occur after stroke, possibly in the lateral “discriminative” pain system.^{85,86}

Thalamic changes

The thalamus is thought to play an important part in the underlying mechanisms of central pain,^{87,88} and CPSP is common after lesions affecting the thalamus. In one study, nine of 11 patients with thalamic lesions and pure sensory strokes had small infarcts in the thalamus, which were all confined to the posterolateral nucleus.⁸⁹ Six of these patients had either no or very discrete sensory findings, and three patients reported dysaesthesia. In a series of patients with thalamic infarcts,⁸ only lesions located in the ventral posterior (ventral posterior lateral and medial nuclei) part of the thalamus caused CPSP. In another study,⁸² lesions of the thalamic ventral caudal nucleus, not affecting the posterior part of the ventral medial nucleus, were sufficient to impair cold sensitivity and produce CPSP.

The thalamus might also be implicated in central pain in patients in whom lesions do not directly involve the thalamus.^{85,90,91} Data from PET studies have shown decreased regional cerebral blood flow in the thalamus of patients with CPSP who have spontaneous pain at rest. This hypoactivity might merely indicate deafferentation, but might also be associated with the pathophysiology of neuropathic pain.⁹² Thalamic hyperactivity has been found during allodynia by use of SPECT and PET.⁸⁵ Increased bursting activity has been found in the ventral caudal nucleus of the thalamus in patients with central pain by use of microelectrodes during brain surgery.^{93,94} Recent animal studies of central pain in primates and rodents indicate that increased excitability of thalamic nuclei is a result of maladaptive homeostatic plasticity due to loss of normal ascending inputs via the spinothalamic tracts (figure 2D).^{63,64} Although these bursting patterns might not be specific for patients with chronic pain,⁸⁸ bursting activity in patients with central pain seems to differ in location and characteristics compared with patients who are pain-free with similar deafferentation.⁹⁵ Electrical stimulation by microelectrodes of certain areas in both the lateral and medial thalamus can elicit pain.⁹⁶ There is an increased occurrence of stimulus-evoked pain sites in the ventral caudal and posteroinferior regions of the thalamus, and microstimulation is more likely to cause a burning sensation in patients with CPSP compared with other patients with chronic pain.^{88,97,98}

Therefore, the thalamus probably has a substantial role in some patients with central pain, either as a

	Dosage (per day)	Outcome	Number of patients	Number of withdrawals	Number needed to treat	Design
Oral and transdermal						
Oral amitriptyline ¹⁰⁴	75 mg	Positive	15 (CPSP)	0	1.7	Three-phase, cross-over
Oral carbamazepine ¹⁰⁴	800 mg	Negative	14 (CPSP)	0	..	Three-phase, cross-over
Oral lamotrigine ¹⁰⁵	200 mg	Positive	30 (CPSP)	10	NA	Cross-over
Oral pregabalin ¹⁰⁶	300–600 mg	Positive	40 (mixed CP: 19 CPSP, 21 SCI)	7	4.0	Parallel, flexible-dose
Transdermal ketamine ¹⁰⁷	50–75 mg	Negative	33 (mixed CP: 15? CPSP)	0	NA	Parallel, three-arm
Intravenous trials						
Morphine ¹⁰⁸	9–30 mg	Negative	15 (mixed CP: 6 CPSP, 9 SCI)	1	NA	Cross-over
Lidocaine ¹⁰⁹	5 mg/kg	Positive	16 (mixed CP: 6 CPSP, 10 SCI)	0	NA	Cross-over
Propofol ¹¹⁰	0.2 mg/kg	Positive	44 (mixed CP: 22 CPSP)	0	NA	Cross-over
Naloxone ¹¹¹	8 mg	Negative	20 (CPSP)	2	NA	Cross-over
--=not applicable. CP=central neuropathic pain. CPSP=central post-stroke pain. NA=not available. SCI=spinal cord injury.						
Table 2: Class I randomised, double-blind, placebo-controlled trials in CPSP						

pain generator or by abnormal processing of ascending input. Deafferentation, loss of inhibitory GABA-containing neurons in the thalamus,^{66,99} and remote microglial activation^{90,91} have also been suggested to underlie thalamic changes after CNS lesions.

Other changes

The dynamic reverberation theory suggests that central pain arises as a consequence of derangement of an oscillatory pattern inside a sensory corticothalamocortical reverberatory loop running between the thalamus and the cortex (figure 2E).⁶⁵ Melzack¹⁰⁰ proposed a neural network, or neuromatrix, that subserves body sensation and has a genetically determined substrate that is modified by sensory experience. He suggested that this network produces abnormal painful sensations, such as phantom limb pain, when deprived of sensory input. Structural reorganisation of the thalamus (ventral caudal nucleus) and the somatosensory cortex have been shown in other central pain states^{101–103} and in animal studies by use of functional imaging and neurophysiological tests. Structural reorganisation has not been examined in CPSP, and whether reorganisation in other central pain states has a direct causal association with the pain or is secondary to changes occurring at other levels of the CNS is unclear.

Management of CPSP

CPSP is, as is the case for other neuropathic disorders, often difficult to treat; the treatment response is mostly moderate, and the dosage is limited by side-effects, particularly in elderly patients. In clinical practice, the treatment of patients with CPSP is often based on trial and error until pain relief is found, and the result is usually a combination of several drugs. There are only a few randomised controlled studies on CPSP treatment (ie, class I studies; table 2),^{104–111} and there are no published trials on polypharmacy for CPSP. The only study on prevention of CPSP so far is a prospective, double-blinded, placebo-controlled study of amitriptyline (75 mg per day)

in 39 patients with acute thalamic stroke, who were followed-up for 1 year.²⁵ No significant prophylactic effect was found in this small study.

Antidepressants

Tricyclic antidepressants have a well-established beneficial effect in various neuropathic pain states,³⁴ and are first-line drugs for neuropathic pain.¹¹² Amitriptyline (75 mg per day) significantly reduced pain in patients with CPSP.¹⁰⁴ The effect was correlated with plasma concentrations of amitriptyline, with many responders having plasma concentrations of more than 300 nmol/L, but was independent of the depression scores. Mild to moderate side-effects were common, particularly tiredness and dry mouth.

Selective serotonin–norepinephrine-reuptake inhibitors are effective in relieving painful diabetic neuropathy,^{112,113} and, although this drug class has not been assessed for central pain, these inhibitors might be a safer choice than tricyclic antidepressants in patients with, for example, cardiac disease. Selective serotonin-reuptake inhibitors seem to be less effective than other antidepressants in the treatment of neuropathic pain.¹¹⁴

Anticonvulsants

Anticonvulsant drugs are a broad range of drugs that exert their analgesic actions through several mechanisms, including the reduction of neuronal hyperexcitability. The efficacy of gabapentin and pregabalin on peripheral and central neuropathic pain is well documented.³⁴ In one study of pregabalin, there was a clinically significant effect of treatment on pain levels in patients with central neuropathic pain.¹⁰⁶ The treatment was well tolerated, and the occurrence of adverse events did not differ between the treatment groups. The most commonly reported side-effects were dizziness, decreased intellectual performance, somnolence, and nausea. Lamotrigine has been studied in a single trial for CPSP and was well tolerated and

had a moderate effect on pain.¹⁰⁵ In other central pain and neuropathic pain disorders, the efficacy of lamotrigine has been questionable, and this drug has a limited role in neuropathic pain treatment.¹¹² In a single study of carbamazepine (800 mg per day), there was no significant effect on pain.¹⁰⁴

Opioids

Opioids effectively relieve neuropathic pain but are not considered as first-line drugs.¹¹² Treatment with oral opioids significantly reduced pain (23% mean decrease in pain) in a mixed neuropathic pain population (n=81; n=10 with CPSP). There was a high withdrawal rate in patients with CPSP (n=7), and these patients reported less benefit from the treatment.¹¹⁵

Intravenous drug trials

Results from trials of intravenous drugs might indicate the underlying mechanisms that are involved in CPSP. Treatment with intravenous morphine, lidocaine (a sodium-channel blocker), and propofol (a GABA_A agonist) alleviated pain or elements of pain during infusion,^{108–110} but subsequent oral treatment with morphine and mexiletine was not well tolerated owing to side-effects.

Panel 4: Grading system for CPSP

Criteria to be evaluated for each patient (based on a grading system for neuropathic pain by Treede and co-workers).¹¹ CPSP is defined as “possible” if criteria 1, 2, and 3 are fulfilled, “probable” if criteria 1, 2, and 3 plus either criteria 4 or 5 are fulfilled, and “definite” if criteria 1–5 are fulfilled.

- 1 Exclusion of other likely causes of pain**
No other obvious cause of pain
- 2 Pain with a distinct neuroanatomically plausible distribution**
Either pain localised unilaterally in the body and/or face or unilaterally on one side of the body with contralateral involvement of the face
- 3 A history suggestive of stroke**
Sudden onset of neurological symptoms with onset of pain at or after stroke onset
- 4 Indication of the distinct neuroanatomically plausible distribution by clinical neurological examination**
Findings of positive or negative sensory signs in the painful area on clinical examination, pain localised within a territory of sensory abnormality, and anatomically plausible distribution of sensory abnormalities
- 5 Indication of the relevant vascular lesion by imaging**
Visualisation of a lesion that can explain the distribution of sensory findings (either CT or MRI)

CPSP=central post-stroke pain.

Neurostimulation therapy

Neurostimulation therapy, such as motor cortex stimulation,¹¹⁶ deep brain stimulation, and transcranial magnetic stimulation, is used for treatment-resistant cases of CPSP. There are only a few randomised placebo-controlled studies of neurostimulation therapy for CPSP or central pain, and published papers mainly consist of case series and case reports.

The mechanisms that underlie the effect of motor cortex stimulation are unknown, but studies have indicated changes in cerebral blood flow in several areas, including the thalamus, after successful motor cortex stimulation.^{117,118} In two recent reviews, the 1-year success rate in patients with CPSP was concluded to be about 45–50%.^{119,120} Severe complications are rare; the most common complications reported are seizures (intra-operatively or during the trial period), infections, and hardware problems.¹²⁰ The success rate of motor cortex stimulation seems to be lower in cases of post-stroke pain than in spinal cord injury and peripheral neuropathic pain.^{119,121} More studies are needed to determine the long-term efficacy and safety of motor cortex stimulation.

Transcranial magnetic stimulation of the motor cortex is a non-invasive method. The effects on pain are often modest and short lasting, but adverse events are rare. Recurring sessions of repetitive transcranial magnetic stimulation of the motor cortex have been shown to extend pain relief.^{122,123} The result of this treatment might be a useful predictor for the efficacy of motor cortex stimulation.¹²⁴

The main targets of deep brain stimulation in patients with CPSP are the sensory (ventral posterior) thalamus and the periventricular grey matter. Reported efficacy rates range from 25% to 67%.^{125,126} The results of deep brain stimulation in CPSP are equivocal, and further trials are needed.¹¹⁹

Treatment algorithm

A broad approach to the treatment of CPSP is essential. Patients with CPSP are likely to have several concurrent medical problems and impairments, and might be receiving several drugs with unwanted side-effects. As evidence-based treatment of this disorder is scarce, guidelines and treatment algorithms for other central and peripheral neuropathic pain syndromes (examples are provided elsewhere^{34,127}) might be helpful in planning the treatment of these patients. Tricyclic antidepressants and gabapentin or pregabalin could thus be considered as first-line drugs, and selective serotonin–norepinephrine-reuptake inhibitors, lamotrigine, opioids, and drug combinations could be a possibility if the first-line treatment fails. At present, there is no evidence for recommendations for preventive treatment.²⁵

Non-pharmacological treatment (eg, psychological treatment such as training in coping strategies and behavioural therapy) might also be of benefit in this, as

in other, chronic pain disorders.³³ The need for rehabilitation after stroke is particularly crucial if the patient also has CPSP.^{14,16,128}

Patients with CPSP can present with different combinations of symptoms and signs. Recently, a mechanism-based treatment approach has been proposed,^{47,129} suggesting that different pain phenotypes indicate different underlying mechanisms, and that treatment should be targeted at mechanisms rather than at diagnosis or disease pathology. However, patients are rarely grouped in clinical trials according to symptoms and signs rather than disease aetiology. Current attempts to make mechanism-based classification systems of neuropathic pain syndromes, such as the German Research Network on Neuropathic Pain,¹³⁰ rely on quantitative sensory testing, but simple bedside tests might also be useful in distinguishing specific pain phenotypes, thus approaching mechanism-based classification and treatment strategies.

Conclusions and future perspectives

Chronic post-stroke pain is common, but this pain is not always due to CPSP, and several types of pain can occur in the same patient concomitantly. It is important to identify the origin and type of pain to find the relevant treatment for the patient, as the efficacy of a drug varies with the underlying pain type (ie, nociceptive pain or CPSP). Recently, a new definition of neuropathic pain was proposed, which might help to differentiate between pain as a direct consequence of the lesion (ie, central pain) and other stroke-related pain (eg, shoulder pain and pain from spasticity). However, at present, there are no standardised accepted diagnostic criteria, clear definitions, evidence-based knowledge, or simple diagnostic tests that will enable us to accurately distinguish between pain types. The diagnosis of CPSP must be based on medical and pain history (from the patient and the medical records), clinical examination, sensory examination, imaging of lesion (by use of CT or MRI), and other measures as appropriate.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed and Embase with the search terms "central pain", "pain and stroke", "post-stroke pain", "thalamic syndrome", "Dejerine and Roussy", "Wallenberg and pain", "brainstem and pain", and "medulla and pain" from 1966 until May, 2009. Only papers published in English were reviewed. The bibliographies of the papers, articles from our own files, and relevant book chapters were also searched. The final reference list was generated on the basis of relevance to the topic covered in this Review, and randomised controlled trials and studies that described large groups of patients with CPSP or that focused on the latest advances were given precedence over case reports.

There is a need for clear diagnostic criteria for CPSP for future research. The criteria should be both restrictive and exhaustive, and ideally enable differentiation of neuropathic pain from other types of pain. Such diagnostic criteria could be based on a grading system, enabling clinicians and researchers to define CPSP as "possible", "probable", or "definite". An attempt at such a grading system is provided in panel 4.¹¹ One of the challenges of the present grading system is that other causes of pain cannot be excluded in patients with established neurological lesions and, therefore, further diagnostic criteria are needed. By using strict diagnostic criteria and the new terminology of neuropathic pain, future studies could give insights into how to make these differential diagnoses.

Contributors

HK searched the literature, analysed the data, and wrote the first draft of this Review. TSJ and NBF reviewed and edited the paper. All authors contributed to the final version of the manuscript.

Conflicts of interests

HK has no conflicts of interest. NBF has received research support from UCB Nordic and Neurosearch A/S and honoraria from Mundipharma. TSJ has received honoraria and travel expenses from Pfizer, PharmEste, Eli Lilly, Grünenthal, Eisai, Endo Pharmaceuticals, and Daiichi Sankyo.

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