Analysis of the Perception of and Reactivity to Pain and Heat in Patients With Wallenberg Syndrome and Severe Spinothalamic Tract Dysfunction

M. Rousseaux, MD, PhD; F. Cassim, MD; B. Bayle, MD; E. Laureau, MD

Background—The aim of the study was to assess the consequences of severe spinothalamic tract lesions resulting from lateral medullary infarct and to show that a specific pain perception can be elicited by strong thermal stimulation.

Case Descriptions—Both patients examined presented with severe thermoalgic dissociation of the limbs contralateral to the lesion, with normal discriminative somatosensory perception and motor strength. They reported pain perception when touching very warm (50°C to 60°C) objects and a brisk, occasionally uncontrolled withdrawal reaction of the arm and hand under the same conditions, without any perception of the heat nature of the stimulus. Warm stimulation, 45°C, elicited no thermal perception or discrimination. Pain perception could be elicited in both patients by increasing the temperature, with a reproducible threshold of 47°C to 49°C. Pain always occurred after a prolonged delay of 8 to 10 seconds in response to threshold heat, and was described as deep and osseous, and clearly different from that perceived on the nonaffected side. The delay was much shorter when the temperature was increased by 4°C to 5°C. Cold stimulation elicited similar pain perception in one patient. Analysis of subjective perception of laser stimulation showed a much higher pain threshold on the affected hand. There were no laser-evoked potentials on this side, which suggested major spinothalamic injury. Assessment of the RIII noxious reflex revealed persistent response withdrawal reactions, with an increased threshold on the affected side, and partial consciousness of the noxious nature of the stimulus.

Conclusions—To our knowledge, this is the first description of the appearance of pain perception of high temperatures in patients with severe spinothalamic injury who are suffering from a complete loss of temperature perception. This implies that noxious thermal stimulation can still be perceived via extra spinothalamic pathways (which are slow and multisynaptic), such as the spinoreticulothalamic tract. Patients with Wallenberg syndrome should be informed and made aware of their residual perception of and reactions to noxious stimulation.

Key Words: cerebral infarction ■ medulla ■ pain ■ spinothalamic tracts

Thermal and painful stimuli are experienced qualitatively and produce a sensation of unbearable pain and avoidance reactions when they exceed a critical threshold. This helps protect the individual from cutaneous lesion. These reactions to heat and pain are mainly carried along the spinothalamic tract and the thalamocortical projections and in the spinal cord, with a multimodal organization. Noxious stimuli also activate the reticular system, which increases arousal. Selective lesioning of the spinothalamic tract in the lateral medulla results in a contralateral thermoalgetic dissociation, which is often incomplete. However, we have no real knowledge of what is preserved in the patients with severe or complete lesion of the spinothalamic tract at the medullary level. Occasional reports suggest that most or all perception of thermal and pain stimuli is lost. Furthermore, the spinal cord is preserved in these patients, so that avoidance reactions should be possible and relatively normal, unlike the usual situation in syringomyelia. The reflex response to nociceptive stimulation has been investigated in selected cases, and seems to be moderately reduced.

This study was carried out to evaluate the consequences of a relatively selective and severe lesion of the spinothalamic tract in the lateral medulla (Wallenberg’s syndrome without lemniscal tract injury), and to show that: specific pain can be perceived after thermal stimulation when a precise threshold is exceeded; warm stimuli to the arm elicit withdrawal reactions; and brief electrical stimulations also elicit withdrawal reactions; and this reactivity can be important in the daily life of patients.

Report of Cases

Patient 1
A 56-year-old man with no past neurological history presented in 1992 with right cervical and occipital pain, diplopia,
rotary vertigo, and loss of balance. Neurological examination revealed right-sided ataxia, Horner’s syndrome, diplopia with skew-deviation, and severe left-sided thermal and pain analgesia on the limbs and trunk, with relative sensitivity of the face. Lingual and pharyngeal examination was normal, as were his motor strength and discriminative sensivities (light touch, 2-point discrimination, monofilament perception, position sense, pallesthesia). MRI (T2 sequences) revealed a right-sided lateral medullary hyperintensity (Figure 1). The right vertebral artery was not opacified on humeral angiography; its distal part (with the posteroinferior cerebellar artery) was supplied by the left vertebral artery.

He recovered from the gait disorder relatively rapidly and had regained full autonomy in daily life when discharged from the rehabilitation center (Barthel Index: 100/100). Follow-up examinations (1993 to 1998) revealed persistent, complete left-sided anesthesia for painful and thermal stimuli, and diplopia in his right gaze. In the first few months after discharge, the patient described particular reactivity to thermal stimuli. His left upper limb underwent a brisk withdrawal reaction when touching warm objects on several occasions, without any consciousness of the temperature. Burning never occurred. The patient later learned to control and inhibit this reaction when approaching warm objects. Furthermore, he once had a severe knife cut on a finger without experiencing any pain and without any withdrawal reaction. This led us to carry out a more complete investigation of his heat and pain perception.

Patient 2
A 60-year-old man, without any neurological history, presented in 1998 with intense rotary vertigo, loss of balance, left facial paresthesia, and a sensation of “warmness” on his right side. Examination showed severe left static and kinetic ataxia, multimodal anesthesia of the left face and tongue, left velar and pharyngeal paresis, Horner’s syndrome, and oblique diplopia. He also suffered from severe thermal and pain anesthesia on the right side, which did not involve his facial and upper cervical areas. Muscle strength was normal. Superficial and deep somatosensory perceptions were slightly reduced on the left leg, but this disorder rapidly disappeared. MRI (T2 sequences) showed a left posterolateral medullary hyperintensity (Figure 2). Angiographic MRI revealed no flow in the left vertebral artery.

The patient slowly recovered his sense of balance and recovered from the swallowing disorder. During the rehabilitation stay, he occasionally had brisk withdrawal reactions of the right arm when touching warm objects (such as a coffee cup). As in the case of patient 1, he learned to control these reactions when approaching warm objects. He also noticed that prolonged contact with warm objects caused deep pain in his fingertips. This feeling was clearly different from any previous experience of pain and from what was perceived on the contralateral side. This pain was described as deep, osseous, and articular. After discharge from the rehabilitation unit, he was severely burned by oil on the right hand while cooking. He perceived pain immediately, but the perception rapidly disappeared, which contrasted with the persistence of severe cutaneous traces for a few weeks.

Evaluation of Sensory Disorders
These evaluations were performed at 6 months for patient 1, with a follow-up 5 years later, and at 1 month in patient 2, with a follow-up at 4 months. Both patients gave their informed consent to participate in the study.

Superficial and Deep Discriminative Sensibilities
Superficial and deep sensibilities were assessed using light touch (from 0 [no tactile perception] to 4 [perception of light
touch using a cotton wool string, without left-right asymmetry], 2-point discrimination, perception of Seemes-Weinstein monofilaments (J 4.31 and F 3.61 at the extremity of each finger), graphesthesia (hands), position sense (small angular displacements; from 0 [no perception] to 4 [perception of a passive movement of 0° to 5°, without sensation of left-right asymmetry]), and pallesthesia (tuning fork) (Table). All were normal in patient 1, especially on the extremities of the upper limbs. Patient 2 had multimodal left facial hypesthesia (trigeminal deficit), mainly in the peribucal area, and discrete right foot hypesthesia (light touch). Discriminative sensitivities were perfectly preserved on the other segments of the body, especially on the upper limbs.

### Perception of and Reactivity to Thermal Stimuli

#### Subjective Perception and Discrimination of Thermal Stimuli (0°C to 45°C)

The patients’ hands were placed in water at temperatures of 0°C to 45°C. Patient 1 had no subjective perception of temperature on his affected hand, and was unable to discriminate between 2 temperatures (0°C and 15°C; 0°C and 30°C; 0°C and 40°C; repeated forced-choice recognition), whereas this ability was perfectly preserved on his nonaffected hand. Patient 2 reported uniform perception of “lukewarmness” on his affected hand, whatever the temperature, but his subjective perception was normal on the nonaffected side. He was also unable to discriminate between temperatures.

#### Perceived and Reactivity to Heat (>45°C)

The patients’ hands were placed briefly in hot water (45°C to 55°C). We measured the time (in seconds) to the appearance of subjective perception and the intensity of perception (from 0 [no pain] to 100% [unbearable pain]). Patient 1 reported distal pain, deep and osseous, in his affected hand, with a threshold of 47°C and with an 8- to 10-second delay. This delay was much shorter at higher temperatures (at 50°C, 3 seconds; at 55°C, 1 to 2 seconds), but the response was never immediate. Pain persisted for 2 to 3 seconds after withdrawal.

### Upper Limb Examination in Both Patients

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<td>RIII latency, ms</td>
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<td>RIII threshold (stimulus intensity), mA</td>
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<td>RIII latency, ms</td>
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of stimulation. He felt no sensation from prolonged immersion (up to 15 seconds) in water at 45°C or 46°C. Pain perception had a lower threshold (44°C) and was more rapid on his nonaffected hand. These results for the first (6 months) and follow-up (5 years) examinations were very similar.

Patient 2 had a very similar pattern of perception. The delay was 8 to 10 seconds at the threshold temperature (49°C), and the subjective intensity was 40/100. The delay was shorter at higher temperatures (at 50°C, 4 seconds; at 55°C, 1 to 2 seconds), and the intensity increased with prolonged exposure (eg, at 51°C: 40/100 at 4 seconds and 70/100 at 8 seconds).

The onset of pain was associated with a controllable need for hand withdrawal in both patients. Reactions to higher temperatures were not assessed. The exposure to the 55°C stimulation was always brief (<2 to 3 seconds). No patient had any persistent pain or cutaneous lesion resulting from the stimulations.

Subjective Perception and Reactions to Cold (<0°C)
We investigated the patients’ reactions to cold stimuli by placing an ice cube in the hand for 30 seconds, placing the hand in a container filled with ice cubes for 30 seconds, and by slowly moving ice over the skin of the limbs and trunk to test for allodynia. Patient 1 had no subjective sensation of cold or pain when an ice cube was placed in his affected hand. Placing the hand in ice elicited a moderate pain reaction (25/100) of the fingers and hand after 15 seconds, which intensified somewhat after 20 seconds (40/100). Cold perception by the right hand was immediate, and a pain reaction occurred after 8 to 10 seconds. The subjective quality of the pain on the 2 sides was clearly different. The pain on the affected side was described as deep, osseous, and identical to that perceived using warm stimulation (>47°C). Cold stimulation never elicited allodynia. Patient 2 had no subjective sensation of cold or pain in any condition on his affected side, whereas his reactions on the nonaffected side were normal.

Perception of and Reactivity to Pain
Subjective Perception of and Reactions to Pinpricks, Hair-Pulling, or Mechanical Stimulation
On repeated stimulation, neither patient had any pain sensation in his affected arm or leg (case 1, left side; case 2, right side) or his trunk, with a clear-cut vertical limit. Pain perception, however, was perfectly preserved on the contralateral side. Strong mechanical stimulation applied to the fingers or hand did not elicit pain.

Subjective Perception of and Reactions to Laser Stimulation
The subjective thresholds of pain were evaluated using brief (1 millisecond) thulium laser stimulation of the dorsum of the hand, following the Treede procedure and using a skin area 5 mm in diameter, with each stimulus in a different place; the intensity was gradually increased then decreased (5 times). Patient 1 had a higher threshold value on his affected side (mean±SD 468±48 mJ) than on his nonaffected side (mean±SD 311±60 mJ) or control values (mean±SD 319±65 mJ). Similar results were obtain with patient 2, with an increased threshold on the affected side (mean±SD 838±71 mJ), in comparison with the nonaffected side (mean±SD 474±54 mJ).

Electrophysiological Investigations
The following investigations were performed to assess the function of the main somatosensory pathways.

Somatosensory Evoked Potentials
The median nerve was stimulated at the wrist level by electrical square-wave pulses (0.1 ms duration; 5.1 Hz). Stimulus intensity was adjusted to produce a minimal thumb movement. Recording was performed with use of active electrodes: they were placed at the Erb’s point, at the cervical level, and at the parietal scalp area (C3 and C4, 2 cm behind C3 and C4, as defined by the Internation 10–20 System), with an ipsilateral or contralateral earlobe reference electrode. Two series of 500 to 1000 acquisitions were necessary to ensure the reproducibility of the waveform. In both patients, parietal potentials (N20) were of normal and symmetric latencies and amplitudes (Figure 3).

Laser Evoked Potentials
The dorsum of the hand was warmed with a thulium laser, with a stimulus length of 1 ms; each stimulus in a different place; 2 series of 20 stimuli each; 8- to 12-second intervals; and intensity of 2× the subjective nociceptive threshold for the “normal” side, without exceeding 700 mJ (600 mJ in the first patient and 700 mJ in the second). Recording electrodes were placed over Cz, reference to linked earlobes. The patients’ evoked potentials were compared with those obtained in 15 normal adults, ranging in age from 20 to 62 years (mean 33 years). No potential was recorded for either patient when the affected side was stimulated (Figure 4). When the preserved side was stimulated, the latency of the negative potential (N1) was 194 ms in patient 1 and 304 ms in patient 2 (control values [mean±SD] 199±18), and the latency of the main positive potential (P2) of 432 ms in patient 2 (control values 325±37). This late potential was difficult to evaluate in patient 1, because the amplitude was severely reduced; he suffered from marked hyperhidrosis on the left side of the scalp and trunk, which could have contributed to the reduction in amplitude when the preserved right hand was stimulated. The amplitude of both potentials (N1 and P2) was normal in patient 2.

The RIII Noxious Reflex
This study evaluated withdrawal reactions to electrical stimulations. The patient laid comfortably in a reclining armchair. Each upper limb was stimulated using electrical stimulation by trains (8 pulses at 400 Hz, 0.1-ms duration) of the ulnar nerve at the wrist (Viking LE, Nicolet). Responses were recorded from surface electrodes placed over the wrist flexors (flexor carpi radialis). Stimulus intensity ranged from 0.1 mA to 30 mA. In the second patient, lower limbs were assessed similarly (sural stimulation at the ankle; biceps femoris recording). On the upper limbs, both patients had a higher response threshold (intensity evoking the RIII reflex with a probability of 80% to 90%) on the affected side than on the nonaffected side. Patient 2 had similar results in the lower limbs (Figure 5). Both patients experienced pain on the
Discussion

We found that a specific type of pain could be elicited by thermal (hot or cold) stimulation of patients with a major spinothalamic injury without evidence of lesion of thelemniscal pathway, once a specific threshold was exceeded. Thermal and electrical stimulation of the affected side elicited withdrawal reactions. Noxious mechanical stimulation was not clearly associated with a sensation of pain and avoidance reaction.

The consequences of severe spinothalamic injury have been investigated in patients presenting with spinal cord lesion. In 2 cases of unilateral injury of the lateral column, Wall and Nordenbos\textsuperscript{12} reported complete insensibility to cold and warm tubes of water on the contralateral side. After bilateral infarction of the anterior two thirds of the cord, Nathan et al\textsuperscript{13} described lost sensation of all painful and thermal stimuli caudal to the lesion (T12). Pinprick was felt as touch. Light touch (cotton, von Frey hairs), 2-point discrimination, and position sense were remarkably preserved, as was graphesthesia. In other patients with unilateral or bilateral anterolateral cordotomy for treating pain due to malignant disease, the sense of movement, knowledge of position, and light touch were similarly preserved.\textsuperscript{13,14} The spontaneous perception of pain was usually reduced in association with reduction in pinprick perception,\textsuperscript{15,16} but pinprick anesthesia was often incomplete. In some descriptions, the greatest deficits were reported to be in the sensation of skinfold pinch and skin cooling.\textsuperscript{15} In others, the loss of temperature sensation was discrete or even absent.\textsuperscript{16} However, in any patient, the perception of relatively high temperature was not assessed.

A lateral medullary infarct is a useful model for investigating the consequences of a selective and severe lesion of the spinothalamic tract.\textsuperscript{8,9,17–19} The severity of the spinothalamic injury in both of our patients was clearly confirmed by the

Figure 3. Somatosensory evoked potentials in patient 2, who presented with a left lateral infarct without impairment of discriminative sensitivities. Potentials are normal on both sides (C’3, C’4), with right (R) or left (L) median nerve stimulation.

Figure 4. Laser evoked potentials in patient 2, who presented with a right anesthesia for pain and heat. There is an absence of any potential when stimulating the right affected side (R) in comparison with the left preserved side (L), which confirms the severe injury of the spinothalamic pathway (intensity of stimulations 700 mJ).
The main finding in both cases of this study was that thermal stimulation did not evoke a sensation of heat or cold but was able to produce pain. This was especially evident in the second patient using pinprick, hair-pulling, and strong mechanical stimulation. In both cases, the dissociation between the preservation of discriminative sensitivities and the alteration of heat and pain perception was more severe and relatively different from what has been described by Casey et al.\textsuperscript{24} in patients with cortical, thalamic, or brain stem lesions.

This raises the question of the mechanism underlying this perception. Assuming that the function of the spinothalamic tract ipsilateral to the lesion is severely altered, there are 3 hypotheses. The first is that perception is conveyed by the spinoreticulothalamic pathway.\textsuperscript{25} This tract, due to its internal location, can be relatively preserved in Wallenberg syndrome. It has projections to the medulla, pons, mesencephalon, and internal thalamus. Its electrical stimulation has no definite consequence in patients with nociceptive pain. In the case of deafferentation pain,\textsuperscript{25} stimulation is able to elicit contralateral burning and pain perception (denervation hypersensitivity). This preservation could explain inferior limb allodynia in the second patient. On the hand of the affected side, the perception of pain was relatively different. No patient reported hyperesthesia or burning sensation, which are 2 main components of the classical allodynic syndrome. The perception was relatively diffuse and deep, however, which could correspond to what we know about the spinoreticulothalamic tract.\textsuperscript{25} A second hypothesis is that pain is mediated by the spinopontoamygdalar pathway, which has been described in animals.\textsuperscript{2,31} However, in humans, activation of the amygdala was not observed in allodynia elicited by subcutaneous capsaicin injection in normal subjects or by cold stimulation in Wallenberg syndrome.\textsuperscript{9,27} The third hypothesis would be that the way to the cortex is contralateral to the infarct and ipsilateral to the affected hemibody. In this alternative, there are at least 3 possible candidates: the ipsilateral spinothalamic, spinoreticulothalamic, and spinopontoamygdalar tracts. Bilateral projections of these systems exist in animals.\textsuperscript{28–30} The lemniscal system may also be involved, because it may take part in visceral nociceptive perception\textsuperscript{2,31}; however, there is no evidence that this pathway plays a role in cutaneous pain. The information processing to the cortex is slow and multisynaptic, as indicated by the delay between the stimulation application and the occurrence of painful sensation.

Patients can still present with motor withdrawal reactions to noxious stimulation, and principally to warm stimulation. The reaction threshold is difficult to evaluate for thermal stimulation. Our clinical observation suggests that, in the first few weeks or months following a stroke, when patients had no experience with their new condition resulting from the spinothalamic tract lesion, avoidance reactions could occur without control. The withdrawal movement was unexpected and could prevent the patient from picking up warm objects. However, the reflex movement could be inhibited later, at least if the noxious character of the stimulus was relatively limited, as when holding a coffee cup. Thus, warm objects could be manipulated without any great problem.

Electrical stimulation gives a more precise evaluation of the reflex response to noxious stimuli. The threshold on the affected side was higher than the threshold on the normal side, as described by other authors.\textsuperscript{7,8,32} Garcia-Larrea et al.\textsuperscript{32} found that in patients with cervicothoracic anterolateral corotomy, the contralateral RIII reflex was always dissociated from subjective pain, e.g., present in the absence of pain perception. Our patients reported disagreeable perception and discrete pain on the affected side. This suggests that pain can also be elicited by nonthermal stimuli. The persistence of
avoidance reactions in such patients is clearly explained by the spinal location of the reflex loop. Roby-Brami et al. showed that the RIII nociceptive reflex is still present in tetraplegic patients suffering from a complete spinal cord transection at the cervical level and that the mean threshold is similar to that of normal subjects.

The increased threshold on the side contralateral to the lesion in patients with spinothalamic injury suggests the lesion of facilitator systems arising from higher structures located in the brain stem or hemisphere, or the relative release and facilitation of inhibitory systems.3,4 Both the first includes spinoreticular fibers to the medial reticular nuclei gigantocellularis and magnocellularis.35 A lesion of this includes spinoreticular fibers to the medial reticular nuclei in patients.8 The second includes the antinociception structures of possible uncontrolled reflex responses to noxious stimuli.

When lesions of spinoreticular fibers to the medial reticular nuclei in patients showed that the RIII nociceptive reflex is still present in tetraplegic patients suffering from a complete spinal cord transection at the cervical level and that the mean threshold is similar to that of normal subjects.

In conclusion, patients with Wallenberg syndrome and severe spinothalamic lesions are still able to perceive pain and retain avoidance reactions to some forms of stimulation, mostly thermal. This helps to explain the relative protection from most aggressive stimulations encountered in daily life. Patients admitted for neurological evaluation or rehabilitation must be informed and made aware of their residual perceptions and of possible uncontrolled reflex responses to noxious stimuli.

References
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