

# Laser-evoked Potentials Correlate With Clinical Evolution in a Case of Spontaneous and Recurrent Complex Regional Pain Syndrome Type I

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**Abstract:** We describe a case of spontaneous complex regional pain syndrome developing first in the left arm and 2 years later in the right foot of a 14-year-old girl. Physical examination showed abnormalities in tactile and thermal sensitivity. Laser-evoked potentials (LEPs) after stimulation of the affected right foot were absent in the acute phase and then progressively recovered over a period of 5 months, in correlation with clinical changes. To our knowledge, no systematic analysis of LEPs in complex regional pain syndrome has been published. We suggest that the observed electrophysiologic alterations could result from a temporary dysfunction of attentional systems, which are assumed to contribute greatly to the LEPs vertex complex. Further studies are needed to test this hypothesis.

**Key Words:** complex regional pain syndrome, laser-evoked potentials, chronic pain

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Complex regional pain syndrome (CRPS) is still poorly understood. In its typical form, it consists of regional pain as well as sensory, motor, and trophic changes appearing after a noxious event. The magnitude of the changes is disproportionate with respect to the severity of the initiating event.<sup>1</sup> Diagnostic criteria have been established,<sup>1</sup> but are currently under discussion,<sup>2,3</sup> and several questions remain unanswered. For example, the initiating event may be absent, the pain may spread from the site of injury to other parts of the body,<sup>4</sup> and some recurrent cases have been described.<sup>5–7</sup> Furthermore, the pathophysiology of this syndrome remains much debated, as both peripheral and central mechanisms are probably intricately.

We describe a case of spontaneous CRPS developing first in the left arm and then in the right foot of a 14-year-old girl. Laser-evoked potentials (LEPs) and psychophysical variables from the right foot were abnormal during the acute stage and then progressively

recovered, suggesting central dysfunctions that will be discussed.

## CASE STUDY

At 14 years of age (February 2000), female patient T.S. presented with pain, increased skin temperature, and functional disability in the left arm; the symptoms and signs appeared spontaneously and were diagnosed, in another hospital, as a CRPS type I. According to the available information, neurologic examination was normal. A bone scintigraphy showed diffusely decreased uptake in the left upper arm. Treated with calcitonin, the episode resolved within 4 months.

At 16 years of age (October 2002), the patient consulted at the Multidisciplinary Chronic Pain Center with pain and edema of the right lower leg. There was still no history of trauma or of any other initiating event. She appeared smiling, but was reserved and shy. She worried about the spontaneity and recurrence of the problem. Symptoms began at the toes and rapidly extended to the whole leg. She complained of muscle weakness and numbness. Episodes of swelling, redness, and warmth alternated with episodes of paleness and coldness. Pain was increased by psychologic stress, tiredness, effort, hot weather, and during menstruation. It was reduced in decubitus, by application of cold and during holidays. Pain was located in the right ankle, knee, and hip; it restrained walking, running, and stairs climbing. The patient, a single child living with her parents, had no problems at school. She danced about 10 hours per week since her fifth year of age but had to stop dancing and also to reduce hobbies and social life because of the pain.

On May 15, 2003, that is, 6 months after the start of the complaints, a first physical examination showed that the right foot was colder (25.5°C) and paler than the left one (29.0°C). Tactile hyperalgesia was diffusely observed at the right leg. Passive range of motion, muscle tone, and muscle strength were normal except for an ankle dorsiflexion deficit of 5 degrees and a small deficit of strength of the left *abductor digiti minimi*. Reflexes were present and symmetric. Complete blood counts and Borrelia serology were normal.

Tactile sensitivity thresholds measured with Semmes-Weinstein filaments for the left and right hands were close to normal, 7.9 g/mm<sup>2</sup> and 6.7 g/mm<sup>2</sup>, respectively (normal values 5.0 to 7.2 g/mm<sup>2</sup> in our laboratory). Thresholds at the right foot were markedly increased compared with the left foot, 13.8 and 6.3 g/mm<sup>2</sup>, respectively.

Thermal sensitivity thresholds were measured with contact heat (Thermotest, Israel). Heat pain threshold was normal at the right hand and decreased at the left hand (45.6°C and 38.1°C, respectively). Both legs showed no perception of heat below 43°C. Above that temperature a burning sensation was reported bilaterally.

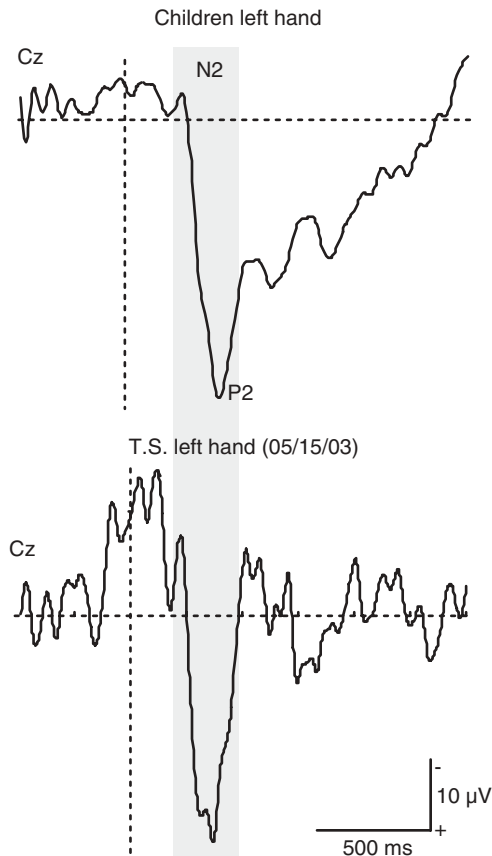
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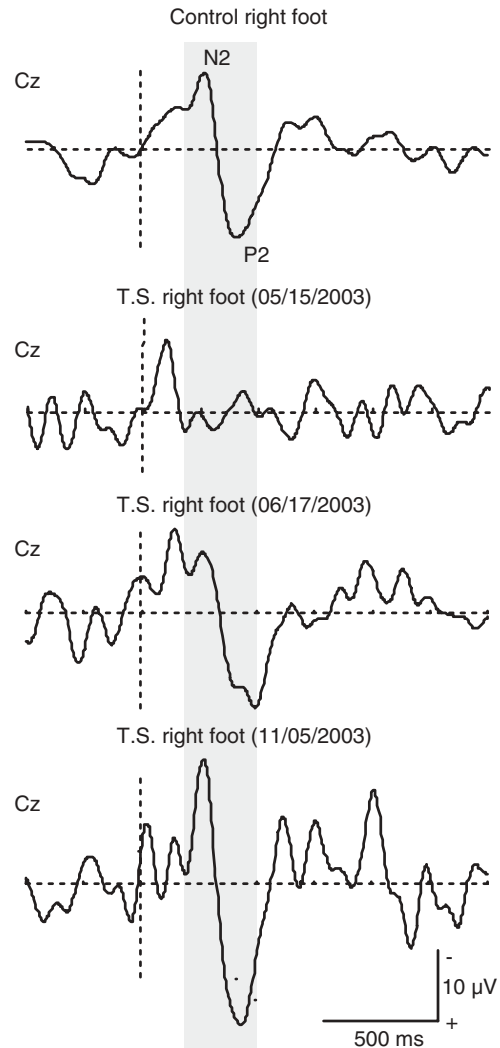
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LEPs were recorded with stimuli of 50-ms duration and a surface area of 80mm<sup>2</sup>. Each examination consisted of 2 sessions of about 20 minutes, each exploring a different body region. A minimum of 30 and a maximum of 50 laser stimuli were delivered during each session, depending on the quality of the recording (eg, ocular artifacts). For a detailed description of the methods, see Ref. 8. About 6 months after the beginning of symptoms in the right foot (May 15, 2003), no LEPs could be detected after stimulation of the right foot dorsum (Fig. 1). The patient did not perceive laser stimuli with intensities of up to 10 mJ/mm<sup>2</sup>. In healthy participants, such stimulus intensities are largely supraliminal for A $\delta$ -nociceptors. Unfortunately, the left foot was not explored with laser stimuli. At the same date, LEPs recorded after stimulation of the left hand were within normal limits regarding shape, latencies, and amplitudes of the N2-P2 complex recorded at the vertex (Fig. 2). Absolute and pain detection thresholds after laser stimulation of the left hand (method of limits) were similar to those obtained in healthy children (second column Table 1). Stimuli were perceived as “pricking pain” and reaction times were short, compatible with the activation of A $\delta$ -nociceptors.



**FIGURE 1.** LEPs recorded at the vertex (electrode Cz) after stimulation of the left hand dorsum in healthy children (grand mean, n=12) and in patient T.S. Number of stimuli, stimulus intensities, latencies, and amplitude of the N2-P2 complex and the area under the curve corresponding to the 200 to 500-ms time interval (gray-shaded zone) are given in Table 1. For a detailed description of experimental protocol, laser stimulator, and electroencephalogram recording parameters, see Ref. 8.



**FIGURE 2.** LEPs recorded at the vertex (electrode Cz) after stimulation of the right foot dorsum in healthy adults (grand mean, n=18; no age-matched records were available) and at 3 different periods (dates in brackets) in patient T.S. Number of stimuli, stimulus intensities, latencies, and amplitude of the N2-P2 complex and the area under the curve corresponding to the 200 to 500-ms time interval (gray-shaded zone) are given in Table 1. For a detailed description of experimental protocol, laser stimulator, and electroencephalogram recording parameters, see Ref. 8.

On June 17, 2003, that is, 7 months after the start of the complaints, LEPs recorded after stimulation of the right foot were similar to those recorded after stimulation of the left foot and comparable to those in healthy adults (no age-matched normative data are available; see third column of Table 1). However, this amplitude was still below the expected values for children.<sup>8,9</sup> Nevertheless, absolute and pain detection thresholds were still abnormally high and detection performance was deteriorated in particular for stimuli directed to the right foot. The sensations, described as “pricking” and “burning,” were less intense at the right foot compared with the left foot. Median reaction times were slightly delayed but compatible with detection of A $\delta$ -nociceptor activation.

**TABLE 1.** Skin Temperature, Stimulation Parameters, Psychophysical and LEP Data in Healthy Participants (Children and Adults) and Patient T.S. (at 3 Different Time Periods)

Date of tests (mm/dd/yy)	Control Children	Control Adults	Patient T.S.					
	Hand	Foot	Left Hand	Left Foot		Right Foot		
			05/15/03	06/17/03	11/05/03	05/15/03	06/17/03	11/05/03
Skin temperature (°C)	32.2 ± 1.4	29.4 ± 1.7	33.3	28.0	29.9	25.5	27.1	28.0
Stimulus intensity (mJ/mm <sup>2</sup> )	5.8	9.2	8.7	8.5	11.1	8.7	8.5	11.1
No. laser stimuli	40	40	40	35	40	30	50	40
Absolute threshold (mJ/mm <sup>2</sup> )	1.1 ± 0.41	4.8 ± 1.6	0.8	6.2	7.3	> 10	—	7.3
Pain threshold (mJ/mm <sup>2</sup> )	4.0 ± 2.1	9.2 ± 0.8	4.0	> 10	9.2	> 10	—	> 10
Reaction time (ms) median	710	365	437	527	677	n.a.	611	1138
Reaction time (ms) IQR	477	88	162	114	312	n.a.	325	1215
Detected stimuli (%)	100	100	95	80	95	0	42	90
N2 (ms)	248 ± 82	273 ± 24	222	297	275	n.a.	275	293
P2 (ms)	433 ± 104	427 ± 36	311	375	437	n.a.	353	479
Amplitude N2-P2 (µV)	71 ± 35.0	26 ± 10.1	44.9	18.2	27.2	n.a.	21.5	39.5
AUC µV (200-500 ms)	8.43	2.78	6.55	1.95	2.52	0.44	2.50	4.05

Mean ± standard deviation.

AUC indicates area under the curve; IQR, interquartile range; n.a., not applicable.

On November 05, 2003, that is, 11 months after the start of the complaints, the vertex complex of LEPs was normal after stimulation of both feet. Peak-to-peak amplitude and area under the curve of the N2-P2 complex was considerably increased compared with the previous records, especially for stimulation of the right foot, but may be considered as normal, given the fact that the amplitude of that complex is very significantly negatively correlated with age.<sup>9</sup> Yet, absolute and pain detection thresholds were still abnormally high. The qualities of sensations evoked by the laser stimulus were comparable to those reported in the previous session. Although detection performance was greatly improved, it was at the expense of considerably increased reaction times.

Treatments proposed for the current pain episode included calcitonin (interrupted because of gastric complaints), paracetamol-codein (small relief of pain with unbearable side effects such as vertigo, nausea, and sleepiness), tramadol (250 to 350 mg a day: pain reduction, nausea), gabapentin (300 mg 3 to 8 times a day: pain reduction, sleepiness), and piroxicam (gastralgia). Physiotherapy was difficult to perform because of the pain. Supportive psychotherapy and relaxation were also initiated. After 2 years of follow-up, analgesics have been discontinued. The pain is markedly reduced and functional limitations are limited to activities such as long distance walking.

### DISCUSSION

In 1994, the International Association for the Study of Pain (IASP) has revised the taxonomic system for disorders previously called Reflex Sympathetic Dystrophy (RSD)<sup>1</sup> and described 4 diagnostic criteria and 2 types of CRPS. The present case fulfils 3 of the 4 diagnostic criteria of CRPS, as presence of an initiating noxious event is missing. However, according to several authors,<sup>2,10</sup> the presence of an initiating event is not required for diagnosis.

There is little data on whether there may be recurring symptoms in children and adults. Rush et al<sup>6</sup> described 1 child with recurrence and involvement of multiple sites. Greipp et al<sup>5</sup> reported that, in a group of

27 children and young adults, 55% had migration and extension of their symptoms. Tong and Nelson<sup>7</sup> described 1 case that was not only recurrent but was also slowly progressive in severity. Maleki et al<sup>11</sup> described 3 patterns of spread of CRPS type I, 2 of which could apply to the present case (independent spread and contiguous spread). Therefore, the present case may be considered as a type I CRPS despite the absence of an initiating event and the recurrence of symptoms in different body regions.

Infrared laser stimulators allow selective activation of Aδ- and C-nociceptors located above the dermo-epidermal junction.<sup>12</sup> After painful laser stimulation, evoked potentials recorded over the scalp of healthy participants are compatible with brain responses to signals ascending through Aδ-fibers. Ultra-late LEPs, related to signals ascending through C-fibers, are only recorded when C-nociceptors are activated in isolation.<sup>12</sup> The brain generators most consistently associated with LEPs are the suprasylvian region (parietal operculum, SII/Insula) and the anterior cingulate cortex.<sup>13</sup> This topography, but also the clear relationship to dynamic aspects of arousal and attention of these late vertex potentials, suggests that they are mostly related to the motivational and cognitive components of pain.<sup>14</sup> For instance, there is converging evidence that these potentials may underlie orienting responses.<sup>13</sup> In other words, LEPs reflect the overall functional state of the nociceptive system rather than simply the intensity of subjective perception.<sup>14</sup> The absence of LEP components may result from a lesion or dysfunction localized anywhere between the peripheral stimulation site and the cerebral cortex. Corollary, the absence of LEP components does not provide the location of the lesion in a patient without additional clinical, electrophysiologic, or imaging data.<sup>15</sup>

In the present case, the absence of LEP components during the acute phase and the progressive recovery of the brain responses, in conjunction with the improvement of the clinical status, could not be attributed to a selective

pathology of A $\delta$ -nociceptors, because in this case, an ultra-late LEP related to the concomitant activation of C-fiber nociceptors should have been observed in a time window of 900 to 1200 ms.<sup>12</sup> It could not either be ascribed to a systemic failure of the nociceptive system, as laser stimulation of the upper and contralateral limbs evoked brain responses within the normal range. It is worthwhile to recall the observations of Truini et al<sup>9</sup> that in some normal but elderly participants, LEPs could barely be detected after stimulation of the foot. However, this was not the case for the younger participants as the amplitude of the N2-P2 complex was very significantly negatively correlated with age. Finally, neurologic examination was normal except for the atypical pattern of sensory disturbances during the acute and subacute phases: increased threshold for tactile sensitivity at the right foot but normal thresholds in left hand and left foot, allodynia for contact heat at the left hand but hyperpathia for contact heat in both feet and normal thresholds for C-fibers (absolute detection threshold) and A $\delta$ -fibers (pricking pain detection threshold) activated by radiant heat directed to the left hand but abnormally high thresholds for both feet. The latter contrasts with the nearly normal performance in percent detection and rather short reaction times to stimulation of the left hand and foot compared with the right foot. Taken together, these observations point to a transitory dysfunction in supraspinal networks processing somatosensory information, which are known to be modulated by emotional and cognitive factors.

Attention modulates cortical body representation and activity in somatosensory cortical networks.<sup>16–18</sup> The effects of attention are primarily mirrored in the somatosensory association cortex S2 and anterior cingulate cortex,<sup>19</sup> both contributing greatly to the generation of LEPs. The N2-P2 complex of LEPs is reduced in amplitude by distraction tasks like calculation and memorization.<sup>20,21</sup> Similarly, decreases of LEPs amplitude have also been shown to accompany sedation and drowsiness after sleep deprivation<sup>20,22</sup> or administration of benzodiazepines.<sup>23</sup> LEPs disappear completely during non-rapid eye movement sleep.<sup>18,22</sup> In severely demented patients<sup>24</sup> and posterolateral thalamic strokes,<sup>25</sup> the amplitude of LEPs is also considerably reduced or even absent in several cases. As a rule, both conditions present with attentional disturbances. The large effect of attention on the modulation of LEPs and the frequently reported attentional deficits and disturbances of the self-perception in CRPS indicate an alteration of higher central nervous system sensory processes, involving more specifically the orienting system.

Patients with CRPS tend to ignore the affected limb rather than to focus their attention to it. Several investigators have reported neglect-like symptoms,<sup>26,27</sup> disturbed self-perceptions<sup>28</sup> and mental representations of movements<sup>29</sup> in the affected extremity of a subgroup of patients. These phenomena were positively correlated with the severity of pain, illness duration, and the extent of sensory deficits. The neglect syndrome is thought to

reflect dysfunction in the central nervous system orienting system, the purpose of which is to use sensory information to alert and set motor programs in response to novel and significant internal and environmental stimuli.<sup>30</sup> In the present case, pain and sensory disturbances were most prominent in the affected region during the acute phase (Table 1). It is, therefore, tempting to hypothesize that neglect-like phenomena may have contributed to the abolition of LEPs during the acute phase, and may possibly also explain the progressive recovery of these brain signals with improvement in the clinical status.

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