Complex regional pain syndrome related movement disorders : studies on pathophysiology and therapy.

Munts, A.G.

Chapter 10

Post-dural puncture headache in complex regional pain syndrome: a retrospective observational study

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Abstract

Objective: To describe the unusual course of post-dural puncture headache after pump implantation for intrathecal baclofen administration in patients with complex regional pain syndrome related dystonia. Design: Case series based on data collected from 1996-2005. Setting: Movement disorders clinic, university hospital. Patients: A total of 54 patients with complex regional pain syndrome related dystonia who were treated with intrathecal baclofen. Results: A high incidence (76%) and prolonged course (median 18 days, range 2 days-36 months) of post-dural puncture headache was found. Radionuclide studies performed in 2 patients with long-lasting symptoms (12-16 months) did not reveal cerebrospinal fluid leakage. In patients without signs of CSF leakage (*n*=38), epidural blood patches administered in 24 patients were effective in 54%, while ketamine infusions administered in 6 patient were effective in 67%. Conclusions: Our observations may suggest that other mechanisms besides intracranial hypotension play a role in the initiation and maintenance of post-dural puncture headache in complex regional pain syndrome and stimulate new directions of research on this topic.

Introduction

Complex regional pain syndrome type 1 (CRPS) is characterized by combinations of chronic pain, allodynia, hyperalgesia, changes in skin colour and temperature, sweating and swelling.[1] The syndrome predominantly develops in women and usually occurs following a tissue injury, for example a fracture or surgery.[1-3] Approximately 20% of the patients with CRPS develop dystonia, which is characterized by fixed flexion postures.

Treatment of dystonia is difficult,[4] although continuous administration of intrathecal baclofen (ITB) was shown to be beneficial in some patients with multifocal or generalised dystonia.[5] Inherent to this mode of drug delivery is the requirement of placement of an intrathecal catheter. As a consequence of the catheter's perforation of the spinal dura, cerebrospinal fluid (CSF) leakage may occur. Subsequent to this procedure, 0-42% of the patients develop headache over the frontal and occipital areas radiating to the neck and shoulders.[6-10] Exacerbation of the headache by adoption of the upright posture, and improvement of the pain by lying down is the sine qua non of post-dural puncture headache (PDPH).[10] PDPH is often associated with nausea and vomiting, neck stiffness, tinnitus, hypacusia, and photophobia, and after a single small diameter puncture rarely lasts longer than a week.[11] Although a low CSF pressure and meningeal inflammation have been suggested to play a role, the actual mechanism producing the complaints in PDPH is unclear.[10,12,13]

We have treated patients with CRPS-related dystonia with ITB since 1996. Over this period we have noticed an unusual high frequency and prolonged duration of PDPH after pump implantation in these patients. Here, we present our experiences and propose a mechanism, distinct from CSF hypotension, as a potential alternative cause of PDPH in this population.

Methods

The medical records of all CRPS patients who underwent pump implantation in the course of studies addressing the efficacy and safety of ITB in CRPS-related dystonia between May 1996 and December 2005 were evaluated. Therefore, the current study is retrospective, not-controlled and observational. All patients met the CRPS type 1 criteria of the International Association for the Study of Pain,[14] either at the time of disease onset or at

the time of presentation at the clinic. Subjects were included if they had dystonia in at least two extremities, and experienced insufficient relief from oral baclofen or if this treatment caused dose-limiting side effects. Before implantation, patients were subjected to a screening procedure to determine responsiveness to ITB.[5,15] The SynchroMed EL or SynchroMed II programmable drug infusion system (Medtronic, Minneapolis, MN) was implanted under general anesthesia by an experienced neurosurgeon (J.V.). One end of the catheter was placed in the intrathecal space through a 17 gauge Tuohy needle (direction of the bevel parallel to the longitudinal axis of the spine), with the catheter tip placed at the midthoracic level. The other end of the catheter was tunneled into the subcutaneous space to the pump, which was positioned in the lower abdomen.

PDPH was diagnosed according to the definition of the International Headache Society: (i) headache that worsens within 15 min after sitting or standing and improves within 15 min after lying, with at least one of the following: neck stiffness, tinnitus, hypacusia, photophobia and nausea; (ii) dural puncture had been performed; and (iii) headache developed within 5 days after dural puncture.[11] It is assumed that the headache resolves spontaneously within 1 week or within 48 h after effective treatment of the spinal leak (usually by epidural blood patch (EBP)) in 95% of cases.[11]

PDPH during the post-operative course was treated with bed rest in horizontal position, pain killers (acetaminophen or non-steroidal anti-inflammatory drugs), EBP or intravenous (IV) ketamine (the latter as from 2004). EBP was administered by experienced anesthesiologists who injected 10-20 mL autologous blood one level caudal to the dural puncture site. This level was chosen to prevent damaging of the inserted spinal catheter. Dose of the ketamine infusion was based on a study from Correll *et al*.[16] Instead of racemic ketamine, we used S(+) ketamine because (at half the dose) this optical isomere has been suggested to be as efficient in reducing pain with fewer cognitive side effects.[17] The infusion rate was started at a dose of 4 mg/h and increased with increments of 2 mg/h or less three times a day if pain relief was insufficient and side effects were acceptable to the patient. The maximum dose was 20 mg/hr. Duration of the treatment was 7-14 days, or shorter if PDPH symptoms disappeared earlier or severe adverse events (as judged by patient or physician) occurred.

Presence, characteristics and duration of PDPH, effectiveness of treatment, as well as occurrence of CRPS exacerbation were recorded on a case report form. Exacerbation was

defined as a serious increase in CRPS-related pain as judged by the patient, or an increase in dystonia or autonomic signs (oedema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain) as observed by the physician.
The frequency of PDPH in patients with and without CRPS exacerbations was compared using a, where a *P* value <0.05 was considered significant.

Two patients who were evaluated for CSF leakage with radionuclide studies, by injecting indium^{111} diethylenetriaminepentaacetic acid (DTPA) into the drug reservoir of the pump,[18,19] are described in more detail.

Table 10.1. Baseline characteristics (*n*=54)

Characteristic	**Value**
Gender (%)	
Male	4 (7)
Female	50 (92)
Age	
Mean, SD (yr)	38.6 ± 12.4
Median, IQR (yr)	40.3 (26.8-49.0)
Duration of CRPS (yr; mean, SD)	10.1 (6.8)
Number of affected extremities (median, IQR)	3 (2 - 4)
Number of extremities with dystonia (median, IQR)	3 (2 - 4)
Preceding trauma, n (%)	
Contusion	19 (35)
Fracture	10 (19)
Surgery	7 (13)
Soft tissue injury	2 (4)
Distorsion	1 (2)
Spontaneously	15 (28)
VAS pain (mean, SD)	7.4 (1.8)
Sensory abnormalities, *n* (%)	
Hyperesthesia, hyperalgesia or allodynia	28 (52)
Hypesthesia or hypalgesia	39 (72)

IQR = interquartile range.

Results

Fifty-four CRPS patients (50 female) who underwent a pump-catheter implantation were identified (7 patients, in whom clinical characteristics where not different from the

remaining patients, had dropped out during the screening procedure). Mean (SD) age was 39 (12.4) years with a range from 17-64 years. The median number of extremities affected by CRPS was 3: both sides of the body were involved in 44 patients, only right in 7, and only left in 3; upper and lower extremities were involved in 47 patients, only upper in 3, and only lower in 4 (Table 10.1). PDPH occurred in 41 patients (76%) after the implantation procedure (Figure 10.1). A history of migraine was present in 9 patients. Forty-four percent of the migraine patients developed PDPH, against 82% of the patients without migraine.

Three patients (7%) showed signs of CSF leakage (i.e., subcutaneous swelling). In one of these patients, the subcutaneous swelling with PDPH disappeared spontaneously after 5 weeks. Because this patient rated the symptoms of PDPH severity as mild, no treatment was started. In the second patient, PDPH resolved within 48 h after an EBP that was administered 11 days after implantation. In the third patient, PDPH persisted for 12 months after implantation, in spite of the disappearance of subcutaneous swelling after two EBPs administered at 10 and 17 days after implantation. Radionuclide imaging was performed three months after pump implantation and showed no signs of CSF leakage. PDPH was of such severity that she was confined to bed till six months after implantation. At this stage, two IV ketamine treatments were administered over a three week period which resulted in a gradual decrease of PDPH allowing the patient to become wheelchair-bound. Subsequently, PDPH gradually decreased. At 12 months post-implantation PDPH had resolved.

Thirty-eight of the 41 PDPH patients (93%) had PDPH without signs of CSF leakage. Duration of PDPH in these patients varied from 2 days-36 months, with a median of 18 days and an interquartile range of 8 days-3 months. Of the 24 cases who received an EBP, PDPH resolved within 48 h in 13 (54%). In 9 patients with enduring complaints of PDPH, EBPs were repeated once (*n*=5) or twice (*n*=4) without any result. One of these patients experienced PDPH for 16 months and 3 EBPs were unsuccessful. One month after pump implantation, radionuclide imaging was performed which showed no signs of CSF leakage. She was not treated with IV ketamine because PDPH resolved before 2004 (when IV ketamine was introduced at our department).

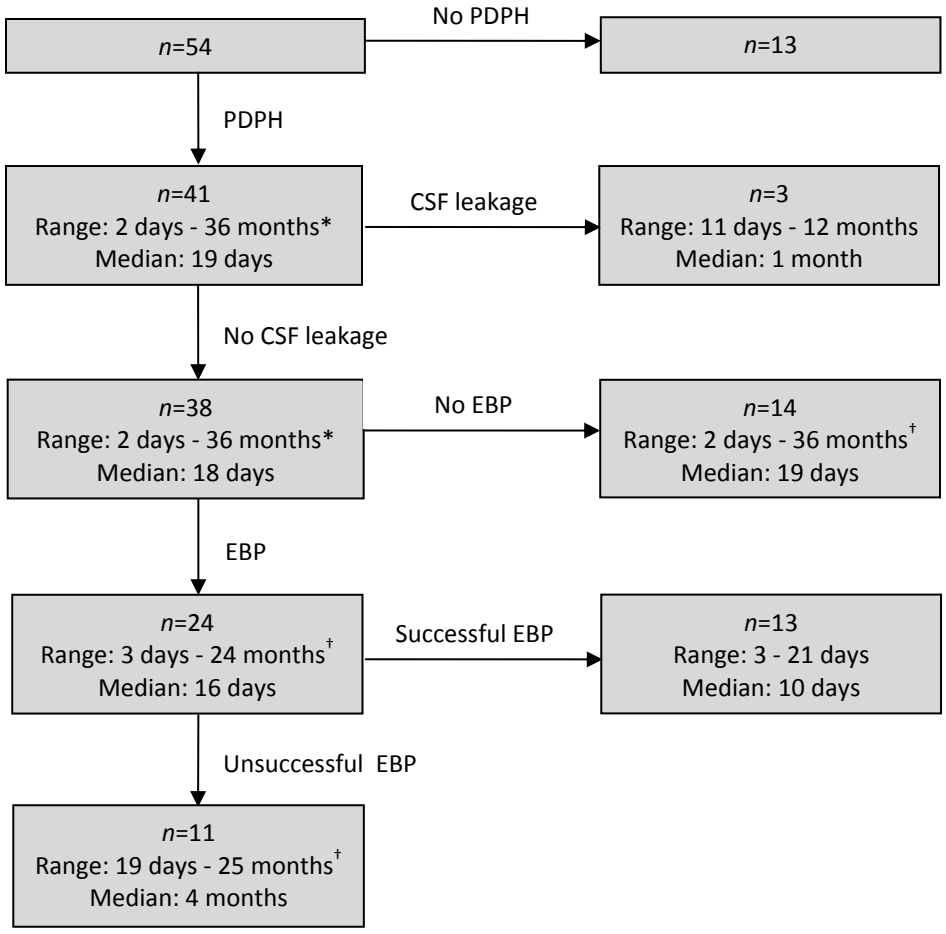

Figure 10.1. Study population flow chart.
CRPS = complex regional pain syndrome; CSF = cerebrospinal fluid; PDPH = post-dural puncture headache.
*Persistent symptoms in 2; †persistent symptoms in 1.

Six patients with PDPH but without overt signs of CSF leakage received IV ketamine (Table 10.2). PDPH resolved in four patients (67%) during 2-10 days of treatment. In two of these patients a prior EBP had had no effect. IV ketamine gave no improvement in two patients, one of whom also had had a prior EBP without effect. Non-serious adverse events related to IV ketamine including feeling high (*n*=2), malaise (*n*=1) and nausea (*n*=1), occurred in 3 patients.

Table 10.2. Ketamine IV in PDPH patients without signs of CSF leakage (*n*=6)

Patient	Duration from surgery to ketamine	Ketamine succesful?	Earlier EBP?	Duration PDPH	Also CRPS exacerbation?	Duration CRPS exacerbation
A	4 days	+	-	8 days	+	24 months[a]
B	4 days	-	+	4 months	+	3 months
C	7 days	+	-	17 days	-	NA
D	9 days	-	-	3 months	+	3 months
E	12 days	+	+	19 days	+	32 months[a]
F	13 days	+	+	19 days	+	unknown

CRPS = complex regional pain syndrome; EBP = epidural blood patch; NA = not applicable; PDPH = post-dural puncture headache.
[a]Persistent symptoms.

Following pump implantation, 15 patients (28%) experienced an exacerbation of CRPS. Fourteen of these patients also had PDPH without signs of CSF leakage. One patient had an exacerbation of CRPS without PDPH. Compared to patients without PDPH, patients with PDPH, but without signs of CSF leakage (*n*=51), more often experienced an exacerbation of CRPS (χ^2 = 3.964, df = 1, *P*=0.046, difference in proportions 29%, 95% CI 0.2-46.2%). The exacerbation lasted 7 days-51 months, with 4 patients still experiencing symptoms at a recent follow-up visit.

Discussion

In this study, 76% of the CRPS patients developed PDPH after pump implantation for intrathecal drug delivery. In 38 of the 41 PDPH patients, there were no overt clinical signs of CSF leakage. The duration of symptoms clearly exceeded the usual duration of PDPH known for patients that have been implanted, with 50% of the cases experiencing PDPH that lasted between 18 days to 36 months.

An EBP was effective in 54% of the patients. An explanation for the high incidence of PDPH in our population may be that needles with a large diameter, which are associated with a greater risk for PDPH,[20] were used. This explanation seems less likely because several earlier studies that used a catheter for ITB with a similar diameter, have reported PDPH in 0-42%,[6-9] which clearly differs from the 76% encountered in our population.

An EBP to reduce CSF leakage is the standard treatment of PDPH, but evidence of its efficacy (in comparison with a sham procedure) is still lacking.[11,21] Although the loss of CSF and subsequent decrease of CSF pressure is not disputed, the actual mechanism underlying the symptoms in PDPH is still unclear.[10] CSF leakage related PDPH was evident in some of our implanted patients and we cannot exclude that CSF leakage occurred at a subclinical level in those patients without overt signs of CSF leakage. However, both prevalence and duration of symptoms of PDPH in CRPS patients without CSF leakage deviated conspicuously from the values that are reported in patients implanted for other indications. Additionally, in two of our cases with long-lasting (12-16 months) PDPH, radionuclide studies did not reveal CSF leakage. Together, our findings suggest that, in CRPS at least, other causes than a reduced CSF pressure may underlie the initiation or maintenance of PDPH.

Compared to patients without PDPH, patients with PDPH more often experienced an exacerbation of CRPS. This may suggest that biological mechanisms involved in CRPS play a role in the initiation or maintenance of PDPH as well. Compelling evidence suggests that aberrant inflammation, in which both neurogenic and immunogenic components play a role, underlie the clinical features of the acute phase of CRPS.[22-24] Patients with CRPS may also develop symptoms and signs of vasomotor dysregulation, in which both a decreased central sympathetic activity and disturbed endothelium mechanisms play a role. As a consequence, vessels show a reduced vasomotor tone.[25-27] According to the Monro-Kellie doctrine, the sum of volumes of the brain, CSF and intracranial blood is constant with an intact skull.[10] It has been suggested that in PDPH a loss of CSF is compensated by vasodilatation[28] which has been illustrated by pachymeningeal gadolinium enhancement on magnetic resonance imaging.[12] Surgery or needle punctures are both well-known triggers of CRPS, but may also incite an exacerbation in patients with established disease.[29,30] If, and to what extent CRPS may cause an inflammatory response as well as a vasomotor dysregulation of meningeal structures is unknown. Nevertheless, increased pooling of blood in possibly sensitised meningeal vessels with disturbed vasomotor regulation may have contributed to PDPH in CRPS.

IV ketamine had a beneficial effect on PDPH in four of our six patients. This finding may suggest that ketamine elevated CSF pressure, as has been reported previously,[31] which consequently leaded to resolution of PDPH. However, this explanation is unlikely because

there is compelling evidence to suggest that even in larger dosages, ketamine does not effect or even lower CSF pressure.[32,33] Our patients had long-lasting CRPS with sensory and motor features reflecting central involvement. Allodynia and hyperalgesia, present in half of our patients, are well-known features of central sensitisation.[34] Dystonia in CRPS has been attributed to a disinhibition of nociceptive withdrawal reflexes, likely also a reflection of central sensitisation.[34] Key in central sensitisation, is the activation of the *N*-methyl-D-aspartate (NMDA) receptor[35] and ketamine is a powerful suppressor of central sensitisation.[36] In CRPS patients, several open studies using ketamine have found beneficial effects on pain.[16,37,38] So, the beneficial response of PDPH to ketamine could be explained by its action as a non-competitive NMDA receptor antagonist in reversing central sensitisation. Alternatively, meningeal inflammation has been demonstrated in PDPH[12,13] and ketamine has an anti-inflammatory effect.[39-41] This may suggest that PDPH in CRPS reflects an aberrant meningeal inflammatory response induced by the insertion of an intrathecal catheter.

Obviously, there are a number of limitations in this study. First, we performed radionuclide imaging to exclude CSF leakage in only two patients and the reliability of this technique in demonstrating or excluding a leakage has not been established. However, this limitation is applicable for any other method used for this purpose. The most appropriate diagnostic study for evaluating intracranial hypotension would probably be measurement of CSF opening pressure. However, additional lumbar punctures potentially may further exacerbate the condition and were therefore not considered. Otherwise, PDPH is a clinical diagnosis.[11] Second, the efficacy of EBP and IV ketamine was evaluated in a small population (*n*=6) and in a non-randomised way, which may have led to bias. Third, retrospective studies are subject to misclassification and information on the exact duration of symptoms is less accurate than those that would have been obtained in a prospective study.

Nevertheless, our observations on PDPH may suggest that other mechanisms besides low CSF pressure play a role in the initiation and maintenance of PDPH in CRPS and stimulate new directions of research on this topic.

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