Mechanisms and Predictors of Chronic Facial Pain in Lateral Medullary Infarction

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The purpose of this study was to identify clinical predictors and anatomical structures involved in patients with pain after dorsolateral medullary infarction. Eight out of 12 patients (67%) developed poststroke pain within 12 days to 24 months after infarction. The pain occurred in the ipsilateral face (6 patients) and/or the contralateral limbs and trunk (5 patients, 3 of whom also had facial pain). Ipsilateral facial pain was significantly correlated with lower medullary lesions, including those of the spinal trigeminal tract and/or nucleus, as documented by magnetic resonance imaging. The R2 blink reflex component was abnormal only in patients with facial pain. Likewise, pain and temperature sensation in the ipsilateral face was decreased in all patients with facial pain but not in patients without pain. Ipsilateral touch sensation in the face was also decreased in all patients with facial pain, but the lesions revealed on magnetic resonance imaging did not involve the principal sensory nucleus of the fifth cranial nerve, and the R1 blink reflex latencies were normal. Although facial pain was correlated with lesions of the spinal trigeminal tract and/or nucleus, none of the lesions involved the subnucleus caudalis, which contains most nociceptive neurons. These findings suggest that facial pain after medullary infarction is due to lesions of the lower spinal trigeminal tract (axons of primary afferent neurons), leading to deafferentation of spinal trigeminal nucleus neurons.

By definition, central pain is caused by lesions of the brain and spinal cord. First described by Dejerine and Roussy in 1906 as a component of thalamic syndrome,1 it can also be caused by other supratentorial lesions.2 Recently, central poststroke pain was reported as a frequent complication of lateral medullary infarction.3–5 Current knowledge indicates that lesions causing pain are associated with impaired temperature and pain sensibility, indicating involvement of the spinothalamocortical tract, whereas a lesion of the medial lemniscus is neither necessary nor sufficient.6 The purpose of this study was to identify clinical predictors and mechanisms of poststroke pain in patients with lateral medullary infarction. The lateral medullary infarction was determined by the presence of a lesion on magnetic resonance imaging (MRI) and at least two of eight characteristic clinical signs of the Wallenberg’s syndrome.7 Until now, even high-resolution MRI has not been able to demonstrate directly anatomical structures involved in patients with pain. Therefore, we projected individual lesions onto the appropriate levels of the anatomy atlas, a method that had been validated before.8 Clinical signs and symptoms, quantitative sensory testing, and electrophysiological tests were utilized to evaluate the functional state.

Methods

Patients

Over a period of 1 year, 58 patients with acute brainstem infarction were examined, 5 of whom showed clinical signs of a lateral medullary infarction. Seven additional patients were identified retrospectively and followed up. All patients consented to the investigation according to the Declaration of Helsinki. The study was approved by the local ethics committee.

Clinical Examination and Structured Pain Interview

All patients were interviewed and examined by the same author (S.F.). The clinical data for the acute state of the patients included retrospectively were taken from hospital charts. Characteristics of pain were identified by a structured interview, a modified questionnaire of the German Society for the Study of Pain and the German Red Cross Pain Centre Mainz (kindly supplied by B. Nagel, German Red Cross Pain Centre Mainz, Germany).
Sensory and pain thresholds for thermal and mechanical stimuli were tested on both sides of the face (upper cheek).

**Table 1. Clinical, Electrophysiological, and MRI Findings in Lateral Medullary Infarction (Wallenberg’s Syndrome)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pain in Ipsilateral Face</th>
<th>Pain in Contralateral Limbs or Trunk</th>
<th>Time Between Infarction and Onset of Pain</th>
<th>Contact of MRI Lesion with the Trigeminal Spinal Tract and/or Nucleus</th>
<th>Contact of MRI Lesion with the Spinotheralamic Tract</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>−</td>
<td>18 months</td>
<td>●</td>
<td>●</td>
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<tr>
<td>2</td>
<td>+</td>
<td>−</td>
<td>4 months</td>
<td>○</td>
<td>○</td>
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<tr>
<td>3</td>
<td>+</td>
<td>−</td>
<td>2 months</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>1 month</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>+</td>
<td>24 months</td>
<td>●</td>
<td>●</td>
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<tr>
<td>6</td>
<td>+</td>
<td>+</td>
<td>2 months</td>
<td>○</td>
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<tr>
<td>7</td>
<td>−</td>
<td>+</td>
<td>3 month</td>
<td>○</td>
<td>○</td>
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<tr>
<td>8</td>
<td>−</td>
<td>−</td>
<td>12 days</td>
<td>○</td>
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<td>9</td>
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<td>−</td>
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<td>−</td>
<td>○</td>
<td>●</td>
</tr>
</tbody>
</table>

**Magnetic Resonance Imaging**

All patients had biplanar high-resolution T2-weighted imaging of the brainstem within the first 2 weeks after acute stroke except Patient 7, who was studied 2 years following infarction. The slice orientation was parallel (sagittal sections) and perpendicular (axial sections) to the sagittal brainstem cuts of the anatomical brain atlas of Schaltenbrand and Wahren.9 The individual slices were normalized (according to their brainstem outlines) and projected onto the appropriate levels of the anatomy atlas. The technique and evaluation of this method have been described previously.8

**Electrophysiological Examination**

The blink reflex was evoked by stimulation of the supraorbital nerve (0.1 msec duration, 3–20 mA, interstimulus intervals of 10–20 seconds) as described previously in detail.10

The blink reflex consists of an early ipsilateral response (R1), mediated by interneurons in the principal sensory nucleus, and a late bilateral response (R2 and R2c), mediated by interneurons in the caudal parts of the spinal trigeminal nucleus. Lesions of the trigeminal spinal tract and/or nucleus (TSTN) lead to abnormalities of R2 and R2c, whereas R1 remains unaffected. The blink reflex was considered abnormal based on the following criteria:10

- R1: loss of R1, latencies above 12.0 msec, or side differences of ≥ 1.2 msec
- R2: loss of R2, latencies above 42.4 msec, or side differences of ≥ 5 msec
- R2c: loss of R2c, latencies above 44.4 msec, or side differences of ≥ 7 msec

Electrically evoked somatosensory potentials (SEPs) were obtained using a standard technique according to the International Federation of Clinical Neurophysiology (IFCN) Committee Guidelines.11

**Quantitative Sensory Testing**

Sensory and pain thresholds for thermal and mechanical stimuli were tested on both sides of the face (upper cheek).

Temperature thresholds for warm and cold stimuli were examined by the method of limits using a 13.3-cm² thermode (TSA 2001, Medoc, Ramat, Yishari, Israel). Base temperature was set to 32°C and the rate of temperature change was 1°C/sec. For threshold determination, the patients had to indicate when they felt the thermode becoming warm or cold (sensory thresholds) or painful (thresholds for heat pain and cold pain). For the thermal sensory limen procedure (TSL), alternating warm and cold stimuli were given. The patient pressed a button when recognizing either warmth or cold, which reversed the temperature change.12 Details and normal values have been published.13,14 Mechanical thresholds for light touch and pain were determined by calibrated v. Frey hairs (Ø1.1 mm, 0.5–4100 mN).15 Stimulus-response functions for pricking pain were obtained with a series of punctate mechanical stimulators (Ø 200 μm, 8–512 mN), which are more specific than v. Frey hairs for activating Aδ nociceptors.16 In every test area, the different intensities were applied five times each in a balanced order. Following every stimulus, the patient was asked to give a rating of pain magnitude on a verbal rating scale (0, not painful; 100, maximal imaginable pain). The stimulus intensity that was perceived as painful in 50% of the applications was taken as the individual threshold value.15

**Statistics**

We used paired t tests to compare contralateral and ipsilateral sensory and pain thresholds of the face. Stimulus-response functions of pain ratings for punctate mechanical stimuli were analyzed by two-way analysis of variance (the main factors were chronic facial pain vs no facial pain and ipsi- vs contralateral face). Significant differences between groups were tested by post hoc Scheffé tests. Differences in incidence of MRI-based estimation of lower medullary lesion of the TSTN between patient subgroups with or without ipsilateral pain were tested by chi-square test. In addition, the presence of persistent facial pain and lower medullary TSTN lesions were also analyzed by Spearman-Brown rank correlation. Throughout the paper, data are presented as mean plus or minus the standard error of the mean (SEM).
Results
Clinical Findings
Of the 12 patients with Wallenberg’s syndrome (10 men and 2 women, mean age 63 years, range 50–74 years) 8 (67%) developed a chronic pain syndrome. The latency between stroke and onset of pain was mostly shorter than 4 months (Table 1). Six out of 8 patients localized the pain in the face ipsilateral to infarction. In 3 of these 6 patients pain also occurred in the contralateral limbs and trunk. Chronic facial pain was always ipsilateral, occurred mainly in the periorbital region, and was associated with foreign-body or pressure sensation of the eye in 2 patients. Pain was described as a superficial sensation of burning (5 patients), stinging (4 patients), or heat (4 patients), but deep pain (2 patients) or both deep and superficial pain (1 patient) were also reported. Six of 8 patients reported pain attacks lasting seconds to minutes occurring several times daily (5 of them mentioned trigger factors); 3 of them also had persistent pain. One patient who had suffered minor injury of the ipsilateral nostril with his stroke developed a delayed wound healing, atrophy of nostril, and deep facial ulcerations maintained by a compulsive urge to scratch these areas. Corneal reflexes were abolished or diminished in all 6 patients with ipsilateral facial pain but also in 2 of 6 patients without facial pain (see Table 1).

The average disturbance of daily activities (rating scale 0–9) was 3.0 (range 0–7). The average ratings of minimal and maximal pain intensities (rating scale 0–100, excluding completely pain-free periods) were 44 (range 20–90) and 61 (range 40–90), respectively. No patient took any analgesics at the time of the interview.

MRI Lesions
Figure 1 shows three representative examples of the types of MRI lesions observed in this study. Five of 6 patients with pain of the ipsilateral face (Patients 1–5) had lesions that covered the TSTN in the lower medulla at one or more levels (see Table 1). The remaining patient with facial pain (Patient 6) had no sign of lesion of the lower medulla in the MRI but exhibited a functional deficit (abnormal blink reflex R2/R2c and quantitative sensory testing [QST] results). Only 1 of the 6 patients without facial pain (Patient 9) had a partial lesion of the lower medulla but without functional deficit. Another patient without facial pain (Patient 11) had a radiologically complete lesion in one of the cranial slices, but this lesion was functionally incomplete, as shown by normal blink reflex and QST results. Thus, there were 5 of 6 lesions involving the TSTN at the lower parts of medulla in patients with facial pain but only a partial lesion in 1 of the patients without pain ($\chi^2 = 5.33, p < 0.05$). Facial pain was correlated with the extent of the lower medullary lesions (Spearman-Brown rank correlation: $r = 0.74, p <$
whereas there was no such correlation between facial pain and lesions of the upper medulla. The lower boundary of the lesions was between levels 330 and 375 of the Schaltenbrand atlas. As a consequence, none of the lesions reached the subnucleus caudalis, which extends caudally from level 420 (verified by comparison of the Schaltenbrand9 and Paxinos atlases17) or even from level 465 (level of pyramidal crossing18).

The 5 patients with pain of the contralateral limbs and trunk had lesions involving the spinothalamic tract (STT), but there were also 6 of 7 patients without pain in the limbs and trunk showing similar STT lesions.

**Electrophysiology**

Sparing of the lemniscal pathways was demonstrated by normal SEPs in 9 patients (Patients 1, 3, 4, 6–9, 11, and 12). Abnormal SEP findings in the remaining 3 patients were bilaterally symmetrical and were attributed to diabetic peripheral neuropathy (see Table 1).

All patients had normal R1 blink reflex latencies. Patients without pain also had normal R2 and R2c blink reflex responses, but R2 and R2c blink reflex responses were abnormally delayed in all patients with pain of the ipsilateral face.

**Quantitative Sensory Testing**

In all 6 patients with facial pain, sensory thresholds for light touch were significantly elevated ipsilaterally to infarction ($p < 0.001$; Table 2). In contrast, none of the patients without facial pain had any alterations of tactile thresholds. Likewise, mechanical pain thresholds of the ipsilateral face were significantly elevated only in patients with facial pain ($p < 0.05$). Sensory thresholds for cold and heat and the TSL were abnormal on the cheek ipsilateral to infarction in each patient with facial pain, and there was a significant side-to-side difference for the group of patients with facial pain ($p < 0.05$ for TSL). Heat and cold pain thresholds were also

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**Fig 1.** T2-weighted MRI images (upper panel) and extent of the identified lesion superimposed on the appropriate cut of the anatomical atlas of Schaltenbrand and Wahren (lower panel) of three typical patients who developed persistent pain after lateral medullary infarction. (Left) Patient 4, who developed persistent pain of the ipsilateral face and the contralateral trunk and limbs. (Middle) Patient 7, with pain of contralateral trunk and limbs but no ipsilateral facial pain. (Right) Patient 3, with pain of the ipsilateral face only.
The reported incidence varies between 9 and 83% (for review see Sacco et al19). In our data, pain was observed in 8 of 12 patients (67%), with an onset between 12 days and 24 months after the acute brainstem lesion. The characteristic features of the pain were a sensation of superficial burning, stinging, or heat presenting constantly, in attacks, or both, and the pain was triggered or exacerbated by touch, cold, or warmth. Vuilleumier et al20 reported pain following medullary infarction in 7 of 28 consecutive patients (25%). The lower incidence may be explained by the shorter follow-up (1–16 days). MacGowan et al1 also reported 16 of 63 patients’ (25%) developing pain up to 6 months after infarction, mostly affecting the ipsilateral periorbital region. However, they only selected patients with severe pain and frequent allodynia. In our study, pain intensity and disturbance in daily activity were mostly low. Our experience suggests that mild pain is rather frequent after dorsolateral medullary infarction but may be overlooked if the patient is not specifically asked about it.

Stimulus-response functions for pricking pain in the ipsilateral cheek were shifted downward in only 6 patients with facial pain but were symmetrical in the 6 patients without pain. Each patient with facial pain showed abnormal thresholds of pain and temperature in the cheek ipsilateral to infarction, as revealed by QST. These patients also had abnormal, late blink reflexes, whereas patients without facial pain had normal responses. A R2 and R2c blink reflex abnormality after unilateral stimulation reflects impairment of the afferent limb of the reflex loop (spinal trigeminal tract

**Table 2. Quantitative Sensory Testing**

<table>
<thead>
<tr>
<th>Thresholds</th>
<th>Patients Without Facial Pain</th>
<th>Patients with Facial Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contralateral</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Touch vF (log2 units)</td>
<td>$-0.8 \pm 0.1$</td>
<td>$-0.5 \pm 0.4$</td>
</tr>
<tr>
<td>Pain vF (log2 units)</td>
<td>$0.6 \pm 0.1$</td>
<td>$0.7 \pm 0.1$</td>
</tr>
<tr>
<td>Cold sensory (°C)</td>
<td>$8.8 \pm 0.5$</td>
<td>$9.0 \pm 0.7$</td>
</tr>
<tr>
<td>Warm sensory (°C)</td>
<td>$446 \pm 0.1$</td>
<td>$512 \pm 0.1$</td>
</tr>
<tr>
<td>TSL (°C)</td>
<td>$+1.7 \pm 0.2$</td>
<td>$+1.3 \pm 0.2$</td>
</tr>
<tr>
<td>Cold pain (°C)</td>
<td>$3.6 \pm 0.5$</td>
<td>$3.0 \pm 0.5$</td>
</tr>
<tr>
<td>Heat pain (°C)</td>
<td>$15.5 \pm 2.3$</td>
<td>$19.5 \pm 1.9$</td>
</tr>
</tbody>
</table>

**Fig 2. Stimulus-response functions for pricking pain to punctuate stimuli (200 μm probes) tested in the face (cheek) contralateral (open symbols) and ipsilateral (filled symbols) to infarction. (A) In patients without persistent facial pain, similar stimulus-response functions were found in both sides of the face. (B) In patients with persistent facial pain, pain to punctuate stimuli was normal in the contralateral face but strongly reduced in the ipsilateral face.**

**Discussion**

Dorsolateral medullary infarction is one of the potential causes of chronic poststroke pain.6 The reported incidence varies between 9 and 83% (for review see Sacco et al19). In our data, pain was observed in 8 of 12 patients (67%), with an onset between 12 days and 24 months after the acute brainstem lesion. The characteristic features of the pain were a sensation of superficial burning, stinging, or heat presenting constantly, in attacks, or both, and the pain was triggered or exacerbated by touch, cold, or warmth. Vuilleumier et al20 reported pain following medullary infarction in 7 of 28 consecutive patients (25%). The lower incidence may be explained by the shorter follow-up (1–16 days). MacGowan et al1 also reported 16 of 63 patients’ (25%) developing pain up to 6 months after infarction, mostly affecting the ipsilateral periorbital region. However, they only selected patients with severe pain and frequent allodynia. In our study, pain intensity and disturbance in daily activity were mostly low. Our experience suggests that mild pain is rather frequent after dorsolateral medullary infarction but may be overlooked if the patient is not specifically asked about it.

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Matched those of patients without facial pain. In patients without facial pain, the stimulus-response functions of both sides of the face did not differ ($p = 0.60$, Scheffé test; Fig 2A).
and/or nucleus) if suprasegmental influences can be ruled out,\textsuperscript{21–24} as was the case in our patients. This type of blink reflex abnormality is a frequent finding in Wallenberg’s syndrome.\textsuperscript{8,25}

In high-resolution MRI, all patients with facial pain had lesions of the TSTN, especially in the lower parts of the medulla (inferolateral infarctions, according to Vuilleumier et al\textsuperscript{20})). It is generally accepted that nociceptive and thermal inputs from trigeminal areas are predominantly processed in the caudalmost parts of the spinal trigeminal nucleus (subnucleus caudalis) by high-threshold nociceptive-specific and convergent (wide dynamic range) neurons.\textsuperscript{26–28} Neurosurgical evidence has demonstrated that only this part of the spinal trigeminal nucleus is essential for human trigeminal pain perception\textsuperscript{29} and that interruption of the caudally descending fibers (trigeminal tractotomy) in humans abolishes pain perception in the ipsilateral face.\textsuperscript{30}

Our data show that TSTN lesions are associated, not only with sensory loss, but also with chronic facial pain. In patients without pain, MRI documented sparing of the TSTN, which corresponded to normal QST thresholds of the ipsilateral face and normal blink reflex responses. In contrast to the correlation between TSTN lesions and ipsilateral facial pain, we found no correlation between involvement of the spinothalamic tract (STT) and the occurrence of a pain syndrome of the contralateral trunk and limbs. Each patient developing pain had a lesion of the STT, but this was also found in 6 out of 7 patients without contralateral pain. Therefore, an STT lesion may be a prerequisite for, but not the only factor in, pain development.

STT lesions are by definition central because they involve the axon of the second neuron. In TSTN lesions, however, there are two possibilities: the trigeminal tract may be involved with or without additional lesion of the trigeminal nucleus. Lesions involving the trigeminal nucleus impair the second neuron, similarly to STT lesions (central lesion). Lesions involving the trigeminal tract and sparing the nucleus may impair the axon of the first neuron only. This results in deafferentation of the second neuron (as in plexus avulsion). It is impossible to anatomically distinguish between trigeminal tract and nucleus lesions on axial MRI scans. However, an atlas-based analysis of the craniocaudal extent of the lesions allows such a distinction. Figure 3 illustrates anatomical details of the trigeminal sensory system. The three branches of the trigeminal nerve enter the brainstem and descend as the spinal trigeminal tract parallel to the trigeminal spinal nucleus, giving off branches to the three subdivisions of the nucleus, the most caudal part of which is the subnucleus caudalis. The lesions observed in our patients covered the subnucleus interpolaris and/or the subnucleus oralis together with the part of the spinal trigeminal tract next to it (as shown in Fig 3). This means that neurons inside the spinal trigeminal nucleus below the lesion (i.e., the subnucleus caudalis, which contains most of the nociceptive trigeminal neurons) become deafferented. Spontaneous activity of the deafferented second neuron may evoke chronic deafferentation pain.\textsuperscript{31–33} The interpretation of facial pain in Wallenberg’s syndrome as being of peripheral origin is supported by the finding that facial pain occurs only ipsilaterally,\textsuperscript{3,20} whereas sensory loss may be found ipsilaterally, contralaterally, or bilaterally also.\textsuperscript{34} We therefore postulate a trigeminal tract lesion as the source of the facial pain.

MacGowan et al\textsuperscript{3} reported elevated pain and temperature thresholds bilaterally in the face, mainly in patients without pain. Lack of pain development in such
patients with injured TSTN may be due to a more medial extension of the lesion into the medullary reticular formation also involving the crossing trigeminothalamic tract, which may prevent development of pain. In our patients, the medial part of the medulla was intact, as documented by MRI, normal SEP (sparring of the medial lemniscus), and normal QST results on the contralateral cheek.

QST also revealed an elevation of touch thresholds in the ipsilateral cheek in all patients with chronic facial pain but not in those without pain. Disturbed tactile sensation is not recognized as a common sign of lateral medullary infarction, although it is occasionally observed. Touch perception of the face is related to the principal trigeminal nucleus, which was spared by the lesions in our patients (see MRI data and normal R1 blink reflexes). In humans, approximately 90% of fibers of the spinal trigeminal tract have diameters of less than 4 \( \mu \text{m} \), and likely subserve pain and temperature receptors. However, a small portion of the descending spinal trigeminal tract likely subserves tactile perception, as shown by the impairment of tactile sensitivity that may result from medullary trigeminal tractotomy. Thus, the subnucleus caudalis may be more important for touch sensation than commonly thought, and its deafferentation may explain why trigeminal hypoesthesia also occurs in Wallenberg’s syndrome.

In summary, the following lines of evidence suggest that chronic facial pain following lateral medullary infarction is due to a lesion of the primary afferent fibers running in the descending spinal trigeminal tract:

1. Patients with morphological and functional evidence of damage of the TSTN and ipsilateral sensory deficit develop ipsilateral facial pain.
2. The lower part of the trigeminal nucleus (subnucleus caudalis) is spared by the lesions.
3. Patients with damage of the ascending trigeminal thalamic tract and contralateral deficit do not develop pain.

Thus, chronic facial pain in Wallenberg’s syndrome is due to a peripheral type of lesion within the central nervous system. Simple and adequate tests for a lesion of the descending spinal trigeminal tract include ipsilateral QST and the blink reflex R2/R2c component. Prospective studies are needed to establish the predictive value of these tests. This study was supported by the Deutsche Forschungsgemeinschaft (HO 293–10/1).

References


