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Demystifying post-stroke pain: from etiology to treatment

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Abstract

Pain following stroke is commonly reported but often incompletely managed, which prevents optimal recovery. This is in part due to the esoteric nature of post-stroke pain and its limited presence in current discussions of stroke management. The major specific afflictions that affect patients with stroke who develop pain include central post-stroke pain (CPSP), complex regional pain syndrome (CRPS), and pain associated with spasticity and shoulder subluxation. Each disorder carries its own intricacies that require specific approaches to treatment and understanding. This review aims to present and clarify the major pain syndromes that affect patients who have suffered from stroke in order to aid in their diagnosis and treatment.

Introduction

Pain after stroke is a common symptom that is poorly understood by many practitioners. It can be easily overlooked due to its variable characteristics, concurrent comorbid medical issues, or impairments in cognition or communication. While pain can create its own disabilities secondary to a decrease in function, its effect on the recovery of patients post-stroke can substantially impact a patient's future quality of life by preventing optimal participation and gains during rehabilitation. Indeed, as is the case with many other chronic pain syndromes, post-stroke pain (PSP) is often refractory or responds incompletely to medication and other treatments and is thus challenging to control for many patients.

Estimates of the prevalence of PSP vary widely, with one recent large study estimating that 10.6% of all patients with ischemic strokes experience some type of chronic PSP[1]. Among these patients, central post-stroke pain (CPSP) is the most frequent diagnosis, followed by

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peripheral neuropathic pain, pain due to spasticity, and joint subluxation[1]. Additionally, complex regional pain syndrome following stroke has been observed on a similar scale[2]. Pain syndromes after stroke are in some ways unique to each patient and are often insufficiently managed. In this review, the most common types of pain encountered by persons with stroke are delineated, and a basis for the pathophysiology of their pain is provided to emphasize the rationale for current treatment modalities.

Literature Search

Literature cited was collected using PubMed searches between May 2014 and December 2015. Initially a broad search of "(poststroke OR post-stroke) pain", was used to identify the key issues that would be discussed and yielded 7105 results. Based on those results, subsequent searches focused on the topics that would become the sections and subsections of this article, including "central poststroke pain", "complex regional pain syndrome AND stroke", "spasticity AND stroke AND pain", "shoulder AND stroke AND pain", and "subluxation AND stroke AND pain". Subsequently, "central poststroke pain AND treatment" produced 67 results, "complex regional pain syndrome AND stroke AND treatment" produced 103 results, "spasticity AND stroke AND pain AND treatment" produced 233 results, "shoulder AND stroke AND pain AND treatment" produced 308 results, and "subluxation AND stroke AND pain AND treatment" produced 70 results. Efforts were made to focus on clinical trials and studies that differentiated issues in persons with strokes from other neurological disorders. Larger studies with clearly defined outcome measures were preferred, however smaller studies were utilized for areas that have not been thoroughly studied but showed promise for future research. Special attempts were made to include the most recent studies in the disorders detailed below, along with other studies of historical significance.

Central Post-Stroke Pain

Central Post-Stroke Pain (CPSP) is a term used to describe the symptom of pain arising after a stroke that is secondary to a lesion within the central nervous system [3]. As in the case of all strokes, the location of the infarct, and the function of the neurologic structures involved, dictate the character of the deficit. In the case of CPSP, the lesion includes some portion of central pain pathways, and this damage creates the sensation of pain with minimal or no stimulation of the peripheral pain receptors.

CPSP can be difficult to characterize, as it can be subjectively described by a patient in a variety of ways. Descriptions can range from aching, dull, and throbbing to sharp, stabbing, shooting, or burning pain[4]. The onset of CPSP can be quite variable as well, most commonly beginning 1 to 3 months after stroke, with the majority of affected patients developing symptoms by 6 months[5]. Additionally, CPSP can be particularly difficult to evaluate since it can be accompanied by other pain syndromes including those resulting from pathology outside of the central nervous system. In a cross-sectional study of 40 CPSP patients, 27 (65.5%) were also diagnosed with myofascial pain syndrome, a non-neuropathic painful disorder characterized by painful, stiffened muscles with taut bands and discernible trigger points[5,6]. Symptoms of CPSP can be induced or spontaneous. Induced pain describes an

increase in sensitivity to stimulation (hyperesthesia), which can be further dissected into pain that is evoked by a non-painful stimulus (allodynia), or as an increased sensitivity to a normally painful stimulus (hyperalgesia)[7]. Spontaneous pain, however, is independent of stimuli and may be continuous or paroxysmal. Induced pain can be clarified and classified with a careful bedside sensory exam, while spontaneous pain remains subject to the patient's description. Taking these factors into account, CPSP still remains a diagnosis of exclusion.

Pain and the brain: Anatomical associations of CPSP

Central Post-Stroke Pain was first described by Dejerine and Roussy in 1906 when they coined the phrase "syndrome thalamique", or thalamic syndrome[8]. They described a series of patients with intolerable pain on their hemiplegic sides who were later found to have suffered strokes to the thalamus. The thalamus was widely accepted for many years as the only source of this pain (and subsequently became known as Dejerine-Roussy Syndrome), however more recent case reports and studies have shown that the thalamus is only one of many structures that may be implicated in CPSP. It has been found that CPSP can arise in patients whose lesion involves any of the tracts responsible for transmission of pain as they pass throughout the entire CNS[5]. Below, some of the relevant tracts, and specific brain structures, associated with CPSP are listed.

The contribution of the spinothalamic tract—The most studied tract associated with pain is the spinothalamic tract, which transmits the modalities of pain, temperature, and deep touch from the body. The spinothalamic tract courses from the lateral portion of the spinal cord, through the lateral medulla and pons, to the ventral posterolateral nucleus (VPL) of the thalamus, finally terminating in the post-central gyrus (Figure 1a). Lesions or injury to any part of this tract can potentially result in CPSP, however, some structures are more highly associated with this syndrome than others.

CPSP was originally described as a thalamic pain syndrome, and it continues to be the most commonly documented and studied neural structure associated with CPSP[5,9]. Modern studies have shown that specific areas within the thalamus are more correlated to the development of CPSP than others. A number of studies have shown that CPSP patients have lesions within the VPL and/or the ventral posteromedial (VPM) of the thalamus (Figure 1b)[10–14]. A more recent study using MRI and digital radiographic atlases in patients with thalamic strokes with and without CPSP found that the CPSP group had lesions largely involving the VPL, with some also involving the VPM nucleus[15,16]. Specifically, lesions in the posterolateratal and inferior parts of the VPL were most associated with CPSP. A few of the CPSP patients in this study did have lesions confined to the pulvinar nucleus as well, an area that processes visual input. The development of CPSP in these patients was thought to be due to the shared vascular supply and close proximity to the VPL[15] (Figure 1b), again implying the strong association of the VPL and CPSP. Indeed, another study found that thalamic lesions involving the area where the ventral posterior nuclei and the pulvinar meet were 81 times more likely to lead to CPSP than other thalamic lesions, confirming this area as high risk for CPSP, and opening the door for potential preemptive treatments against CPSP as a future avenue of research[16].

The contribution of medullary tracts—In addition to the spinothalamic pathway, lesions in the trigeminothalamic and the lemniscal pathways can result in CPSP symptoms of both the body and the face. The trigeminothalamic pathway functions for the face in a similar manner as the spinothalamic pathway for the body in that it transmits the same modalities of sensation: pain, temperature, and deep touch. It receives afferent input from cranial nerves V, VII, IX, and X, which is relayed to the spinal trigeminal nucleus within the caudal pons and medulla before travelling up to the VPM of the thalamus. Lateral medullary syndrome (Wallenberg Syndrome) is a well-documented constellation of symptoms arising from a stroke to the lateral medulla, which characteristically causes, among other deficits, facial pain and numbness ipsilateral to the lesion with contralateral body and limb numbness. In Wallenberg Syndrome patients, 25–44% have been described as suffering from CPSP, most commonly in the face ipsilateral to the lesion, but with a smaller percentage experiencing pain in the contralateral body and limbs[17,18]. These symptoms can arise acutely, within the first few days, but more often, they occur within weeks to the first 6 months after stroke. The most common types of pain described are constant, burning, and lancinating, with frequent allodynia[17]. This association of facial CPSP with bodily sensory deficits can be explained by the proximity of the spinal trigeminal nucleus to the fibers of the spinothalamic tract, both located in the lateral portion of the brainstem[17].

In contrast to the burning and lancinating pain symptoms associated with infarction of the lateral medulla, a study on medial medullary strokes found that 21 out of 59 (35.6%) patients were diagnosed with CPSP with the pain being described as “numb”, “cold”, and “painful”; no patients described their pain as burning[19]. It is possible that the qualitative difference in pain in these patients can be attributed to the fact that the pain tracts described above are spared. Instead, the medial medulla contains fibers from the dorsal column-medial lemniscal pathway which governs the transmission of vibratory, positional, and fine touch sensation; as well as the spinoreticulothalamic system which is thought to modify the signal from the spinothalamic tract by projecting to neural structures important for the emotional perceptions of pain [20]. These consistent differences in the characteristics of lesions only millimeters apart illustrate the dependence CPSP has on the affected neural substrate and how infarct location translates into the symptoms patients perceive.

The contribution of the cerebral cortex—Within the cerebral cortex, some areas have been implicated in CPSP while others have not. The primary sensory cortex, located in the post-central gyrus, is rarely associated with the development of CPSP, however, other cortical structures may be[5,21]. One study of 24 patients found that ischemic injury to the operculum and insular cortex was linked to the development of CPSP, whereas ischemic lesions in the post-central gyrus did not [21]. The posterior insular cortex and medial operculum have been shown in functional imaging and electrophysiology studies to play a major role in processing pain and temperature signals from the spinothalamic pathway, so much so that these adjacent structures have been argued to make up a “primary area for pain” [22].

What is known about the pathophysiology of CPSP

The pathophysiology by which CPSP arises after stroke remains uncertain. Several factors have been identified as significant predictors for the development of CPSP and may provide some insight into the mechanism of onset. These include previous history of depression, greater stroke severity, younger age, and smoking[1].

Shortly after their description of the Thalamic Syndrome, Head and Holmes proposed a theory of disinhibition to explain CPSP: injury to the sensory pathways would lead to a compensatory overactivation within the thalamus, thus causing spontaneous pain or allodynia[23]. This theory continues to be the most widely accepted explanation for CPSP and was reaffirmed in a study using single photon emission computerized tomography (SPECT) [24]. In this study, two CPSP patients with hyperpathia were found to have hyperactivity in the contralateral thalamus when pain was evoked on their hemiparetic sides. Three subjects without hyperpathia did not show that finding. This theory of disinhibition relies on the fact that some parts of the sensory tract, as described above, must remain intact and some sort of synaptic reorganization or an overall shift in neuronal circuitry occurs for processing pain. Indeed, diffusion tensor tractography studies (a derivation of diffusion weighted MRI that allows for neural tracts to be evaluated) have revealed that CPSP is more likely to occur in patients whose lesion only partially involved the spinothalamic tract compared to those whose lesion showed complete involvement[25]. Therefore, for most patients who develop CPSP, some continuity of the spinal thalamic tract is maintained.

Opioid receptor (OR) binding has also been linked to clinical pain[26,27] and it may play a role in the etiology of CPSP. A study by Willoch et al., used a non-selective, radioloabeled OR ligand ([^{11}C]diprenorphine) and PET scanning to assess OR binding in five long-lasting CPSP patients and twelve healthy controls[28]. Their results showed significantly decreased binding in CPSP patients of the OR ligand in the ventroposterior thalamus, periventricular grey matter, the insular cortex, the accessory sensory cortex (S2), the posterior parietal cortex, the lateral prefrontal cortex, and the cingulate cortex; all areas within the pain processing circuitry. This study provides new insights to the neurochemical nature of structures that have already been implicated in CPSP, although it does not provide the entire story of how opioids are involved in the pathophysiology of CPSP. For example, it is interesting that several of these same structures have been shown on other PET scan studies to have *increased* metabolic activity in CPSP patients[29]. With a measured deficit in opioid receptor binding capacity, it may be easier to see how some reports on the administration of opioids to CPSP patients have been discouraging[30] and opioid use can contribute to heightened pain sensitization in other neuropathic pain syndromes[31,32]. Taken together these studies demonstrate that the role of opioids in the pathophysiology of CPSP is likely complicated and more detailed mechanistic studies are needed.

More recent studies in mice have implicated the long-chain fatty acid receptor, GPR40. It had previously been shown that GPR40 mediates β-endorphin release[33], and more recently, shown in an established mouse model of CPSP that providing a GPR40 agonist suppresses pain scoring in experimentally affected mice[34]. While these studies may not be directly translatable to humans, they provide a basis for an additional biochemical pathway as well as a potential treatment option.

Treatments for CPSP

As with other types of neuropathic pain, a variety of neuromodulating and psychoactive medications have been found to be useful for the treatment of CPSP. While data supporting their use specifically for CPSP may be somewhat limited, a few studies have been performed and have been presented below. We believe that this area will continue to grow as awareness and more studies on CPSP patients are undertaken.

Anticonvulsants—Many antiepileptic drugs have been used in the treatment of neuropathic pain, some of which have been studied in CPSP patients. Calcium channel modulators such as pregabalin and gabapentin, are a popular choice for neuropathic pain in multiple pain states. Pregabalin has the most thorough testing in this category, having been used in a placebo-controlled, double-blind study in 219 patients[35]. In this study, the drug did not significantly reduce the mean pain score, but did improve patient reported sleep, anxiety, and other quality of life measures. On the other hand, 70% of patients receiving pregabalin reported adverse effects; dizziness, somnolence, edema, and weight gain were the most commonly reported. A more recent study evaluated the long-term efficacy of pregabalin in 103 patients with central neuropathic pain, of which, 60 were diagnosed with CPSP[36]. Among the CPSP group, 50% reported at least a 30% reduction in their Short-Form McGill Pain Questionnaire Visual Analog Scale suggesting that, for those who respond to the medication, there is a significant improvement in subjective pain over a 52-week period. 78% of all patients completed treatment, indicating good tolerability despite the high incidence of side effects. This study is encouraging in its establishment of an effective treatment over a longer period than its predecessors, though limited as an open-label study lacking a placebo control. As such, gabapentin is often the first antiepileptic medication selected in the treatment of neuropathic pain due to its flexibility in dosing and relative affordability. However, data regarding the safety and efficacy of gabapentin in the treatment of CPSP remain scarce.

Other anticonvulsants used to treat pain are sodium channel blockers. Carbamazepine is currently considered a second-line treatment in CPSP patients, but it is also known for its side effects, which can include Stevens-Johnson syndrome and aplastic anemia, as well as its interactions with other medications. It has been found to be less efficacious with a higher incidence of adverse effects when compared to amitriptyline and failed to achieve a significant reduction in pain when compared to placebo, though only 14 patients in that study received the drug[10]. Despite this, carbamazepine continues to be used in this setting due to its historical success in patients with neuropathic pain. Lamotrigine has been studied in a placebo-controlled, double-blind study where it significantly reduced global pain scoring in 27 of 30 patients[37]. Clinically significant results were achieved at a dose of 200mg per day. While lamotrigine may be safer than other antiepileptic drugs, two of the 30 patients in this group developed a drug rash, one of which required withdrawal from the study. Lamotrigine has been associated with Stevens-Johnson syndrome as well[38]. Phenytoin and zonisamide have both been tested in limited sample sizes, but have shown the potential of offering some relief in CPSP[39,40]. Levetiracetam was recently tested in a placebo-controlled, double-blind study of 42 patients and failed to achieve significant pain relief or any secondary outcome goals[41].

Anti-depressants—Amitriptyline, a tricyclic antidepressant, was the first antidepressant to be shown to be significantly effective in CPSP in a small study from 1989[10]. This study showed that the medication was safe and effective in treating CPSP at a dosage of 75mg daily. Amitriptyline has been considered for use as a prophylactic treatment for CPSP[42]. However, the only trial published had a low sample size, which suggested efficacy but with no clinical significance[42]. The most common side effects of amitriptyline include dry mouth, constipation, urinary retention, and orthostatic hypotension. Additionally, it is important to consider that tricyclic antidepressants can lower the seizure threshold [43].

Selective serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRIs) are also potential candidates for pain patients. In CPSP, the only SSRI that has been tested is fluvoxamine[44]. It has been shown to significantly reduce pain in CPSP patients when started within one year of the stroke. However, if started after one year, it was found not to be effective. The SSRI paroxetine as well as the SNRIs venlafaxine, desvenlafaxine, and duloxetine have been used in a variety of neuropathic pain applications but have yet to be studied specifically in CPSP[45,46].

Corticosteroids—While methylprednisolone has not been studied in any prospective studies of CPSP patients, a retrospective study suggested some potential benefit[47]. In that study, 146 charts of persons with stroke admitted to an acute inpatient rehabilitation ward were reviewed; 12 (8.2%) of whom were diagnosed with CPSP. Within this group, it was found that the patients receiving methylprednisolone had significantly reduced pain-scoring one day after starting treatment and one day prior to discharge. Additionally, these patients required as-needed pain medications less often than those not receiving steroids, however this result was marginal. Doses of methylprednisolone used in the study were reported as six-day tapers starting with 24 mg on day one and decreasing by 4 mg daily.

While most of the medications listed above are associated with sometimes severe and dangerous side effects, the role of the physician should include assessing which medications will be best tolerated by a individual patient based on age and other comorbidities to ensure a safe treatment regimen and maximal medication adherence.

Non-pharmacologic treatments—There are several non-pharmacological treatments available to treat CPSP in cases refractory to medication or where medications cannot be tolerated. Some of the most promising treatments are listed here. Deep brain stimulation (DBS) is a procedure involving the implantation of a medical device into the brain that sends signals, through stereotactically placed electrodes, to targeted neural structures. It has been effective in managing refractory Parkinson’s disease, depression, and chronic pain syndromes. Multiple studies and case reports have shown that it can offer various degrees of relief, sometimes even allowing for complete discontinuation of pain medications[48]. A study of 15 patients from 2006 demonstrated effectiveness of DBS implanted in the thalamus and periventricular/periaqueductal grey matter; 12 of these patients (80%) followed through with permanent implantation after initial trial implantation, seven of whom were able to discontinue all analgesics. The remaining five switched from regular opiates to only as-needed non-opiate analgesics[49]. Among 45 CPSP patients included in a meta-analysis from Bittar 2005, 53% went through with permanent implantation, and 58% of whom achieved

long-term pain relief[50]. Historically, the most effective target structures are the periventricular grey matter and the VPL of the thalamus[48], however one recent case report has also demonstrated a good response to stimulation of the nucleus accumbens in a CPSP patient[51].

In addition to DBS, other surgical techniques such as cingulotomy, or targeted destruction of a small portion of the anterior cingulate cortex, have found success in treating psychiatric illnesses and pain disorders[52]. Few cases have been reported regarding cingulotomy in persons with stroke, however a 2012 study of three patients with CPSP showed an improvement in Visual Analog Scoring of 51.9% over the first month following the procedure[53]. These patients also had deep-brain stimulators implanted, which were activated after the one-month mark making long-term results difficult to predict for cingulotomy alone. Further research is needed to fully determine whether this is a viable option for medically-refractory CPSP.

Repetitive transcranial magnetic stimulation (rTMS) is another treatment that has been used for a number of neurologic and psychiatric disorders. In rTMS, a coil is placed over the patient's scalp and is used to deliver a magnetic pulse that induces an electrical discharge in a targeted region of cerebral cortex. Multiple studies have been performed on patients with neuropathic pain, including CPSP patients and have shown it to be associated with minimal side effects[48]. A recent open-label, non-controlled study from Japan showed that weekly rTMS sessions involving motor cortex stimulation over 12 weeks (18 patients) and one year (six of the original 18 patients) led to significant reductions in Visual Analog Scale scoring[54]. Eight patients with severe dysesthesia were found to have the least relief from pain, suggesting that rTMS may be a therapy better suited for milder CPSP patients. Reported side effects were limited to two patients describing transient slight scalp discomfort. While this is a relatively small study that lacks a control group, previous studies have shown significant benefits from rTMS for patients with neuropathic pain syndromes on a wider scale[55], and given the benign risks of therapy, further studies specifically in CPSP patients are warranted.

Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS), sometimes referred to as reflex sympathetic dystrophy, is a condition characterized by burning pain, increased sensitivity to tactile stimulation, and vasomotor changes including edema and changes in skin temperature and color[2]. CRPS can be further classified into CRPS Type I, which develops in the absence of evidence of direct injury to a nerve and is generally the subset observed in persons with stroke; and CRPS Type II, which follows discrete peripheral nerve damage. Additionally, the term shoulder-hand syndrome has been used to describe CRPS in hemiplegic patients[56].

CRPS was first described following stroke in a retrospective study from 1977 in which 68 of 540 (12.5%) inpatient rehabilitation patients were diagnosed with shoulder-hand syndrome[57]. A more recent study among 95 patients with stroke admitted to a Turkish rehabilitation hospital in 2006 showed that 30.5% went on to develop CRPS[58]. Age, gender, side of involvement, and stroke etiology were not shown to predispose to CRPS, however

flaccidity, glenohumeral subluxation, and poorer functional recovery did significantly increase risk. Aside from acute rehabilitation inpatients, two studies which followed persons with stroke causing hemiplegia longitudinally showed an incidence of CRPS of 23% and 48.8%[59,60]. Both studies implicated spasticity as a risk factor and one also identified shoulder subluxation and loss of range of motion[59]. To fully analyze the burden of CRPS on the stroke community, a large-scale longitudinal study including the general population of persons with stroke is needed.

Pathophysiology of CRPS

The pathophysiology of CRPS in otherwise healthy patients remains a subject of much debate, and can be further obscured by the presence of a stroke. Thus, much of what is known about the onset of CRPS is from studies not involving stroke.

The classic theory holds that CRPS is the result of local hyperactivity of the sympathetic nervous system[2]. This is supported by data showing an alteration in temperature regulation between the affected and non-affected limbs in CRPS patients[61], as well as a study showing that stimulation of the sympathetic nervous system with localized cooling and startle response worsened pain in CPRS patients, but less-so after sympathetic blockade[62]. Historically, patients have been treated for CRPS with sympathetic blockade, strengthening the argument for a sympathetic origin of the disorder; however, further analysis of the efficacy of that procedure suggests that this may not always be the case[63]. A comprehensive review of 29 studies, including 1144 patients showed that 29% had a full response to sympatholytic blockade, 41% had a partial response, and 32% had no response[63], suggesting that other mechanisms may be involved.

Other mechanisms have been proposed including sensitization of the somatic sensory pathway, overactivation of inflammatory responses, and hypoxia[2], however there remains limited data attempting to link CRPS to a stroke lesion specifically. One study from 1994 that followed 36 post-stroke CRPS patients was able to examine the shoulder capsules of 7 patients on autopsy and found evidence of previous trauma, suggesting that CRPS may be due in part to pre-existing or post-stroke musculoskeletal injury, as much as, or more than the central stroke lesion[64]. Noting the pathologic postmortem findings, the authors initiated a protocol of strict protection of the shoulder from subluxation, painful positioning, and trauma; this reduced the incidence of CRPS post-stroke from 27% before the protective protocol to 8%.

Treatment of CRPS in Persons with Stroke

As has been mentioned, CRPS and its management have been widely studied although specific studies concerning persons with stroke are limited. With any neurologic deficits following a stroke, physical therapy and early mobility are of vital importance to reducing long-term disability, and seem to help the symptoms associated with CRPS as well. A recent controlled study of 52 patients admitted to an acute rehabilitation facility with a diagnosis of CRPS following stroke participated in a four-week course of upper extremity aerobic exercise, where 89.9% of patients in the experimental group reported significant pain relief as well as a reduction in other CRPS-associated symptoms[65].

Two studies have suggested a benefit from corticosteroids in patients with CRPS following stroke. The first was a placebo-controlled non-blinded clinical trial from 1994 in which 34 patients with hemiplegic stroke who developed CRPS were started on medium-dose oral corticosteroids and 31 of the 34 achieved near-total relief from symptoms[64]. More recently, a randomized controlled trial of prednisolone and piroxicam in 60 patients with stroke diagnosed with CRPS showed significantly greater improvement in pain scoring in the prednisolone group, where patients received 40 mg daily for one month, than in the piroxicam group[66].

A longitudinal study comparing post-stroke inpatients to historical controls measured the incidence of CRPS in the setting of prophylactic calcitonin administration, and showed a significant reduction in the onset of CRPS among treated patients[67]. Patients in the experimental group received 20 units of elcatonin, a synthetic eel calcitonin, weekly during admission, and were shown to have the greatest benefit if treatment was started within the first four weeks following stroke.

Sympathetic blockade, typically by means of targeting the stellate ganglion with anesthetic injection has been used in CRPS in the past. As discussed above, sympathetic block has been shown to offer some degree of relief to CRPS patients, though more recent analyses suggest that it may not be effective and higher powered studies are needed to fully define its efficacy[63,68].

Overall, pharmacologic clinical trials in post-stroke CRPS seem to be greatly lacking and are a potentially valuable area for future research; however drugs that have shown benefit or the possibility of being beneficial in patients with CRPS in non-stroke populations include the NMDA receptor antagonists ketamine and memantine, the anticonvulsants gabapentin and carbamazepine, as well as bisphosphonates[2,69,70].

Non-pharmacological therapies include mirror therapy, a technique in which a patient watches the unaffected arm perform a motor task in a mirror. With the affected arm hidden behind the mirror, the patient is able to imagine and attempt to perceive normal function from the hemiparetic limb. Cacchio et al has shown the effectiveness of mirror therapy in post-stroke CRPS in two studies from 2009[71,72]. The first, a study of 24 patients with eight in the experimental mirror therapy group and the rest in placebo groups, showed a significant decrease in Visual Analog Scale scoring in seven of the eight patients[72]. After four weeks, 12 of the patients crossed over to mirror therapy, 11 of which were able to similarly achieve significant pain scoring relief thereafter. The second was a placebo-controlled randomized trial of 48 patients with CRPS following stroke, which showed statistical improvements in both pain as measured by Visual Analog Scale scoring as well as motor function at the end of the four week treatment period and also at a six month follow up visit[71]. The patients receiving mirror therapy in this study were given 30-minute sessions five times per day for two weeks, followed by one-hour sessions five times per day for two more weeks in addition to a conventional stroke rehabilitation program[71]. In addition to the above therapies, proper management of chronic CRPS should also involve a foundation of routine activity and exercise.

Pain associated with spasticity

Spasticity is an involuntary, often painful, contraction of muscle groups from an exaggeration of the stretch reflex[73]. It can be seen with lesions to the central nervous system that include upper motor neuron insults, and is commonly seen in stroke as a long-term sequela. The prevalence of spasticity following stroke can be quite variable, and has been reported as developing in 17 to 43% of patients three to 12 months following a stroke[73].

One of the devastating consequences of spasticity is the development of contractures. At this stage, the muscle body and tendon have shortened secondary to the chronic hyperactivity, and the limb may have become irreversibly non-functional[73]. While spasticity may be present in the absence of pain, contractures are often quite painful. In addition, spastic, immobile limbs are at an increased risk for skin breakdown, which can yield further painful complications. This underscores the importance of recognizing and managing spasticity early and appropriately.

Treatments for Spasticity

The cornerstone of spasticity treatment is maintaining range of motion of the affected muscle groups with exercises and passive stretching. This is often facilitated by a trained physical therapist or nurse, but can and should be continued by the patient or the patient's family. Without such activity, a person with stroke who develops spasticity will consequently develop contractures. For this reason, the treatment modalities described below should be considered as an adjunct to physical therapy, and their individual risks and benefits should be evaluated on a case-by-case basis.

Pharmacologic treatment for spasticity has been aimed at relieving the chaotic firing of the intact lower motor neurons or disrupting their propagation to the muscle. As such, the vast majority of studies analyzing treatment in post-stroke spasticity focus on spasticity as the primary outcome measure rather than pain, making a complete analysis specific to post-stroke pain secondary to spasticity more difficult to ascertain compared to the other topics discussed above. The most common medications prescribed in this setting are antispasticity medications, specifically, baclofen, tizanidine, dantrolene, and diazepam[74]. Antispasticity medications have the capability to interfere with the patient's preserved muscle strength, which can hinder progress during physical therapy, and each of the above medications can cause some degree of CNS impairment including confusion, dizziness, or psychiatric disturbance[74]. Anticonvulsants, such as gabapentin and pregabalin, have been used with some success in managing post-stroke spasticity and can be helpful in treating the associated pain. A systematic review from 2004 analyzing the pharmacologic management of spasticity, including several studies on post-stroke spasticity, concluded that evidence for improvement in patients' quality of life when on antispastic and anticonvulsive medications is weak. However, this shortcoming was attributed in part to poor reporting[75]. The review also suggested that adverse effects, especially drowsiness, sedation, and muscle weakness, were quite common. Because of these risks of systemic adverse effects, alternative treatment should be fully explored so that medications can be kept at their lowest doses possible.

Baclofen is unique among antispasticity medications in that it can be delivered intrathecally as well as orally. Intrathecal baclofen pumps have been shown to significantly improve functional independence measurement scores (FIM), quality of life, Modified Ashworth Scale grading, while maintaining minimal adverse effects[76]. One small study from 2009 of eight hemiplegic persons with stroke-associated spasticity concluded that given the high doses needed to suppress spasticity, most patients developed decreased ambulation from baclofen-induced muscle weakness, and the only two patients who went on to have permanent pumps implanted did so due to their subjective improvements in pain[77]. However, in this study, pain was not an initial primary outcome measure and was not quantified by the other patients in the study. While delivering the drug directly to the spinal cord may eliminate some of the systemic adverse effects, intrathecal baclofen pumps carry their own set of risks. In a prospective study on the adverse events of intrathecal baclofen, the majority of complications were due to the surgical implantation procedure (58% of cases), followed by pump malfunction (28%), and finally baclofen itself (18%)[78]. Approximately half of these adverse events extended admission times by a mean of 16 days, however, none were directly associated with long-term morbidity or death. In addition, morphine has been shown to be safe and effective when combined intrathecally with baclofen for the treatment of pain associated with spasticity[79]. Intrathecal treatment of painful spasticity should be considered when oral medication is ineffective or poorly tolerated.

Botulinum neurotoxin is another therapy that has the benefit of being delivered directly to the affected muscle. It has been exhaustively tested for numerous neurologic, muscular, and other spasticity disorders with minimal side effects[80]. A recent study in Germany evaluating the safety and efficacy of botulinum neurotoxin in post-stroke arm spasticity found that 58% of patients had a reduction in pain associated with spasticity[81]. Eighty-four percent of these patients achieved some benefit, pertaining to range of motion, functionality, or ability to tolerate physical therapy. The highest risks of adverse effects from botulinum neurotoxin are generally operator-dependent. As a paralytic agent that interferes with acetylcholine transmission, the most serious side effects come from respiratory failure or dysphagia from poorly placed injections or inadvertent systemic delivery that paralyzes respiratory or esophageal musculature, and can mimic systemic botulism, though this is exceedingly rare[80]. Less serious symptoms are more commonly reported, such as transient malaise, rash, dizziness, and dry mouth[74]. Overall, administration by a highly-trained physician with appropriate knowledge of musculoskeletal anatomy limits the adverse effects of botulinum toxin and treatment outcomes are generally favorable.

Nerve blocks or motor point blocks, typically using phenol or alcohol, can also alleviate spasticity symptoms by disrupting the integrity of afferent and efferent nerves, leading to denervation of the muscle spindles[73]. This technique has not yet demonstrated the same degree of efficacy in terms of alleviation of pain compared to botulinum toxin focal antispasticity therapy, and can be associated with adverse effects, such as post-injection swelling, muscle weakness, and in the case of neurolysis of mixed motor and sensory nerves, post-injection dysesthesia[82].

Several other techniques used in the treatment of spasticity such as, therapeutic ultrasound[83,84], transcutaneous electrical stimulation[85,86], and rTMS[87,88] have shown

success in functional measures in patients with spastic strokes and relieving their degree of spasticity, but their direct impact on pain is not well-established. If a contracture develops and the above strategies prove insufficient, surgical intervention may be necessary to release the contracture, relieve painful muscle strain, and optimize function[89].

Subluxation and other painful disorders of the hemiplegic shoulder

When a hemiplegic limb is left unsupported, external forces may place extra stress on that joint leading to subluxation. The most commonly involved limb in post-stroke pain syndromes is the arm at the shoulder joint most likely due to the effects of gravity. This often occurs during the early stages of stroke recovery when the paretic limb is flaccid, and should be monitored carefully in the acute inpatient setting. Prevention of subluxation should be considered in all hemiplegic patients, and begins with proper support of the limb while the patient is in bed or undergoing physical therapy.

The incidence of shoulder subluxation following stroke has been reported to be quite variable. A study consisting of 15,754 patients enrolled in the PRoFESS trial showed that shoulder subluxation occurs in 0.9% patients with ischemic strokes[1]. A cohort study from Thailand showed that among 327 patients admitted to an inpatient rehabilitation unit, 37.3% developed shoulder subluxation[90]. The discrepancy between these two large studies may be a result of the former's inclusion of a wider range in severity of strokes, whereas the latter includes those only severe enough to warrant inpatient rehabilitation. When limiting the analysis solely to hemiplegic patients, it has been reported that 17% will develop shoulder subluxation[91].

Shoulder subluxation is only one of many potentially painful complications of hemiplegia specific to the shoulder joint. The term hemiplegic shoulder pain has been used broadly to describe shoulder pain in persons with hemiplegic stroke secondary to a variety of causes including subluxation, sensory changes, muscle imbalance, and adhesive capsulitis, as well as CRPS and spasticity, which have been addressed above[92,93]. This section will focus on the painful sequelae of shoulder subluxation but will also include mention of other hemiplegic shoulder pain issues that have not yet been covered.

Treatments for subluxation and other causes of shoulder pain

The initial inclination may be to immobilize the subluxed extremity with various slings or orthoses as would be performed in a healthy patient with a traumatic shoulder dislocation. Unfortunately, immobilization also increases the risk of other pain syndromes including adhesive capsulitis and joint contracture and should be avoided[94]. An alternative option may be to provide a sling that allows for limited mobilization of the arm, such as the Bobath roll or cuff slings. These devices may not provide adequate reduction of the joint and should be used only for short periods[95]. Slings that are prescribed when subluxation causes pain should be easily donned and removed and should be accompanied by a regimen of range of motion exercises during times when the sling is off. For these reasons, the long-term use of slings in a hemiplegic shoulder subluxation is not recommended. For persons with impaired mobility, using a wheelchair lap board or arm trough to maintain proper positioning but also allow for mobility may be beneficial.

Shoulder strapping is another supportive approach that has yielded more promising results. This requires a physical therapist to place broad strips of elasticized tape over the shoulder and arm to add stability and support while preserving mobility. One study of 33 hemiplegic patients showed that over a 28-day period, the group that received prophylactic shoulder strapping was significantly less likely to develop pain compared to placebo and control groups[96]. However, strapping carries the risk of non-adherence secondary from discomfort of the adhesive tape or from tight application of the tape that restricts blood flow[95]. It also must be reapplied every two to three days, making it difficult to maintain in the outpatient setting.

Some of the more current advances in treatment of subluxation revolve around strengthening the limb and joint. Functional electrical stimulation (FES) is a procedure that uses single or multiple transcutaneous electrodes over given muscles or percutaneous intramuscular electrodes, for the purpose of applying a current and stimulating muscle activity. FES has proven to be very useful in preventing subluxation, but not significantly effective in reducing the joint when subluxation has already occurred[97]. However, intramuscular FES has been shown to be effective in reducing pain in a multicenter randomized study of 61 patients with stroke and resulting shoulder subluxation and pain when started one year or less after stroke onset[98]. These patients received treatment for six hours per day over six weeks and achieved significantly decreased pain up to six months post-treatment[98]. Patient compliance is an issue since the FES protocol requires daily therapy over several weeks at an outpatient location in addition to the discomfort experienced from the electrical stimulation[95].

Similarly, peripheral nerve stimulation (PNS), or current delivered to the peripheral nerve as opposed to the muscle, has been shown to be beneficial in the reduction of pain[99,100]. A 2014 randomized controlled trial of 25 patients in which the experimental group received three weeks of peripheral nerve stimulation showed sustained significant pain relief up to 12 weeks after therapy[100]. In addition, a recent case report in a hemiplegic shoulder pain patient who received a fully implantable peripheral nerve stimulator showed efficacy at the 12-month mark, demonstrating the long-term effectiveness of this technology, and avoiding the issue of frequent outpatient visits to receive therapy[101].

Conclusion

Post-stroke pain is a complicated phenomenon encompassing both nociceptive and neuropathic pain etiologies. It is comprised by a variety of disorders, of which the most common include central post-stroke pain, complex regional pain syndrome, pain due to spasticity, and hemiplegic shoulder pain. The management and treatment of these syndromes include pharmacological, orthotic, biomechanical, electrophysiological and surgical therapies. The optimal treatment for an individual patient will often require a combination of therapy modalities; nevertheless, a better understanding of the basis for development along with current and future treatment options for pain syndromes that impair stroke recovery is the first step in early diagnosis and therapy for patients.

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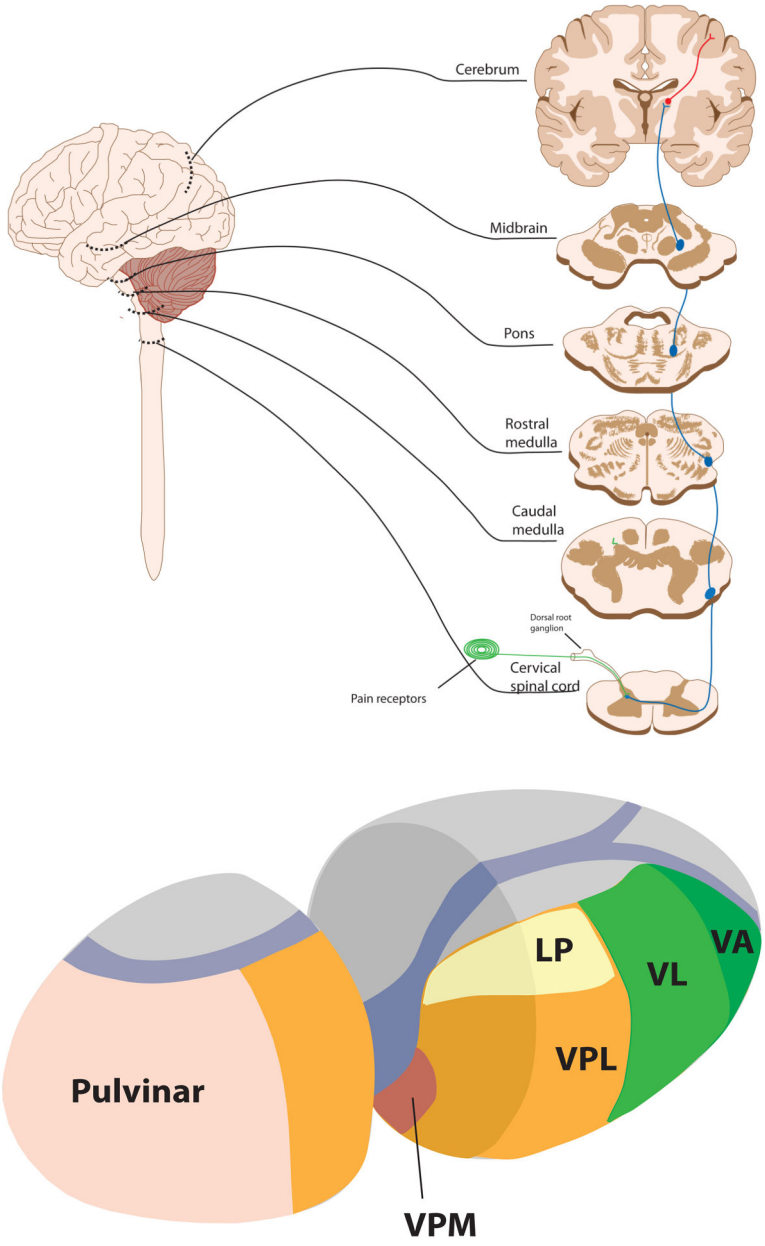

Figure 1.
(a) the spinothalamic tract. (b) the nuclei of the thalamus.