# Complex regional pain syndrome related dystonia : exploratory metabolomics and therapeutic studies

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**Chapter 4**

# Baclofen-induced Chorea in Complex Regional Pain Syndrome-Related Dystonia

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**ABSTRACT**

Dystonia in complex regional pain syndrome (CRPS) is often treated with baclofen, a γ-aminobutyric acid B agonist. The authors report four CRPS-patients who developed baclofen-induced chorea, which coincided to a large extent with body regions that were initially affected by dystonia. Treatment with tiapride resolved the chorea, suggesting that striatal dopaminergic hyperactivity underlies baclofen-induced chorea.

**INTRODUCTION**

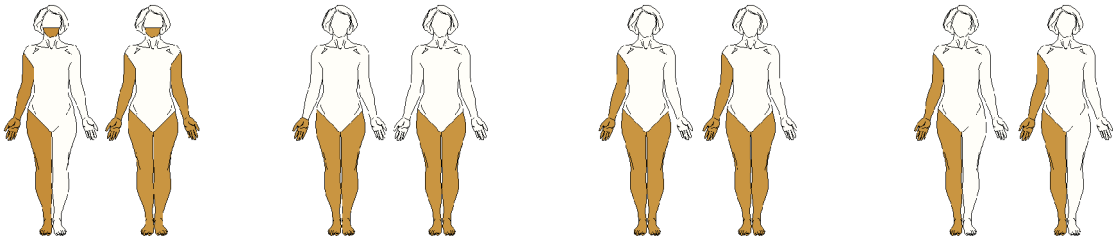
Complex regional pain syndrome (CRPS) is a chronic disorder characterized by persistent pain, vasomotor and trophic features, which usually is preceded by tissue injury.[1] Approximately 20% of patients with CRPS also develop fixed dystonia.[2] Baclofen, a γ-aminobutyric acid B (GABA-B) receptor agonist is commonly used in the management of spasticity of various causes, but is occasionally used in primary and secondary dystonia. To overcome baclofen's poor ability to pass the blood-brain barrier, intrathecal administration of baclofen (ITB) can be used, requiring only small doses to produce satisfactory clinical improvement. In the course of our research on ITB in CRPS patients with dystonia we encountered several cases with baclofen-induced chorea (BIC). The aim of this study is to characterize these patients and discuss potential mechanisms.

**METHODS**

Since 1996 approximately 300 patients have been evaluated in our clinic for CRPS-related dystonia. Patients were eligible for ITB, if they fulfilled the CRPS I diagnostic criteria of the International Association for the Study of Pain, [1] had fixed dystonia in one or more extremities, and showed an insufficient response to oral baclofen up to a minimal daily dose of 60 mg or had side effects which limited dose-escalation. Seventy-four patients who fulfilled the criteria were implanted with a programmable pump and received continuous ITB for a mean (range) duration of 48 (2 – 147) months at a median (range) daily dose of 650 (150 – 1500) µg. The clinical characteristics of patients, in- and excluded for pump implantation, were similar.

Four patients were identified who developed chorea while on baclofen treatment (three on ITB). All patients were Caucasian and female with a mean (range) age of 52 (48 - 56) years and a mean (range) disease duration of 12 (8 - 17) years. The interval between the onset of CRPS and dystonia was less than a year in all cases. All patients showed a gradual spread of dystonia to other body parts (three multifocal dystonia and one hemidystonia; figure 4.1). None of the patients had a family history of dystonia and other causes of dystonia, including birth injury, head trauma, neuroleptic treatments

**Figure 4.1.** Distribution patterns of dystonia (left figure) and chorea (right figure) of four patients with CRPS. Case 1 also exhibited both dystonia and chorea in the oromandibular region. Case 1 to 3 received ITB. Case 4 received oral baclofen only.



*Case 1* *Case 2* *Case 3* *Case 4*

CRPS = complex regional pain syndrome; ITB = intrathecal baclofen

were not reported or identified in the medical history or correspondence. Laboratory tests, including serum copper and ceruloplasmin as well as computed tomography or magnetic resonance imaging of the brain were normal.

The patients on ITB developed chorea at 3, 4 and 38 months after initiation of ITB at a mean (range) daily dose of 490 (315 – 650) µg with the catheter tip positioned at level L1, T7 en T10, which was comparable to patients without chorea. One patient developed chorea on oral baclofen two months after the start of this treatment at a daily dose of 70 mg. One of the patients on ITB used an oral contraceptive at the time chorea developed. However, a relation with chorea seemed unlikely since the oral contraceptive was initiated 29 years prior to the onset of chorea and its withdrawal did not improve chorea. The other three patients did not use medication with the potential to induce chorea. In all cases there were no symptoms or signs indicative of baclofen intoxication at the time chorea developed. Laboratory screening, including hematocrit and thyroid hormone tests, antinuclear factor, anti-DNA, antiphospholipid antibodies, antistreptolysin titer, acanthocytes, serum copper and ceruloplasmin and CAG repeat expansion mutation analysis for Huntington disease (performed in two patients) ruled out other causes of chorea.

In all cases chorea developed gradually, was continuous while awake, not distractible and simultaneously presented in the proximal and distal part of an extremity. None of the

patients experienced a sensory component related to the movement disorder. The distribution pattern of chorea varied between patients, but largely matched the distribution of dystonia within each patient, except for the occurrence of chorea on the contralateral non-dystonic side in patient 1 (figure 1). Patient 2 suffered from dystonia in both legs and the right hand, but developed chorea only in the lower limbs (figure 1). In all cases, dose-escalation of baclofen improved dystonia, but worsened chorea, and a reduction of baclofen dosage was associated with improvement of chorea and worsening of dystonia. In all four patients tiapride was administered, up to 300 mg in three divided doses, which successfully resolved chorea in all cases.

**DISCUSSION**

We present four patients who developed chorea while using baclofen (three on ITB). Dose-escalation of ITB always improved dystonia but worsened chorea and vice versa. Medical and medication history as well as laboratory tests ruled out other causes of chorea. Phenotypically, akathisia can appear as chorea. Akathisia is characterized by whole body, predominantly axial rocking movements and is associated with a sense of a need to move. In our patients the distribution pattern of movements coincided to a large extent with body regions that were initially affected by dystonia and the movements were not associated with a sensory component. A psychogenic origin was also considered unlikely since there was no acute onset or fast progression, and the movements were not distractible. Our findings thus suggest that these patients developed BIC. Hitherto, BIC has only been reported in three patients on oral treatment who suffered from various disorders.[3-5] ITB is predominantly used in patients with spasticity but surprisingly no cases with BIC have been reported using this treatment. Although a referral bias to our tertiary centre likely inflated the findings, the apparent lack of reports on patients with BIC on ITB may highlight an increased susceptibility to develop BIC in patients with CRPS. The relative variability of the daily dose and long interval between the start of baclofen and the onset of chorea in our patients may question their relation. However, this is not an uncommon finding in other drug-induced

movement disorders and most likely reflects individual differences in susceptibility to drug-induced side-effects. CRPS is associated with a hyperactive state of the spinal cord (central sensitization) which is characterized by enhanced signal transmission in the pain circuitry to the cortex.[6] In CRPS patients with dystonia, different studies have found evidence of impaired central inhibition along the neuraxis but it remains unclear if these findings genuinely reflect a pathophysiological marker of dystonia.[2] When baclofen is infused around the spinal cord it inhibits afferent input by stimulation of pre- and postsynaptic GABA-B receptors. Dystonia in CRPS responds to ITB which may suggest that this type of dystonia is associated with loss of GABAergic inhibition in the spinal cord.[2]

In CRPS, significant changes have been found in the cerebral circuitry involved in motor processing.[7] These changes, which involve the basal ganglia and (pre)supplementary motor area have been suggested to play a role in the motor impairments encountered in patients with CRPS.[7] Hence, in CRPS, spinal sensitization may bring about changes in supraspinal circuitry, finally leading to chorea.

Although several mechanisms may underlie chorea, enhanced activity of striatal dopamine has been proposed as a major mechanism for the development of chorea induced by drugs including levodopa, dopamine agonists and antagonists, and lithium.[8] Interestingly, baclofen is known to exert anti-dopaminergic activity[9] and the drug has also been used to treat chorea in Huntington's disease and tardive dyskinesias. Tiapride is a selective D2/D3 dopamine receptor antagonist in limbic areas, the striatum, and nucleas accumbens without any affinity for other neurotransmitter receptors of the brain.[10] Treatment with tiapride resolved the chorea, indicating that striatal dopaminergic hyperactivity underlies BIC in our patients. Collectively, our observations may suggest that alterations in synaptic processes mediated by GABA-B receptors underlie BIC in a subset of CRPS-patients.

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