Review Article

A Comprehensive Review of Central Post-Stroke Pain

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Abstract:

Although central post-stroke pain is widely recognized as a severe chronic neuropathic pain condition, its consolidated definition, clinical characteristics, and diagnostic criteria have not been defined due to its clinically diverse features. The present study was undertaken to comprehensively review current literature and provide a more complete picture of central post-stroke pain with respect to its definition, prevalence, pathophysiology, clinical characteristics, and diagnostic problems, and to describe the range of therapies currently available. In particular, nursing care perspectives are addressed. It is hoped that this review will help nurses become knowledgeable about central post-stroke pain and provide valuable information for the drafting of effective nursing care plans that improve outcomes and quality of life for patients with central post-stroke pain.

BACKGROUND

Pain is a serious problem after stroke, and two major types of pain must be differentiated in patients with post-stroke pain: central post-stroke pain (CPSP) and pain primarily triggered by peripheral mechanisms (such as shoulder pain, painful spasticity, persistent headache, and musculoskeletal pain) (Klit, Finnerup, & Jensen, 2009; Seifert, Mallar Chakravarty, & Sprenger, 2013). CPSP was originally referred to as Dejerine–Roussy syndrome after the French neurologists who first described an unusual pain syndrome following thalamic stroke (Dejerine and Roussy, 1906).

Although CPSP is widely recognized as a severe chronic neuropathic pain condition, no consolidated definition or clinical characteristics have been agreed upon due to its clinically diverse features. In addition, the prevalence of CPSP has not been precisely determined, partly because of difficulties associated with distinguishing this syndrome from other pain types that can occur after stroke (Klit et al., 2009). Furthermore, the detailed mechanism responsible for CPSP has not been elucidated and no standard treatments have been established (Tamiya, Yoshida, Harada, Nakamoto, & Tokuyama, 2013). CPSP is known to be resistant to conventional analgesics (Nandi et al., 2002; Pickering, Thornton, Love-Jones, Steeds, & Patel, 2009), and although a wide variety of treatment options have been suggested, no universally applicable rules have been presented for treatment selection.

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It has been proposed that CPSP reduces quality of life; undermines rehabilitation efforts; and leads to depression, anxiety, sleep disturbance, drug dependence, and poor social interactions (Hansson, 2004; Kumar & Soni, 2009). Because CPSP has been confused with a number of other conditions, and because treatment strategies for CPSP and pain from other causes differ (Kim, 2009; Kumar & Soni, 2009), an understanding of the clinical features of CPSP is important for its proper diagnosis and successful management. Furthermore, as the aging population continues to increase, CPSP is set to become a more important issue in pain management nursing.

PURPOSE

The present study was conducted to provide a more comprehensive picture of CPSP based on an up-to-date review of CPSP with respect to definition, prevalence, pathophysiology, and clinical characteristics. Diagnostic problems and the range of therapies currently available are also discussed and nursing care perspectives are addressed.

METHODS

Search Methods

Although the present study was not intended as a systematic review, literature searching was systematically conducted to identify all available evidence. The primary patient population of interest was stroke patients with central neuropathic pain; both hemorrhagic and ischemic stroke patients were included. The main outcomes (targets of the literature search) were issues regarding the definition, prevalence, pathophysiology, clinical characteristics, diagnosis, and management of CPSP. In terms of the study designs chosen for review, all study designs—traditional and systematic reviews and randomized controlled, nonrandomized controlled, observational comparative, and case studies—were included to avoid information loss.

The information sources used primarily were the PubMed, CINAHL, MEDLINE, and SCOUP databases, which were searched using the key terms "central post-stroke pain," "central neuropathic pain," "central pain after stroke," and "neuropathic pain after stroke." The search terms were decided upon after several rounds of trials and by continuous discussion between authors until consensus was reached. The search encompassed entire databases and yielded 399 studies (published from 1989 to June 2013). Inspections of these studies resulted in the identification of 212 duplicates. Thus, 187 studies were primarily identified and their abstracts were closely reviewed. However, 76 of the 187 were excluded because they were animal studies (n = 5), not written in English (n = 13), or early studies (n = 58) in which CPSP was not differentiated from other types of neuropathic pain. Further searching was performed by tracking down all related studies cited in the bibliographies of the primarily searched studies, and this resulted in the inclusion of another 21 studies. In the end, 132 studies were included in the present study. A schematic of study selection process is provided in Figure 1.

Data Extraction

For preliminary data collection, 10 studies were randomly selected to devise a data sheet. The devised data sheet included the following information: author; year of publication; study design; subjects; and the definition, prevalence, temporal pattern, clinical characteristics (pain nature, intensity, and location), pathophysiology, and CPSP management. All data were primarily extracted by the first author, and confirmed by the corresponding author. Cross-checking between the authors was conducted and disagreements were resolved by consensus. Because of the heterogeneous nature of the information gathered, methodological quality was not assessed.

RESULTS

Definition of CPSP

Pain has been categorized in a variety of different ways, but is widely classified as nociceptive or neuropathic (Nicholson, 2006). Nociceptive pain refers to pain caused by damage to muscles, bones, skin, or internal organs, and is the type of pain most consider when pain is mentioned. On the other hand, neuropathic pain is defined by the International Association for the Study of Pain (IASP, 1994) as "pain initiated or caused by a primary lesion or dysfunction in the

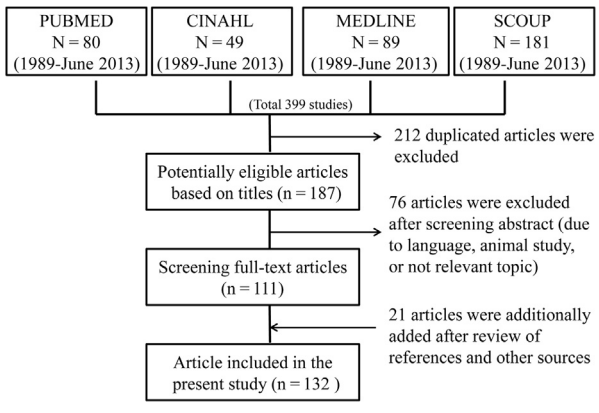

FIGURE 1. ■ A schematic of the study selection process.

nervous system." Treede et al., in 2008, redefined neuropathic pain as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."

Neuropathic pain can be further divided into peripheral and central neuropathic pain based on anatomic locations of lesions or disease (Treede et al., 2008). This distinction is clinically important because the clinical manifestations and underlying pathophysiology of diseases of the central and peripheral nervous system differ (Treede et al., 2008). The common causes of central neuropathic pain are multiple sclerosis, spinal cord injury, Parkinson's disease, and stroke (Klit et al., 2009). On the other hand, peripheral neuropathic pain is caused by a lesion or disease of the peripheral somatosensory nervous system (IASP, 1994), most commonly by AIDS, herpes zoster, or cancer.

CPSP is central neuropathic pain because the pain is caused by a lesion or dysfunction of the central nervous system (CNS; Kumar, Kalita, Kumar, & Misra, 2009). CPSP was first described by Dejerine and Roussy in 1906 and regarded as an unusual pain syndrome following thalamic stroke (Dejerine & Roussey, 1906; Seifert et al., 2013). However, it is now generally accepted that strokes occurring anywhere in sensory tracts can produce CPSP (Kim, 2009; Leijon, Boivie, & Johansson, 1989). Therefore, the term "thalamic pain" was considered incorrect and replaced by CPSP (Jensen & Lenz, 1995; Schott, 1995). However, the term CPSP itself is less than perfect, because many patients describe burning, icy, or squeezing symptoms, rather than pain. For this reason, Kim (2003) proposed that terms like "central post-stroke paresthesia" or "painful paresthesia" might be more appropriate. Nevertheless, because the term CPSP is widely used, we use it throughout this review.

Since Dejerine and Roussy (1906) first described CPSP, a variety of definitions of CPSP have been proposed. According to Andersen, Vestergaard, Ingeman-Nielsen, and Jensen (1995), "CPSP is a neuropathic pain syndrome characterized by constant or intermittent pain in a body part occurring after stroke and associated with sensory abnormalities in the painful body part." Thereafter, several definitions with similar content but with slight differences in the wording have been used: "a syndrome of central nervous system-mediated pain occurring as a consequence of stroke" (Chi, 2005), "abnormal temperature and pain sensitivity involving an area of the body affected by stroke" (Misra, Kalita, & Kumar, 2008), and "a neuropathic pain syndrome associated with somatosensory abnormalities due to CNS lesion following a cerebrovascular insult" (de Oliveira, de Andrade, Machado, & Teixeira, 2012). Recently, Flaster, Meresh, Rao, and Biller (2013) defined CSPS as "a central pain syndrome occurring as a direct consequence of a cerebrovascular lesion, most commonly ischemic stroke but also hemorrhagic stroke, associated with either intracerebral or subarachnoid bleeds."

Prevalence of CPSP

Wide variations in the prevalence rates of CPSP have been reported, as summarized in Table 1. Andersen et al. (1995) reported that 8% (21/267) of stroke patients developed CPSP during the year following stroke. Kumral, Kocaer, Ertübey, and Kumral (1995) found that 9% (9/100) of patients with a thalamic hemorrhage developed CPSP. Subsequently, similar prevalence rates were reported: 11% (Bowsher, 2001), 10% (Weimar, Kloke, Schlott, Katsarava, & Diener, 2002), and 12% (Kong, Woon, & Yang, 2004) (Table 1). It has been noted that the prevalence of CPSP in patients with Wallenberg lateral medullary syndrome is particularly high (Klit et al., 2009), as shown by MacGowan et al. (1997), who reported 25% (16/63) within 6 months. More recently, Hamzat and Osundiya (2010) reported that 79.4% (81/102) of community-dwelling stroke survivors experienced post-stroke pain and documented a CPSP prevalence of 30.9%. To date, the highest CPSP prevalence rate reported was 35% (among 43 stroke patients at 2 years after stroke; Widar & Ahlström, 2002), while the lowest was less than 1% (among 297 stroke patients at 4 and 16 months after stroke; Jönsson, Lindgren, Hallstrom, Norrving, & Lindgren, 2006).

Chen, Stitik, Foye, Nadler, and DeLisa (2002) concluded that the prevalence of CPSP was no different for hemorrhagic and nonhemorrhagic stroke. Furthermore, it is generally considered that the prevalence rate of CPSP is not related to gender, age, or lesion sidedness (Andersen et al., 1995; Klit et al., 2009). However, some studies indicate that CPSP is more prevalent in younger patients (Leijon et al., 1989; Hansen et al., 2012) or women (Hansen et al., 2012), whereas others have shown a dominance in men (Leijon et al., 1989) or in older patients (Bowsher, 2001).

Temporal Pattern of CPSP

Time to CPSP onset after stroke varies considerably (Hansson, 2004; Nicholson, 2004). Leijon et al. (1989) reported that CPSP onset was immediate in 15% (4/27) of patients, occurred within the first month in 37%, and between 1 and 34 months in the remaining 48%; in 78% of cases, CPSP onset occurred within 3 months. Andersen et al. (1995) indicated that CPSP onset occurred within 1 month in 63% (10/16) of

Table 1.
Prevalence of Central Post-Stroke Pain

Authors (Year)	Prevalence % (n)	Numbers of Study Subjects	Timing of Study or Post-stroke Duration
Andersen et al. (1995)	8% (16)	267 stroke patients	1 year after stroke
Kumral et al. (1995)	9% (9)	100 patients with thalamic hemorrhage	-
MacGowan et al. (1997)	25% (16)	63 patients with Wallenberg lateral medullary syndrome	Within 6 months after stroke
Bowsher (2001)	11% (8)	72 stroke patients	Post stroke duration: 2-48 months
Weimar et al. (2002)	10% (12)	119 stroke patients	1 year after stroke
Widar & Ahlström (2002)	35% (15)	43 stroke patients	2 years after stroke
Kong et al. (2004)	12% (13)	107 stroke patients	Post stroke duration: 6-60 months
Jönsson et al. (2006)	Less than 1% (4)	297 stroke patients	4 &16 months after stroke
Lundstrom et al. (2009)	3% (4)	140 stroke patients	1 year after stroke
Hamzat et al. (2010)	30.9% (32)	102 stroke patients	Post stroke duration: 15.9 ± 13.8 months
Klit et al. (2011)	7.3% (44)	608 stroke patients	4.3 years (median) after stroke: range 3.3-5.7 years
Hansen et al. (2012)	10.5% (29)	275 stroke patients	6 month after stroke

patients, between 1 and 6 months in 19% (3/16), and at more than 6 months in 19% (3/16). Similarly, Nasreddine and Saver (1997) reported that CPSP initiated within the first week in 36%, at 1 week to 1 month in 20%, and at 1-6 months in 27%. Although CPSP occurs mostly within the first 6 months, it can develop up to 10 years after stroke (Kumar & Soni, 2009). According to Seifert et al. (2013), CPSP can persist for many years or even throughout life.

Clinical Characteristics of CPSP

The characteristics of CPSP are vague and difficult to describe. Patients usually describe dysesthetic sensations, that is, painful sensations that may be poorly localized or vary dramatically from one day to the next (Nicholson, 2004). Locations, intensities, and durations also vary and pain can be spontaneous or evoked. Spontaneous CPSP is typically continuous, but can be intermittent and of fluctuating intensity (Leijon et al., 1989; Nicholson, 2004).

The Nature of Pain and Other Sensory Symptoms. Dejerine and Roussy (1906) described the thalamic pain associated with CPSP as spontaneous, severe, paroxysmal, intolerable, and burning with hyperalgesia (an overreaction to noxious stimuli) and allodynia (painful sensation in response to non-noxious stimuli). Table 2 summarizes the descriptions of pain associated with CPSP as burning, pricking, aching, lancinating, shooting, squeezing, freezing, lacerating, electrical, cold, numb, swollen, cutting, dull, stabbing, and throbbing (Andersen et al., 1995; Kim, 2003; Leijon et al., 1989; MacGowan et al., 1997; Widar, Ek, & Ahlström, 2004).

Abnormal sensory processing is evident in patients with CPSP, including abnormal painful reactions (allodynia and hyperpathia), abnormal sensations (paresthesia and dysesthesia), changes in detection thresholds (hypoesthesia and hyperesthesia), changes in intensities (hyperesthesia and hyperalgia), or prolonged aftersensation (Boivie, 2006). In particular, allodynia and dysesthesia (an abnormal unpleasant sensation) have been commonly described in CPSP, and are perhaps essential characteristics (Bowsher, 2005; Chen et al., 2002; Landerholm & Hansson, 2011). Andersen et al. (1995) found allodynia or dysesthesia were evoked by simple bedside testing in more than three-fourths of patients with CPSP, and that evoked allodynia and dysesthesia were not observed in pain-free stroke patients with similar somatosensory deficits. MacGowan et al. (1997) reported that 75% of CPSP patients with Wallenberg's lateral medullary infarction had cold-induced allodynia, and Bowsher (2005) showed that 71% of 122 CPSP patients with a thalamic lesion had allodynia that was tactile-, cold-, or movement-evoked.

Abnormal temperature sensitivity is exhibited by most patients with CPSP. In a review study conducted by Meschia and Bruno (1998), almost all patients with CPSP had experienced diminished sensation to temperature in pain-affected areas. Leijon et al. (1989)

Table 2.
Pain Intensity and Characteristics

Authors (Year)	Pain Intensity	Pain Description
Leijon et al. (1989)	12-98 (range) on VAS (100)	Burning, pricking, aching, lancinating, shooting, squeezing, and throbbing
Andersen et al. (1995)	3.3 (mean; range 1-7.7) on VAS (1-10)	Freezing, burning, aching, lacerating, and squeezing sensation with allodynia to cold and touch
MacGowan et al. (1997)	-	Burning, electrical, and cold
Bowsher et al. (1998)	45 (median; range 1-84) on VAS (1-100)	Burning, aching, throbbing, cramplike, pinprick, warm, cold, and hot
Kim (2003)	5.6 (mean; range 3-8) on VAS (1-10)	Numb, burning, aching swollen, and squeezing in various combinations
Widar et al. (2004)	-	Burning, cutting, dull, stabbing, and/or numbness

VAS = visual analogue scale.

noted hypersensitivity to mechanical and/or thermal stimuli in 88% of 27 patients with CPSP, and Kim (2003) reported that all CPSP patients (n = 11 with lenticulocapsular hemorrhage) showed mild or moderate sensory deficit, 5 showed increased temperature perception, and 3 showed dysesthesia on touch or a cold sensation.

Pain Intensity. As summarized in Table 2, Leijon et al. (1989) found that pain intensities in CPSP varied from 12 to 98 mm on a 100-mm visual analogue scale (VAS). Andersen et al. (1995) reported a mean pain intensity on VAS (1-10) of 3.3 with a range from 1 to 7.7, and that pain was mild in 38% (6/16) and moderate to severe in 62% (10/16). Bowsher, Leijon, and Thomas (1998) reported a median pain intensity on VAS (1-100) in 73 patients with CPSP of 45, and Kim (2003) reported a mean pain intensity on VAS (1-10) for CPSP after lenticulocapsular hemorrhage of 5.6 with a range from 3 to 8.

According to Leijon et al. (1989), pain intensity markedly fluctuated on a daily basis. It has been reported that pain can be aggravated by several stimuli, such as movement, touch, temperature, or emotional stress (Kumar et al., 2009; Leijon et al., 1989). Bowsher (1996) suggested that CPSP can be alleviated by relaxation.

Pain Location. CPSP often occurs in the side contralateral to stroke (Chen et al., 2002). Leijon et al. (1989) found most of their 27 patients exhibited hemi-pain and that around 50% experienced only entire right or left side body pain with the exception of the face. MacGowan et al. (1997), in a study of 63 patients with Wallenberg's lateral medullary infarction, reported the most common site was around the eye ipsilateral to the infarct either alone or with contralateral limb involvement, but no case of axial pain involving the trunk. According to Kim (2003), pain occurred more prominently in the leg, usually below the knee, although it also occurred in the face or an arm in 20 patients with CPSP after lenticulocapsular hemorrhage. Hansen et al. (2012) studied the location of CPSP in 30 patients and found upper extremity pain in 37.9%, lower extremity pain in 20.7%, pain of both upper and lower extremities in 10.3%, head pain in 16.0%, both head and lower extremity pain in 3.4%, and one entire side of the body affected in 10.3%.

Pathophysiology of CPSP

The pathogenesis of CPSP has been investigated using clinical and electrophysiological methods, and by magnetic resonance imaging, functional neuroimaging, and diffusion tensor tractography (Bowsher et al., 1998; Goto et al., 2008; Hong et al., 2010; Kumar & Soni, 2009; Misra et al., 2008; Seghier, Lazeyras, Vuilleumier, Schnider, & Carota, 2005). Although the pathogenesis of CPSP has not been fully elucidated, several theories have been proposed. The most commonly mentioned include disinhibition, central imbalance, central sensitization, and alterations in spinothalamic tract function (Hong et al., 2010; Klit et al., 2009; Kumar & Soni, 2009; Seifert et al., 2013).

The pain signals are transmitted to the lateral and medial thalamus via the spinothalamic tract (Willis & Westlund, 1997). The former constitutes part of the lateral thalamocortical pain pathway, which projects to the primary somatosensory cortex (sensory discrimination), secondary somatosensory cortex (pain intensity), and insula (thermal and nociceptive information processing), whereas the latter constitutes part of the medial thalamocortical pathway, which projects to the cingulated cortex and involves affective-emotional aspects of pain (Klit, et al., 2009). Structures

of the CNS, such as the periaqueductal gray area, several nuclei in the bulbar reticular formation, and the cerebral cortex, are known to contribute to analgesia pathways (Willis & Westlund, 1997).

Disinhibition Theory. Head and Holmes (1911) proposed that injury to the lateral thalamus disinhibits medial thalamus activity and causes pain by disrupting inhibitory pathways (GABAergic pathways) between lateral and medial pathways. Investigators later refined this theory and proposed that a lesion of the lateral spinothalamic pathway (the cold-signaling pathway to the insula through the ventro-medial posterior nucleus of the thalamus) disinhibits the medial spinothalamic pathway, which projects to the anterior cingulated cortex through the medial dorsal nucleus of the thalamus, and results in CPSP with burning pain (Craig & Bushnell, 1996; Craig, Chen, Bandy, & Reiman, 2000; Kim, Greenspan, Coghill, Ohara, & Lenz, 2007; Klit et al., 2009). Later, a modified disinhibition theory, the thermosensory disinhibition theory, was proposed to explain burning pain and cold allodynia in CPSP, based on the loss of normal inhibition of the thermal (cold) system of nociceptive neurons (Craig & Bushnell, 1996; Kumar & Soni, 2009).

On the other hand, it has also been proposed that CPSP can be induced by disinhibition from a lesion of the medial lemniscus pathway on the spinothalamic pathway (Head & Holmes, 1911; Kim, 2009). However, this theory is dated and inadequately explains the pathogenesis of CPSP in terms of its almost invariant findings of temperature/pain sensitivity deficit and less affected touch/vibration sensitivity (lemniscus pathways). However, this theory remains plausible because it could explain why few patients with lemniscal sensory disturbances develop long-standing painful sensory symptoms (Kim, 2009).

Central Imbalance Theory. CPSP could be caused by an imbalance between the lateral (sensory-discrimination) and the medial (affective-emotion) pain systems (Klit et al., 2009; Krause et al., 2012; Kumar & Soni, 2009). This suggested mechanism is supported by findings of increased insular activity (lateral spinothalamic system) and decreased anterior cingulated cortex activity (medial spinothalamic system) in CPSP patients with allodynia (Craig & Bushnell, 1996; Greenspan, Ohara, Sarlani, & Lenz, 2004). Such increased insular activities are likely to generate CPSP in association with perceptions of unpleasantness in skin and muscles (Kim, 2009).

Another form of imbalance occurs between the spinothalamic and medial lemniscus pathways. Bowsher (2000) showed spinothalamic tract damage results in the transmission of pain signals through an alternative pathway, and suggested that the medial lemniscus pathway probably undertakes these functions. If this were the case, disturbance of thermal/pain pathways and sparing of tactile-signaling pathways might produce tactile allodynia (Greenspan et al., 2004; Kumar & Soni, 2009; Lorenz, Kohlhoff, Hansen, Kunze, & Bromm, 1998).

Central Sensitization Theory. Central sensitization can be caused by loss of inhibition or increased facilitation of neuronal excitability, leading to increased neuronal excitability. It has been shown that spontaneous pain in CPSP is linked to hyperexcitability in the thalamus or cortex (Vestergaard et al., 1995). In fact, investigators have reported abnormal burst-firing activity in the thalamic nucleus in CPSP (Jensen & Lenz, 1995; Lenz, Kwan, Dostrowsky, & Tasker 1990; Meschia & Bruno, 1998). Such hyperexcitability may result from the activities of excitatory amino acids related to NMDA receptor activation and possibly by the activities of sodium channels (Boivie, 2006; Tuling & Tunks, 1999). These mechanisms are supported by the fact that some drugs, such as NMDA antagonists, sodium/calcium channel blockers, and GABA agonists, effectively reduce the pain associated with CPSP (Klit et al., 2009; Siniscalchi, Gallelli, De Sarro, Malferrari, & Santangelo, 2012).

Alterations in Spinothalamic Tract Function. It is generally accepted that the development of CPSP emanates from a lesion of the spinothalamic tract (Hong et al., 2010; Klit et al., 2009), and evidence indicates that patients with CPSP almost invariably exhibit pain and temperature sensitivity deficit, but sensitivity to touch, vibration, and other phenomena, which are believed to course mainly through lemniscus pathways, are less severely affected (Boivie, 2006; Boivie, Leijon, & Johansson 1989; Bowsher et al., 1998; Holmgren, Leijon, Boivie, Johansson, & Ilievska, 1990; Vestegaard et al., 1995). Hong et al. (2010) found by diffusion tensor tractography that relative tract volumes in affective spinothalamic pathways were significantly smaller in patients with CPSP, and suggested that spinothalamic tract injury is a requirement for the development of CPSP. Taken together, current evidence indicates that impaired spinothalamic function is associated with the pathogenesis of CPSP, and that medial lemniscus involvement is neither necessary nor sufficient.

Diagnosis of CPSP

Table 3 shows the diagnostic criteria of CPSP used in previous studies. Bowsher (1999) proposed the following criteria: a history of stroke, subarachnoid hemorrhage, or cerebral trauma, and pain in the

Table 3.
Diagnostic Criteria

Authors (Year)	Diagnostic Criteria
Bowsher (1999)	1) When coupled with a history of stroke, subarachnoid hemorrhage, or cerebral trauma, and pain, the presence of allodynia makes a diagnosis of CPSP certain 2) The presence of a deficit for temperature sensation or sharpness discrimination makes the diagnosis highly probable 3) A history of paradoxical burning makes it probable
Weimar et al. (2002)	1) Complaint of usually unilateral pain occurring after stroke in the corresponding hemisphere or brain stem 2) Exclusion of a peripheral neurogenic, nociceptive, or psychogenic origin 3) Abnormal sensory testing to temperature and pain using the contralateral mirror image as a control
Klit et al. (2009)	<Mandatory criteria> 1) Pain within an area of the body corresponding to the abnormality of the CNS 2) History suggestive of a stroke and onset of pain at or after stroke onset 3) Confirmation of a CNS lesion by imaging, or negative or positive sensory signs confined to the area of the body corresponding to the lesion 4) Other causes of pain are excluded or considered highly unlikely <Supportive criteria> 1) No primary relation to movement, inflammation, or other local tissue damage 2) Descriptions such as burning, painful cold, electric shocks, aching, pressing, stinging, and pins and needles, although all pain descriptions may apply 3) Allodynia or dysesthesia to touch or cold
Hansen et al. (2012)	1) Development of pain with onset at or after the stroke 2) Pain located on the stroke-affected side of the body 3) No other plausible cause of the pain, including pain isolated to the shoulder joint and nearby region

presence of allodynia, as certain; the presence of a deficit in temperature sensation or sharpness discrimination as highly probable; and a history of a paradoxical burning sensation as probable. Weimar et al. (2002) diagnosed CPSP based on a complaint of usual unilateral pain after stroke in the corresponding hemisphere or brain stem; exclusion of a peripheral neurogenic, nociceptive, or psychogenic origin; and abnormal sensory findings for temperature and pain.

Recently, Klit et al. (2009) recommended more specific diagnostic criteria: mandatory criteria included; pain within an area of the body corresponding to a CNS abnormality; a history suggestive of stroke and an onset of pain at or after stroke onset; confirmation of a CNS lesion by imaging, or negative or positive sensory signs confined to the body region corresponding to the lesion; and the exclusion of or a high improbability of another cause of pain. They also suggested the supportive criteria presented in Table 3. Hansen et al. (2012) diagnosed CPSP using more simple criteria: the development of pain with onset at or after stroke, pain located on the stroke-affected side of the body, and the absence of any other plausible cause of pain.

Obviously, the diagnosis of CPSP should be based on a combination of history, sensory examination findings obtained by applying multiple somatosensory stimuli (thermal, pressure, pinprick, and vibration), and neuroimaging findings of the brain lesion (Seifert et al., 2013). Recently, other useful diagnostic methods have been proposed based on measurements of somatosensory-evoked potentials, laser-evoked potentials, and contact heat–evoked potentials (Baumgartner, Greffrath, & Treede, 2012; Garcia-Larrea et al., 2002; Misra et al., 2008). However, these techniques are not widely available (Seifert et al., 2013).

CPSP Management

Patients with CPSP respond poorly to conventional analgesic therapies (Nandi et al., 2002; Pickering et al., 2009). In general, antidepressants, anticonvulsants, and opioids are used, often in combination (Seifert et al., 2013). However, the efficacies of such drugs are debatable because of a lack of large controlled trials (Creutzfeldt, Holloway, & Walker, 2012). In patients nonresponsive to medications, motor cortex stimulation, deep brain stimulation, and repetitive transcranial magnetic stimulation have been used to relieve CPSP (Hirabayashi et al., 2011).

Pharmacological Treatments.

Antidepressants. Adrenergically-active tricyclic antidepressants (TCAs) are currently viewed as the

first-line drugs for CPSP (Bowsher & Nurmikko, 1996; Kim, 2009; Klit et al., 2009). Of these, amitriptyline is considered the drug of choice, and its effectiveness at relieving CPSP has been consistently reported (Bowsher & Nurmikko, 1996; Creutzfeldt et al., 2012; Flaster et al., 2013; Leijon & Boivie, 1989a; Moore, Derry, Aldington, Cole, & Wiffen, 2012). However, side effects can be troublesome, and not all patients respond (Hansson, 2004). Other tricyclic antidepressants (nortriptyline, imipramine, or desipramine) and selective serotonin and norepinephrine re-uptake inhibitors (venlafaxine, duloxetine, desvenlafaxine, or milnacipran) have also been reported to be effective at alleviating CPSP, but their efficacies remain to be established (Boivie, 2006; Flaster et al., 2013; Leijon & Boivie, 1989a). Selective serotonin re-uptake inhibitors (effective antidepressants with few side effects) are for the most part ineffective at relieving CPSP (Bowsher, 1999; Sindrup, Otto, Finnerup, & Jensen, 2005).

Anticonvulsants. Various anticonvulsants, such as carbamazepine, lamotrigine, gabapentin, pregabalin, and levetiracetam, have also been used to treat CPSP (Backonja, 2002; Chen et al., 2002; Flaster et al., 2013; Liang, Tsai, & Hsu, 2005; Petramfar, Nikseresht, & Yaghoubi, 2010; Siniscalchi et al., 2012; Wiffen, Derry, & Moore, 2011; Wiffen & Rees, 2007). However, some authors have reported that neither carbamazepine nor pregabalin provide meaningful pain relief (Kim et al., 2011; Leijon & Boivie, 1989a); recently, Jungehulsing et al. (2013), in a randomized, double-blind, placebo-controlled study, concluded that levetiracetam did not produce any pain improvement in 33 patients with CPSP. The efficacy of lamotrigine has also been questioned (Dworkin et al., 2007; Wiffen & Rees, 2007).

Opiates. Although opiates are generally considered to be ineffective in CPSP, morphine has been reported to have significant effects on some aspects of pain perception, such as allodynia and thermal thresholds (Frese, Husstedt, Ringelstein, & Evers, 2006). In addition, high doses of some opiates have been suggested to relieve CPSP effectively due to their NMDA receptor antagonist activities (Frese et al., 2006; Rowbotham et al., 2003). Yamamoto, Katayama, Hirayama, and Tsubokawa (1997) concluded that morphine can appear to be effective at reducing CPSP because it reduces concurrent nociceptive pain and psychogenic influence. Other investigators have reported a loss or inactivation of opioid receptors in the cerebral hemisphere in CPSP, which would explain the low efficacies of opioids and the need for high doses to treat CPSP (Jones, Watabe, Cunningham, & Jones, 2004; Maarrawi et al., 2007; Willoch et al., 2004). Regardless of its efficacy, many patients discontinue opiate treatment because of its side effects (Seifert et al., 2013).

Anesthetics. Anesthetics, such as ketamine, lidocaine, and propofol, have also been shown to provide pain relief in CPSP (Canavero & Bonicalzi, 2004; Edmondson, Simpson, Stubler, & Beric, 1993; Flaster et al., 2013; Vick & Lamer, 2001). In particular, ketamine (a NMDA antagonist) has been reported to decrease allodynia and hyperalgesia and to improve functional capabilities (Vick & Lamer, 2001). The major limiting factors regarding the use of ketamine and propofol are their side effects, and the short-acting nature of lidocaine has prevented its widespread use (Bowsher, 1999).

Others. Although naloxone has been reported to provide transient pain relief in CPSP, it is now generally accepted that intravenous naloxone has no value in this context (Bainton, Fox, Bowsher, & Wells, 1992; Kumar et al., 2009). Intrathecal baclofen (an antispasmodic and GABA agonist) has been reported to reduce severe pain in CPSP (Flaster et al., 2013), and other muscle relaxants, such as diazepam, dantrolene, and tizanidine, have been used to treat spasticity-associated pain in CPSP. In a recent study (Pellicane & Millis, 2013), methylprednisolone (an oral steroid) was suggested as a potential therapeutic option, but further study is needed.

Nonpharmacological Treatments.

Motor Cortex Stimulation. Motor cortex stimulation (MCS) modulates various structures and neuronal pathways involved in pain control. It is considered to be a relatively safe invasive stimulation therapy (Nizard, Raoul, Nguyen, & Lefaucheur, 2012). Several case studies have reported that MCS provides satisfactory long-lasting pain control (Herregodts, Stadnik, De Ridder, & D'Haens, 1995; Ito et al., 2006; Katayama et al., 2002; Peyron et al., 1995). Fagundes-Pereyra (2010) reported that MCS effectively treated CPSP in 10 patients, and Tanei et al. (2011) described its effectiveness in 6 of 8 patients with CPSP after thalamic stroke. However, Nandi et al. (2002) concluded that MCS does not consistently alleviate CPSP, especially in the longer term. Similarly, Hosomi et al. (2008) found that chronic stimulation of the central sulcus did not significantly improve long-term results. According to Lazorthes, Sol, Fowo, Roux, and Verdié (2007), the efficacy of MCS depends on the accurate placement of the stimulation electrode over the appropriate area of the motor cortex, and on the programming of stimulation parameters.

Deep Brain Stimulation. Deep brain stimulation (DBS) is an invasive neurosurgical procedure that involves the insertion of deep stimulating electrodes within the periaqueductal or periventricular gray

area, specific thalamic nuclei, or the internal capsule (Kim, 2009). Owen, Green, Stein, and Aziz (2006) reported that DBS of the periventricular gray area and/or sensory thalamus (ventroposterolateral nucleus) constituted an effective treatment in 70% (10/15) of patients with CPSP, but noted wide variations in degree of pain relief. Recently, the effectiveness of DBS on left centromedian thalamic nuclei (Alves & Asfora, 2011) and on the nucleus accumbens and periventricular gray in combination (Mallory et al., 2012) was described. Tanei et al. (2011) concluded that MCS provides an effective treatment for CPSP, and suggested its combination with DBS could provide additional therapeutic efficacy in patients who do not experience satisfactory pain relief from MCS alone.

Repetitive Transcranial Magnetic Stimulation. Repetitive transcranial magnetic stimulation (rTMS) of the motor cortex is a noninvasive procedure that involves the tangential application of an external magnetic coil to the scalp to generate a brief high-intensity magnetic field (Flaster et al., 2013). Khedr et al. (2005) reported that 5 consecutive days of rTMS treatment led to pain relief in 28 patients with CPSP. Goto et al. (2008) reported that rTMS of the primary motor cortex reduced VAS scores by $\geq$ 30% in 8, by <30% in 8, and was ineffective in 9 of 27 CPSP patients. The effect of rTMS is modest and short-lasting, and thus it should not be used as the only treatment for CPSP (Aziz et al., 2007).

Vestibular Caloric Stimulation. In two small-scale studies, it was reported that vestibular caloric stimulation (VCS) relieved CPSP-associated pain effectively. Ramachandran, McGeoch, Williams, and Arcilla (2007) reported that CPSP was substantially alleviated by VCS in their case study (n = 2), and proposed its effect was probably due to activation of the posterior insula and the subsequent inhibition of pain generation in the anterior cingulate. Similarly, McGeoch, Williams, Lee, and Ramachandran (2008) reported a significant immediate treatment effect for cold-water caloric stimulation in 9 patients with CPSP.

Transcutaneous Electrical Nerve Stimulation or Acupuncture/Apipuncture. Transcutaneous electrical nerve stimulation (TENS)-based methods, especially acupuncture-like low-frequency TENS, have been suggested to have temporary effects on CPSP in certain patients, but its efficacy has not been clearly demonstrated (Kim, 2009; Leijon & Boivi, 1989b; Yen & Chan, 2003). Acupuncture and apipuncture have been suggested in conjunction with the standard Western management of CPSP (Robinson, 2008). Yen and Chan (2003) reported that a combination of multidisciplinary Western medical approaches and traditional acupuncture therapy effectively provided pain relief and functional improvement. Recently, Cho et al. (2013) reported VAS pain scores were significantly decreased after 3 weeks of apipuncture point injection in 8 patients with CPSP, and in a case study, Yun and Sun (2010) reported a pain intensity reduction after apipuncture treatment without adverse effects.

Others. Electroconvulsive therapy has also been shown to alleviate CPSP, probably by altering regional cerebral blood flow (Fukui & Nosaka, 2002; Fukui, Shigemori, & Nosaka, 2002a & 2002b). Electromyographic biofeedback, pain coping skills, and behavioral therapies have also been attempted (Edwards et al., 2000). In particular, behavioral therapies, such as relaxation therapy, visualization therapy, and meditation, have been introduced to relieve autonomic instability, depression, anxiety, mood changes, and sleep disturbance in patients with CPSP (Klit et al., 2009; Schott, 1995). Surgical procedures, such as sympathectomy, cordotomy, and thalamotomy, have been occasionally attempted to reduce pain in CPSP (Meyerson, 2001), but these outdated surgical procedures are no longer recommended due to their unpredictable short-term effects and significant morbidities and mortalities (Kim, 2009).

DISCUSSION

Pain is a serious complication after stroke, and may present in various forms such as CPSP, shoulder pain, painful spasticity, persistent headache, or as other musculoskeletal pain conditions (Klit et al., 2009; Seifert et al., 2013). Furthermore, it has been proposed that persistent pain has significant negative effects on everyday life by reducing physical function, social performance, and psychological well-being (Widar & Ahlström, 2002).

In particular, CPSP has been reported to reduce quality of life; to undermine rehabilitation efforts (Kumar & Soni, 2009); and to lead to depression, anxiety, sleep disturbance, appetite loss, drug dependence, poor social interaction, and an inability to work vocationally (Hansson, 2004; Kumar & Soni, 2009). Furthermore, CPSP that is refractory to treatment can cause severe depression, raise the specter of suicide (Gonzales 1994; Frese et al., 2006), and increase the likelihood of self-harm (Bowsher, 2002).

Our literature review revealed that CPSP has been defined on the basis of its unique characteristics, which include neuropathic pain, post-stroke pain, and/or pain with somatosensory abnormalities. The prevalence rates of CPSP vary widely (1-35%), though this may have been caused by the use of different inclusion criteria, definitions, study timings, lesion types, or

study designs (Hansen et al., 2012; Kumar et al., 2009; Kumar & Soni, 2009; Misra, et al., 2008; Seifert et al., 2013). Nociceptive shoulder pain (the most common type of post-stroke pain) has a prevalence rate of 11-40%, and headache a prevalence of 3.5-31% (Hansen et al., 2012; Seifert et al., 2013; Widar & Ahlström, 2002; Jönsson et al., 2006); thus, CPSP is not an uncommon complication after stroke. These findings indicate that an examination for the symptoms and signs of CPSP should be routinely included in post-stroke follow-ups. Most importantly, other types of chronic pain after stroke often co-occur with CPSP, and these should be differentiated for proper treatment (Flaster et al., 2013). In addition, studies on CPSP prevalence rates by gender, age, disease, and brain lesion type are required (Kumar & Soni, 2009; Nasreddine & Saver, 1997).

Although the majority of patients develop CPSP within 6 months of stroke, CPSP can initiate immediately or at up to 10 years after stroke, and it appears that once developed, it can persist for many years (Seifert et al., 2013). Uncertainty regarding onset time is one of the most important clinical considerations because this can cause significant treatment delays (Bowsher, 1999; Hansson, 2004).

Pain in CPSP can be spontaneous or evoked, and spontaneous pain can be continuous or intermittent. Pain intensities vary from mild to severe, and can affect the hemi-body; an entire limb; a portion of a limb; or even small regions of the face, mouth, or hand. CPSP has been described as a burning, numb, aching, swollen, squeezing, cutting, freezing, dull, or stabbing pain, or as another sensation. In many cases, sensory abnormalities (allodynia, dysesthesia, or hyperalgia) and abnormal temperature sensitivity are found. In particular, allodynia can be evoked by tactile, cold, or movement, but sensory alterations in touch and vibration are less frequent. Furthermore, the pain is exacerbated by external stimuli, such as joint movements, cold and light touch, and emotional stress. Because the nature of pain is diagnostically important, details of pain onset; pain quality; abnormal temperature sensitivity; and the presence of allodynia, dysesthesia, or hyperalgesia should be thoroughly assessed.

Several diagnostic criteria have been proposed for CPSP, but no accepted standardized diagnostic criteria are available (Seifert et al., 2013). The criteria most commonly included are pain within an area of the body corresponding to a CNS lesion, a history of stroke, the presence of allodynia or dysesthesia with abnormalities in temperature sensation, and the exclusion of other causes of pain (nociceptive and peripheral neuropathic pain). As suggested by Leijon et al. (1989), somatosensory abnormalities are indeed the only unifying characteristic of CPSP, and, therefore, the presence of allodynia, dysesthesia, or abnormalities in temperature sensation may be of particular diagnostic importance. Most importantly, diagnosis should be based on a combination of history; a clinical or sensory examination; and a radiological evaluation to determine lesion type, location, and size and to exclude other causes of neurologic pain (Klit et al., 2009).

According to previous studies, conventional analgesics appear to be ineffective. Although many pharmacological treatment options have been suggested, no universally applicable selection rules exist. In clinics, amitriptyline (TCA) is generally considered the drug of choice, but when there is no benefit or side effects are troublesome, moving on to another TCA or to a separate and distinct drug category, such as non-TCA antidepressants, anticonvulsants, anesthetics, antispasmodics, or opioids, would seem to be appropriate, despite a lack of verification of their efficacies by clinical trial. Investigators have suggested that the sooner CPSP treatment is commenced after pain onset, the better the prognosis (Bowsher, 1995; Bowsher & Nurmikko, 1996). In terms of CPSP prevention, no prophylactic treatment has been reported (Bovie, 2006), although Lampl, Yazdi, and Roper (2002) showed that prophylactic amitriptyline reduces, but does not completely prevent, CPSP.

MCS and DBS appear to be useful in patients nonresponsive to medications. However, available evidence has been generated by uncontrolled studies or is mostly anecdotal. Nevertheless, such methods may be considered in patients with severe pain refractory to pharmacotherapy (Flaster et al., 2013). MCS and DBS are associated with low rates of adverse reactions, the most common being infection at the site of pulse generator implantation (Bhatia et al., 2011). Acupuncture and apipuncture have also been suggested in conjunction with standard Western management methods, but the efficacies of these methods have not been clearly determined (Yen & Chan, 2003). Some nonpharmacological procedures are relatively new, and, thus, available evidence is sparse (Aziz et al., 2007).

CPSP is complex, and effective treatment must address the full range of its symptoms. Accordingly, a comprehensive intervention involving a combined pharmacologic and nonpharmacologic approach is needed. Although psychosocial interventions have been used adjunctively, interventions that combine psychosocial and medical factors have been consistently reported to increase patients' abilities to control chronic pain (Schott, 1995; Webster & Edwards, 2002). In addition, there is evidence that combined

interventions may alter negative pain-related behaviors, such as inactivity, and improve the consistency of medication use for pain relief (Webster & Edwards, 2002).

Because the symptoms of CPSP are diverse and its pathogenesis differs on an individual basis, some drugs may be effective in only certain cases (Kim, 2009). For this reason, Klit et al. (2009) recently proposed a mechanism-based treatment approach based on the premise that different pain types reflect different underlying mechanisms and that treatment should be targeted at mechanisms rather than based on diagnosis or disease pathology (Klit et al., 2009; Woolf & Max, 2001). Further studies on mechanism-based pain classification and treatment strategies are needed.

In the present study, all research designs (traditional and systematic reviews, and randomized controlled, nonrandomized controlled, observational comparative, and case studies) were reviewed to avoid information loss. However, methodological quality was not assessed because of the heterogeneous nature of the information gathered; thus, the present study can hardly claim to overcome the problems of methodological heterogeneity in the literature.

NURSING IMPLICATIONS

Because CPSP is not rare and earlier treatment may result in a better prognosis, routine post-stroke follow-up should include examinations for its signs and symptoms. In particular, delayed onset of CPSP may cause significant treatment delays because patients have passed out of the care of stroke experts when symptoms occur (Bowsher, 1999; Hansson, 2004). Therefore, nurses should understand that the onset of CPSP can be significantly delayed and that efforts should be made to detect CPSP during follow-ups.

Due to the difficulties of diagnosing CPSP, nurses should obtain details on pain history, including onset, quality, duration, and location, and on the presence of other sensory abnormalities, such as allodynia, dysaesthesia, or abnormalities in temperature sensation. Patients should be asked to indicate the area/location of pain on a body diagram and to describe their pain experiences as comprehensively as possible. It is important that pain assessments should be conducted by nurses with specialized knowledge of CPSP. In particular, elderly patients with CPSP may have difficulties verbalizing their experiences of pain due to impaired cognitive function or difficulties in communication (Widar et al., 2004). In such cases, nurses should obtain information using different techniques and from spouses, other family members, or other relevant personnel.

Because more than one type of pain is present in 36.5% of stroke patients (Seifert et al., 2013), the presence of other causes of pain should be determined. Peripheral nociceptive pain after stroke, most commonly post-stroke shoulder pain, can coincide with the symptoms of CPSP, and preexisting peripheral nociceptive pain can also occur after stroke (Roosink, Geurts, & Ijzerman, 2010). This type of information is important for diagnostic and management purposes because treatment strategies for CPSP and pain due to other causes differ (Kim, 2009).

Nurses should inform, counsel, and teach patients about the nature of CPSP. Widar et al. (2004) reported that one of the most common problems regarding long-term pain after stroke is a lack of patient knowledge and understanding of the cause and extent of pain and of available treatment options, and, therefore, the provision of a comprehension of pain should be adopted as a coping strategy (Widar et al., 2004). It is important that family members understand CPSP, because they can negatively or positively reinforce pain behavior (Widar & Ahlström, 2002; Widar et al., 2004), particularly in dependent elderly.

Nurses should also inform patients that CPSP is difficult to abolish and that the goal of treatment is to reduce pain (Kim, 2009). It should be stressed that medications may help, but are frequently unsatisfactory. Family members also need to understand that definitive relief of CPSP may not be achievable. This information would help patients and family caregivers learn not to depend on other unnecessary therapies (Kim, 2009). Moreover, the risks and benefits of available pharmacological and nonpharmacological approaches to CPSP management need to be taught. Although definitive relief may not be achievable, an intelligent, informed examination of the full range of options available offers patients a real possibility of pain relief (Segatore, 1996).

CPSP often causes autonomic instability, which can be exacerbated by physical or emotional stress (Bowsher, 1995 & 1999), and patients frequently suffer from depression, anxiety, mood changes, or sleep disturbances due to anger or frustration (Widar et al., 2004; Kim, 2009). According to previous reports (Nogueira & Teixeira, 2012; Widar et al., 2004), patients have managed pain using various coping strategies, which include communication, distraction, making the pain comprehensible, planning activities, changing body position, taking medication, and by comparing before and after stroke or by comparing themselves to others who have suffered a stroke. Therefore, nurses should teach patients various behavioral therapies, such as relaxation therapy, visualization therapy, or

meditation, and encourage patients to practice such techniques to maximize therapeutic effects.

CONCLUSIONS

Although it is widely recognized as a severe chronic neuropathic pain, no consolidated definition, clinical characteristics, or diagnostic criteria are available for CPSP. The present study was undertaken to review the literature to provide a more complete picture of CPSP in terms of its definition, prevalence, pathophysiology, clinical characteristics, diagnostic problems, range of therapies currently available, and nursing care. Despite its remarkable diversity in clinical characteristics and prevalence rates and its diagnostic difficulties, CPSP has unique pain quality features and is accompanied by other sensory abnormalities, such as allodynia, dysaesthesia, or abnormalities in temperature sensation. Aging populations mean that CPSP will become an even more important problem. Nurses should be knowledgeable of CPSP, provide precise information to patients and their families, and develop effective nursing care plans that improve outcomes and quality of life for patients with CPSP.

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