Pain is a common complaint following stroke, reported in 11–55% of stroke survivors. Poststroke pain can arise from muscles, joints, or viscera, or from the peripheral or central nervous system. The most common types of poststroke pain include hemiplegic shoulder pain, pain due to painful spasms or spasticity, poststroke headache, and central poststroke pain. Patients may have several types of poststroke pain concomitantly.

Risk factors for poststroke pain include young age, female sex, stroke severity, spasticity, diabetes, sensory disturbance, depression, and pain before stroke onset. Up to 40% of stroke patients who develop poststroke pain have other pre-existing pain conditions. Poststroke pain can reduce quality of life, increase fatigue, complicate rehabilitation, disturb sleep, affect mood and social functioning, and increase long-term mortality. Since the incidence of stroke increases with age and life expectancy is rising, the prevalence of poststroke pain, including central poststroke pain (CPSP), is also likely to increase in the future. It is important to assess the presence of pain in stroke survivors because of its negative impact on quality of life and rehabilitation.

Central Poststroke Pain
CPSP is a central neuropathic pain condition in which pain arises as a direct result of a cerebrovascular lesion in the central somatosensory nervous system. Other common causes of central neuropathic pain include multiple sclerosis, spinal cord injury, syringomyelia and syringobulbia, tumors and abscesses in the central nervous system (CNS), and other inflammatory CNS diseases (e.g., myelitis). Like poststroke pain in general, CPSP has a negative effect on quality of life in stroke survivors. Central poststroke pain was first described by the French neurologist Déjerine and the Swiss-French neuropathologist Roussy in 1906 in their famous paper “Le syndrome thalamique.” The authors reported a small series of patients with a constellation of neurological symptoms and severe pain attributed to a vascular lesion in the thalamus. This pain syndrome became known as the “Déjerine-Roussy syndrome” or “thalamic pain syndrome.” Experts later demonstrated that extrathalamic vascular lesions can also cause pain, and so the term “central poststroke pain” is preferable.

Diagnosing CPSP
It is important to distinguish between nociceptive and neuropathic pain in stroke patients, as the choice of treatment often differs in these conditions. However, there are no particular features in the history or the clinical findings that can separate neuropathic and musculoskeletal pain with certainty, and making such a distinction...
can sometimes be difficult. A further complication is the fact that stroke patients often have other pain conditions. Also, some poststroke pain conditions may be mixed pain types, as in the case of shoulder pain. In 2008, a new grading system emerged for neuropathic pain with different inclusion criteria for neuropathic pain, but these criteria did not include the exclusion of other causes of pain. Therefore, in 2009 we published a proposal for diagnostic criteria for CPSP based on the grading system, including mandatory and supportive criteria. The mandatory criteria for the diagnosis of CPSP include the following: pain within an area of the body corresponding to the CNS lesion, a history suggestive of a stroke and onset of pain at or after stroke onset, confirmation of a CNS lesion by imaging and/or negative or positive sensory signs confined to the area of the body corresponding to the CNS lesion, and, if possible, exclusion of other causes of pain such as nociceptive or peripheral neuropathic pain. The supportive criteria include: no primary association with movement, inflammation, or other local tissue damage; certain descriptors such as burning, painful cold, electric shocks, aching, pressing, stinging, and pins and needles; and allodynia or dysesthesia to touch. In the same paper, we published a grading system, based on the diagnostic criteria, enabling researchers to classify CPSP as “possible,” “probable,” or “definite” (Table 1).

As implied by the proposed diagnostic criteria, the diagnosis of CPSP is based on the stroke and pain history and the clinical examination with a focus on the sensory findings. If possible, the vascular lesion should be visualized by imaging, either computed tomography (CT) or magnetic resonance imaging (MRI). Other useful tools include pain drawings and standardized pain questionnaires, including neuropathic pain scales such as the DN4 (Douleur Neuropathique en 4 Questions) and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale. Sometimes it is necessary to perform supplementary investigations, such as quantitative sensory testing (QST), additional imaging, or neurophysiological examinations, to rule out other causes of pain.

**Prevalence**

The reported prevalence of central poststroke pain varies between 1% and 12%. In a population-based study from Denmark, based on a questionnaire of 608 stroke patients and a clinical examination of 51 patients with possible CPSP, the minimum prevalence of definite or probable CPSP was 7.3% (N = 35) and 8.6% (N = 41) if CPSP-like dysesthesia was included. The median time of follow-up was 4.4 years.

In a Finnish study of CPSP in young patients with ischemic stroke with a median follow-up time of 8.5 years, a total of 49 out of 824 patients had CPSP, corresponding to a prevalence of 5.9%. Out of the remaining 775 patients, 246 had sensory abnormalities and 529 had neither sensory

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### Table 1

Grading system for central poststroke pain (CPSP)*

<table>
<thead>
<tr>
<th>Criteria to Be Evaluated for Each Patient</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Exclusion of other likely causes of pain</td>
<td>No other obvious cause of pain No primary relation to movement, inflammation, or other local tissue damage Descriptors such as burning, painful cold, electric shocks</td>
</tr>
<tr>
<td>2. Pain with a distinct neuroanatomically plausible distribution</td>
<td>Pain localized unilaterally or crossed face/body in a body area corresponding to a cerebrovascular lesion</td>
</tr>
<tr>
<td>3. A history suggestive of a stroke</td>
<td>Sudden onset of neurological symptoms with pain starting at or after stroke onset</td>
</tr>
<tr>
<td>4. Demonstration of the distinct neuroanatomically plausible distribution by a clinical neurological examination</td>
<td>Findings of positive and/or negative sensory signs in an anatomically plausible distribution and pain localized within a territory of sensory abnormality</td>
</tr>
<tr>
<td>5. Demonstration of the relevant vascular lesion by imaging</td>
<td>Visualization of a lesion that can explain the distribution of sensory findings, either CT or MRI</td>
</tr>
</tbody>
</table>

* Possible CPSP: Criteria 1 + 2 + 3 fulfilled. Probable CPSP: Criteria 1 + 2 + 3 fulfilled plus either 4 or 5. Definite CPSP: Criteria 1–5 fulfilled.
In some patients, pain onset is either immediate or within the first 1–3 months after a stroke. In the majority of patients, pain developed immediately (58%) or within the first month after a stroke (20%).

CPSP can develop after both ischemic and hemorrhagic vascular lesions anywhere in the somatosensory part of the CNS, but there are some indications that the incidence of CPSP may be higher following lesions in certain areas of the brain, including the thalamus, the opercular-insular region, and the brainstem. Given that all patients with CPSP have sensory abnormalities, it is not surprising that patients with sensory abnormalities have an increased risk of developing CPSP. Findings of early evoked dysesthesia or evoked pain at stroke onset are also associated with an increased risk of developing CPSP.

Pain Characteristics

The time reported from stroke to pain onset varies. In the majority of patients, pain onset is either immediate or within the first 1–3 months after a stroke. The onset of pain is often insidious.

The symptoms range from bother-some dysesthesia to severe pain. The majority of patients report moderate pain. In a population-based study, the reported median pain intensity was 5 on a numeric rating scale (range 0–10). The pain can be spontaneous, evoked, or both. Pain-evoking factors can be internal stimuli, such as stress and emotions, or external stimuli, such as touch and cold. Pain usually seems to be chronic, often life-long and constant, but in a few patients, the pain reduces over time.

Sensory descriptors used in patients with CPSP include burning, aching, pricking, lacerating, shooting, squeezing, throbbing, sharp, stabbing, painful pins and needles, dull, and cramping.

Clinical Findings

Sensory function can be examined using simple bedside testing, such as cotton wool for touch, a sharp or pointed stimulus for pain, a metal thermal roller (or any metal object) for cold sensation, and a soft brush for dynamic allodynia. The area of pain in patients with CPSP varies in size and distribution. In some patients only small areas are involved, such as parts of the face or one foot. In other patients, the pain affects larger areas such as one side of the body, an arm or a leg, or one entire half of the body (always contralateral to a hemispheric vascular lesion). The pain is always located within an area of sensory abnormalities. As in other neuropathic pain conditions, there is often a combination of “positive” and “negative” sensory findings on the sensory examination. Thus, there may be loss of sensitivity to one sensory modality combined with hypersensitivity to another sensory modality, such as loss of sensitivity to heat and hypersensitivity to touch. Hyperalgesia, dysesthesia, and allodynia are common findings in patients with CPSP. For a definition of these terms, see the pain taxonomy published by IASP. In one study, pinprick hyperalgesia was present in 57%, cold allodynia in 40%, and brush-evoked dysesthesia in 51% of patients with CPSP.

Abnormal pain and temperature sensation is found in almost all patients with CPSP. The sensory processing of temperature and pain occurs via the spinothalamic tract and the spinothalamothalamic projecting system. Abnormal pain and temperature sensation is quite common in stroke patients without CPSP. For this reason, some experts suggest that a lesion of the spinothalamic tracks is necessary, but not sufficient, to cause CPSP. There are further indications that patients with a partial lesion of the spinothalamic-thalamocortical pathways may be more prone to develop CPSP compared to patients with complete lesions in these pathways.

Other Findings

There are no universal non-sensory neurological findings in CPSP. The clinical non-sensory findings in patients with CPSP reflect the location and size of the vascular lesion and are not correlated to the pain. Choreoathetoid movements, which were part of the original description of “thalamic pain” as described by Dejerine and Roussy, only rarely occur in patients with CPSP.
Imaging studies have illustrated that a lesion anywhere in the somatosensory pathways, including the thalamus and the thalamocortical projections (especially to the opercular-insular region)\cite{20,20} can cause CPSP.\cite{21} PET studies have documented flow changes in the thalamus in patients with CPSP, both at rest and with evoked pain.\cite{19,51} Neurophysiological recordings with microelectrodes have measured abnormal spontaneous and evoked activity in the thalamus of patients with CPSP.\cite{28,45} More recently, MRI with diffusion tensor tractography has illustrated changes in the spinothalamic tracts.\cite{30}

It is still puzzling why, in patients with almost identical stroke lesions and clinical findings, some patients develop CPSP and others do not.

Pathophysiology

The underlying pathophysiology of CPSP is not well understood. It is still puzzling why, in patients with almost identical stroke lesions and clinical findings, some patients develop CPSP and others do not. As already mentioned, lesions of the spinothalamic tracts have been implicated in the development of CPSP. A structural MRI study of stroke patients with thalamic lesions, with and without pain, found a high odds ratio for developing CPSP in patients with lesions involving the ventral posterior nucleus/pulvinar border zone of the thalamus, an area previously linked to signaling of pain and temperature.\cite{54} Given that all patients have pain within an area of sensory abnormalities, deafferentation is also thought to play an important role. The fact that findings of hypersensitivity is common and can precede the development of CPSP in stroke patients implies that mechanisms involving neuronal hyperexcitability, such as central sensitization or disinhibition, may be involved.\cite{38} Alterations in activity seen on functional imaging and changes in electric activity as illustrated by neurophysiological findings suggest that neuroplasticity may also play a role.

Treatment

Treatment of CPSP is difficult owing to the limited efficacy of the available drugs and their dose-limiting side effects. Treating CPSP is therefore a continuous challenge. Only a few double-blinded, placebo-controlled trials have been published on CPSP. These trials are summarized in Table 2.\cite{32}

In line with other neuropathic pain conditions, CPSP may respond to pregabalin and amitriptyline,\cite{15} although one negative study has been published.\cite{34} Lamotrigine may be effective against ongoing pain and cold-evoked pain in CPSP;\cite{17} but its effect in other neuropathic pain conditions is inconsistent. Duloxetine relieved dynamic mechanical and cold allodynia in patients with CPSP or spinal cord injury,\cite{60} but the effect on ongoing pain did not reach statistical significance (P = 0.056). Given the limited evidence for treatment of CPSP, it seems reasonable to try treatments that have efficacy in other central pain conditions or peripheral neuropathic pain conditions, and the results of trials in CPSP do not contradict general treatment recommendations for neuropathic pain. Tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), pregabalin, and gabapentin are proposed as first-line treatment, while tramadol is recommended as second-line and strong opioids as third.
line-treatment. At present there is no evidence for combination therapy in CPSP and only limited evidence for its use in other neuropathic pain conditions. It may, however, be indicated in patients with partial relief from taking two drugs. When deciding on treatment, the clinician should keep in mind potential side effects and contraindications, but also concomitant symptoms, such as depression or sleep disorders, that may respond well to certain treatments. Other concomitant nociceptive pain conditions should be identified and managed as well.

Nonpharmacological treatment—including repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS) and motor cortex stimulation (MCS)—has been reported in case series and brief reports, but there are no controlled trials in this field. In a recent review of interventional treatment of neuropathic pain, the authors conclude that owing to low-quality evidence, recommendations for MCS and DBS are “inconclusive” in the treatment of CPSP. In this review, the authors recommend that spinal cord stimulation (SCS) should generally not be used for CPSP, on the basis of a single unfavorable case series. Single sessions of rTMS can give short-lasting pain relief in patients with CPSP and other pain conditions. There are some indications that repeated application of rTMS may offer longer-lasting pain relief.

In our clinic, we use a personalized pharmacological treatment strategy, taking into account concomitant medication and other diseases and symptoms, such as depression or sleep problems, and continuously weighing benefits and side effects. We usually start with an antidepressant (TCA or SNRI), gabapentin, or pregabalin. The typical starting dose of the TCA is 25 mg at night, increasing slowly (especially in the elderly) by 10 mg per week. If the TCA is not tolerated or is contraindicated, an SNRI can be used at night instead. The starting dose of gabapentin is usually 300 mg, increasing by 300 mg every 3–7 days up to a maximum dose of 2400 mg/day. If gabapentin is not tolerated, pregabalin can be tried with a starting dose of 25 mg/day. If pain relief is not sufficient, a combination of antidepressants and antiepileptics can be tried. Tramadol can be used as an add-on medication. The most common side effects of gabapentin and pregabalin include sedation, dizziness, and edema. TCA side effects include cardiac, anticholinergic, and sedation issues. If necessary, we refer patients to the pain clinic’s physiotherapist or psychologist for individual treatment.

### Future Perspectives

There is a great need to identify better treatment regimes. Unfortunately, at present, only a few high-quality double-blinded randomized trials have focused on the treatment of CPSP.

In recent years, several animal models mimicking CPSP have been developed. We hope they will offer new insight into the pathophysiology of CPSP, enabling the development of mechanism-based treatment trials.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/day)</th>
<th>Outcome</th>
<th>No. Patients</th>
<th>Drop-outs</th>
<th>NNT</th>
<th>Reference</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin</td>
<td>125–600</td>
<td>Positive</td>
<td>40 mixed CP (19 CPSP, 21 SCI)</td>
<td>7</td>
<td>4.0</td>
<td>Vranken et al. 2008</td>
<td>Parallel, flexible-dose</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>200</td>
<td>Positive</td>
<td>30 CPSP</td>
<td>10</td>
<td>NA</td>
<td>Vestergaard et al. 2001</td>
<td>Crossover</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>75</td>
<td>Positive</td>
<td>15 CPSP</td>
<td>0</td>
<td>1.7</td>
<td>Leijon et al. 1989</td>
<td>Crossover, 3-phase</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>800</td>
<td>Negative</td>
<td>14 CPSP</td>
<td>0</td>
<td>-</td>
<td>Leijon et al. 1989</td>
<td>Crossover, 3-phase</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1000–3000</td>
<td>Negative</td>
<td>42 CPSP</td>
<td>9</td>
<td>-</td>
<td>Junghulsing et al. 2013</td>
<td>Crossover</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>150–600</td>
<td>Negative</td>
<td>219 CPSP</td>
<td>36</td>
<td>-</td>
<td>Kim et al. 2011</td>
<td>Parallel, flexible-dose</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60–120</td>
<td>Negative</td>
<td>48 mixed CP (13 CPSP, 34 SCI, 1 other)</td>
<td>4</td>
<td>-</td>
<td>Vranken et al. 2011</td>
<td>Parallel, flexible-dose</td>
</tr>
</tbody>
</table>

Abbreviations: CP, central pain; CPSP, central poststroke pain; NNT, number needed to treat; SCI, spinal cord injury.
Combination therapy is often used in clinical practice. Future trials in this field should guide us to the best combinations and dosages.

Looking at several combined predictors of CPSP such as localization in certain thalamic regions and findings of early evoked pain and dysesthesia could perhaps identify patients at higher risk for the development of CPSP. In these patients, preventive trials could be feasible. Also it could be of interest to study the natural history of CPSP in long-term follow-up studies. Such studies could hopefully contribute to our understanding of the prognosis and mechanisms behind CPSP.

References

1. International Association for the Study of Pain. IASP pain taxonomy. Available at: http://iasp-pain.org/taxonomy


