Dystonia in complex regional pain syndrome : clinical, pathophysiological and therapeutic aspects

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Hyperacusis in patients with Complex Regional Pain Syndrome related dystonia

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Abstract

Introduction: In Complex Regional Pain Syndrome (CRPS), patients may have manifestations of central involvement, including allodynia, hyperalgesia or dystonia. We noted that more severely affected patients may experience hyperacusis, which may also reflect central involvement. Aim of this study is to evaluate the occurrence and characteristics of hyperacusis in patients with CRPS related dystonia.
Methods: Presence of hyperacusis, speech reception thresholds (SRT), pure-tone thresholds (PTT) and uncomfortable loudness (UCL) were evaluated in 40 patients with CRPS-related dystonia.
Results: PTT and SRT were normal for all patients. Fifteen patients (38%) reported hyperacusis and this was associated with allodynia/hyperalgesia and with more affected extremities. UCLs of patients with hyperacusis were significantly lower than UCLs of patients without hyperacusis.
Conclusion: Hyperacusis is common among severely affected patients with CRPS related dystonia and may indicate that the disease spreads beyond those circuits related to sensory-motor processing of extremities.

Introduction

Complex Regional Pain Syndrome (CRPS) is frequently preceded by a trauma (70-90%). In the acute phase, the clinical presentation is dominated by various combinations of sensory and autonomic symptoms and signs.[1,2] Some patients with chronic CRPS may also develop movement disorders (MDs) like tremor, myoclonia and dystonia.[3]
Because of our clinic's special interest in MDs and CRPS, we had the opportunity to evaluate the more severely affected patients in whom CRPS evolved into a disabling disorder with prominent dystonia of multiple extremities. In the course of these evaluations, we noted that some patients reported hyperacusis,[4] that is, an intolerance of ordinary sound levels. Hyperacusis is primarily associated with painful sensations to sound, which eventually may result in avoidance-like behavior, whereas phonophobia is an anxious sensitivity towards specific sound, largely independent of its volume.[5] Contrary to phonophobia, hyperacusis is not directly related to fear to sound.[6] Hyperacusis can arise from damage to the inner ear and 8th nerve, but has also been associated with central nervous system involvement as may occur in migraine.[7,8]
In CRPS, patients may experience an increased response to a painful stimulus (hyperalgesia) or even pain when the skin is gently touched (allodynia). Both sensory features have been associated with abnormal excitability of nociceptive neurons within the central nervous system, a process known as central sensitization.[9] Pathophysiological studies in CRPS have provided evidence of functional changes at different levels of the central nervous system changes.[10,11]
Taken together, the increased sensitivity to ordinary sound levels in patients with CRPS may suggest that this is yet another manifestation of central involvement in this disorder. Against this background we evaluated the occurrence and characteristics of hyperacusis in patients with CRPS related dystonia.

Methods

Patients

Patients with a diagnosis of CRPS and dystonia in one or more extremities who were referred to our department for treatment of dystonia between January 2000 and May 2006, were included in this study. Patients were generally referred from pain clinics and from departments of anaesthesiology, rehabilitation medicine and surgery. Patients had to meet the CRPS diagnostic criteria of the International Association for the Study of Pain (IASP).[12] According to these criteria patients must have (1) continuing pain, allodynia or hyperalgesia, in which the pain is disproportionate to any inciting event, (2)

evidence at some time of oedema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain, and (3) no condition that would otherwise account for the degree of pain and dysfunction. Exclusion criteria were other disorders that could cause auditory impairment. The study protocol was approved by the hospital ethics committee and all patients gave informed consent.

Audiogram

Pure-tone audiogram thresholds (PTT), uncomfortable loudness (UCL) and speech reception thresholds (SRT) were assessed with an ENT audiometer by a certified audiologist using a standard method.[13,14] Briefly, for the determination of PTT, patients wearing a headphone had to press a button when they heard a tone in the frequency range of 250-8000 Hz that was presented at 5 dB increments (within the range of 0 dB to 120 dB). To establish the patient's UCL, tones were presented in similar manner as for determination of the PTT and patients had to indicate when they considered the sound level as uncomfortably loud. The speech reception threshold was determined with the standard CVC (Consonant-Vowel-Consonant) word list on CD (prerecorded female speaker) of the Dutch Society of Audiology.[15] All words were balanced on a rms level, sub-lists were homogeneous with regard to speech reception scores and normative values were available. Each list consisted of equivalent sub-list of 11 Dutch three-phoneme monosyllables. Based on the individual pure tone threshold, tests were done at a fixed presentation level around the pure tone threshold. The first list of words is always presented at a level of +20 dB above the threshold. For most subjects this will result in a 100% phoneme score. Afterwards, lists are presented at levels in steps of 10 dB down until the subject can hardly understand the tokens and reaches a score below 50%. The threshold is then determined by simple linear interpolation of the percentages found for the levels just above and below 50%.

For the PTTs and UCLs a low Fletcher Index (FI-low: mean over the frequency range 500 Hz-2000 Hz) and a high Fletcher Index (FI-high: mean over frequency range 1000 Hz-4000 Hz) were calculated. In general, normal values for the SRT and PTT do not exceed 20dB.[16] An UCL threshold of 100 dB is considered normal and values below 100 dB indicate the presence of hyperacusis.[17]

Clinical characteristics

Demographic and clinical information was collected and included pain intensity, number of affected extremities, type of motor impairments, presence of allodynia or hyperalgesia, and presence of hyperacusis. Additionally, the Pain Coping and Cognition List (PCCL) was administered.[18] The PCCL includes a subscale on pain catastrophizing (12 items), which was used as an approximate to assess the potential relation between a more focused attention to external stimuli and hyperacusis.

Data analysis and statistics

Data were analyzed with SPSS 12.01 (SPSS Inc., 2003), using parametric tests for normally distributed continuous data and non-parametric tests for other data. Pearson's correlation coefficient was used to compare SRT, PTT, and UCL between both ears of each patient. The significance threshold was set at $p<0.05$.

Results

Demographic information and CRPS characteristics of the forty included patients are presented in table 1, whereas table 2 enlists the differences in CRPS characteristics between patients with and without hyperacusis.

Since the correlations of SRTs, PTTs, and UCLs (both for FI-low and FI-high) between the right and left ear of each patient were high (all > 0.7; $p< 0.001$), we used the mean thresholds of both ears in the subsequent analyses. The SRT and the PTT (FI-low and FI-high) for all patients were within the normal range (Table 3). The mean UCL for both FI-low and FI-high were significantly lower ($p <0.001$ for both thresholds) in our patient group compared to the normal population value of 100 dB.

Patients with hyperacusis had significantly lower UCLs at all the indicated frequencies compared to patients without hyperacusis (Figure 1). Disease duration did not differ significantly between patients with hyperacusis (13.1 years) compared to patients without hyperacusis (10.4 years; $p = 0.365$). Seven of the 15 patients with hyperacusis reported tinnitus.

Thirty-one patients had 3 or 4 affected extremities of which 15 reported hyperacusis. Interestingly, none of the nine patients with 1 or 2 affected extremities reported hyperacusis (Fisher's exact test, $p =0.015$). However, patients with 1 or 2 affected extremities did not differ significantly in UCL thresholds (FI-high nor FI-low) from patients with 3 or 4 affected extremities.

Patients without hyperalgesia and/or allodynia less frequently reported hyperacusis compared to patients with these sensory symptoms (Chi-square; $p =0.026$). The odds ratio on hyperacusis in patients with hyperalgesia / allodynia was 7.0 (95% CI: 1.7-12.4). The UCLs did not differ significantly for both FI-low and Fl-high between patients with hyperalgesia/allodynia and patients without these symptoms.

Patients with hyperacusis had lower scores on the pain catastrophizing subscale of the PCCL (2.5 vs 3.2; $p < 0.05$).

Table 1. Demographic data and CRPS characteristics of patients.

Number of patients	40
Female/Male	38/2
Mean (SD) age in years	41.9 (10.2)
Mean (SD) duration of complaints (years)	11.4 (7.5)
Type of onset	
unknown	11
contusion	10
fracture	10
operation or IV	9
Location of onset	
Upper extremity (L/R)	6/9
Lower extremities (L/R)	9/16
Number of affected extemities	
1	2
2	7
3	12
4	19
Spreading pattern	
none	2
ipsilateral	22
heterolateral	12
diagonal	4
Mean (SD) VAS pain (0-100 mm)	71.4 (16.3)
Movement Disorders	
dystonia	21
dystonia + tremor	6
dystonia + myoclonia	11
dystonia + tremor + myoclonia	2
Allodynia and/or hyperalgesia	
Yes	25
No	15
Hyperacusis	
Yes	15
No	25

VAS, Visual Analogue Scale

Table 2. Differences between patients with and without hyperacusis

	No Hyperacusis	Hyperacusis	P-value
Number of patients	25	15	
Female / Male*	25 / 0	13 / 2	0.061
Mean (SD) age in years**	42.7 (9.6)	40.6 (11.3)	0.538
Mean (SD) disease duration in years**	10.4 (4.9)	13.1 (10.5)	0.365
Type of onset			
unknown	8	3	
contusion	7	3	
fracture	4	6	
operation or IV	6	3	
Location of onset			
Upper extremity (L/R)	3/5	3/4	
Lower extremities (L/R)	4/13	0/8	
Number of affected extemities			
1	2	0	
2	7	0	
3	6	6	
4	10	9	
Spreading pattern			
none	2	0	
ipsilateral	12	10	
heterolateral	9	3	
diagonal	2	2	
Mean (SD) VAS pain (0-100 mm)**	68.7 (16.1)	75.4 (16.4)	0.278
Movement Disorders			
dystonia	15	6	
dystonia + tremor	5	1	
dystonia + myoclonia	4	7	
dystonia + tremor + myoclonia	1	1	
Allodynia and/or hyperalgesia*			
Yes	13	13	0.026
No	12	2	

* Chi-square ** T-test for independent samples

Table 3. Values of thresholds

Measurement	Mean value (dB)	95% CI
PTT FI-Low	12.1	8.9;15.4
PTT FI-High	15.5	11.4;19.5
SRT	10.3	7.7;12.9
UCL FI-Low	79.9	71.4;88.3
UCL FI-High	78.9	70.4;87.5

The means and 95% confidence interval (CI) of the thresholds for all 40 patients. PTT: pure one threshold; SRT: speech reception threshold; UCL: uncomfortable loudness; FI-low/high: low/high fletcher index.

Figure 1. UCL levels of patients with and without hyperacusis

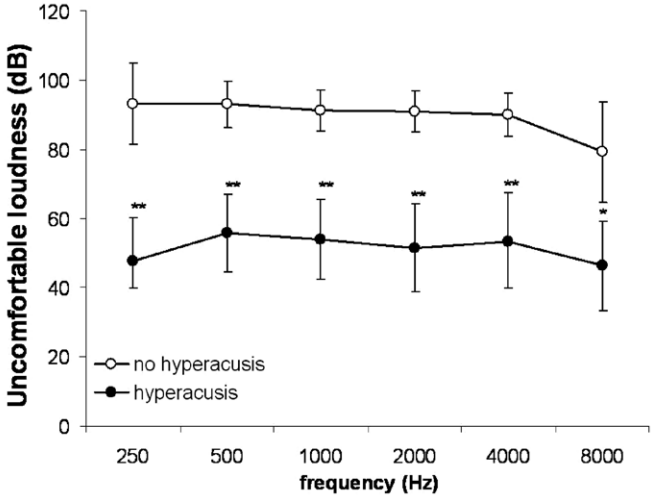

Figure 1: Uncomfortable loudness levels with 95% confidence interval in CPRS patients with (N=15) and without hyperacusis (N=25); ** $p < 0.001$, * $p < 0.05$, compared to patients without hyperacusis. High and low fletcher index for patients with hyperacusis (52.6 dB and 53.8 dB, respectively) were significantly lower ($p<0.001$) compared to the high and low fletcher Index of patients without hyperacusis (91.0 dB and 91.7 dB, respectively).

Discussion

Although our findings are limited to an extreme phenotype, to the best of our knowledge this is the first study to evaluate hyperacusis in CRPS. Thirty-eight percent of the patients with CRPS related dystonia in our study reported hyperacusis, whereas the prevalence of hyperacusis in the general population is less than 2%.[19] Auditory function, evaluated by means of the PTT and SRT, showed no differences between the patients and general population data. UCLs of CRPS patients not experiencing hyperacusis were normal. In contrast, UCLs of patients with hyperacusis were significantly lower than UCLs of patients without hyperacusis. It is unlikely that the presence of hyperacusis is explained through a more focussed attention to external stimuli, since then also higher scores on pain catastrophizing would have been expected in patients with hyperacusis compared to patients without hyperacusis, but, surprisingly, the opposite was found.

Interestingly, patients with hyperacusis more often experienced allodynia and/or hyperalgesia, which are manifestations of central sensitization. This phenomenon concerns the increased sensitivity of spinal neurons, despite a lack of change of afferent input.[20] Patients with hyperacusis also had more extremities with dystonia, which is associated with central disinhibition.[21,22] The degree of spread of dystonia, therefore likely reflects a marker of severity of central involvement. Although the difference was not significant, patients with hyperacusis had a mean duration of disease of 2.7 years longer than those without hyperacusis, which may hint at the possibility that with further progression of the disease, some of the patients without hyperacusis in this study ultimately would develop hyperacusis. Together, the sensory and motor features of this phenotype provide circumstantial evidence that hyperacusis in these patients initiates centrally. The high correlations of SRTs, PTTs, and UCLs between both ears in each patient make an unilateral peripheral cause unlikely and further support the central involvement in hyperacusis. However, the question remains how the pathophysiology of hyperacusis and the central features of CRPS intersect.

Key to central sensitization is the disturbed inhibitory-excitatory balance, which is associated with multiple biological changes in the central nervous system. These biological changes may include increased activity in excitatory pathways where substance P, excitatory neurotransmitters and adenosine triphosphate act via voltage-gated calcium channels and/or diminished activity in inhibitory pathways via gamma-aminobutyric acid (GABA) and glycine.[23] Interestingly, these neurotransmitters and neuropeptides not only play a role in synaptic transmission of the auditory system, but also act as tropic agents that modulate auditory signal processing as a results of sensory experience.[24,25] By altering auditory type I neural excitability to glutamate, these neuropeptides, for example, could induce hyperacusis and contribute to the induction, maintenance, or

exacerbation of tinnitus in the auditory periphery.[26]
In CRPS, central sensitization may spread in an ipsilateral somatotopic distribution up the neuraxis to involve nociceptive processing at the level of the thalamus or higher cortical centers.[27] Because different sensory inputs converge at the level of the thalamus, central sensitization may affect auditory circuitry. On the other hand, hyperacusis in our patients was related to the perception of discomfort, and not to the sound perception threshold. Hence, the "annoyance factor" of hyperacusis may hint at a role of the limbic activation as has been implicated for other features of CRPS and tinnitus.[28-31]
A potential limitation of this study is that the included patients reflect an extreme phenotype of CRPS, limiting any conclusion regarding the prevalence of hyperacusis in CRPS patients in general. The association between hyperacusis and dystonia could be more thoroughly evaluated if data regarding the occurrence of hyperacusis in severely affected patients without dystonia would have been available. It is also important to realize that the assessment technique of evaluating UCL thresholds relies on patient-provided information, rendering the findings sensitive to subjective influences. Our findings may stimulate the development of objective assessment techniques that aim to evaluate manifestations of central sensitisation in the auditory system.
In conclusion, we found that hyperacusis is common among severely affected patients with CRPS related dystonia. Hyperacusis in these patients may reflect the spreading of central sensitization to auditory circuitry.

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