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CASE REPORT

Cerebrospinal fluid levels of glial cell-derived neurotrophic factor correlate with spinal cord stimulation frequency in patients with neuropathic pain: a preliminary report

KF McCarthy[1,2] and C McCrory[2]

Study design: Case series.
Objectives: To evaluate relationships between spinal cord stimulation (SCS) parameters and levels of glial cell-derived neurotrophic factor (GDNF).
Setting: Ambulatory pain clinic of St James's Hospital, Dublin, Ireland.
Methods: Nine patients with an implanted SCS and Failed Back Surgery Syndrome (FBSS) were administered the Brief Pain Inventory and Short Form (36) Health Survey. Following a lumbar puncture, levels of GDNF in cerebrospinal fluid (CSF) were assayed and correlated with stimulation parameters. Controls were patients with arthritic back pain who were matched for age, gender and SF-36 score.
Results: Concentrations of GDNF in CSF are higher in patients with FBSS than controls ($P=0.002$) and correlate with SCS frequency ($P=0.029$).
Conclusion: Concentrations of GDNF in CSF are higher in neuropathic pain and appear to be related to stimulation frequency. Further work is needed to evaluate this potential relationship, both in neuropathic pain and in other contexts such as locomotor dysfunction.
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INTRODUCTION

Over the past 45 years, spinal cord stimulation (SCS) has been employed primarily as a means of reducing the intensity of neuropathic and vascular pain. However, in addition to a role in relieving pain, there is emerging evidence of a potential role for lumbosacral SCS in relieving spasticity and improving motor function after spinal cord injury.[1]

The glial cell-derived neurotrophic factor (GDNF) family of ligands promotes the survival of several distinct neuronal populations, such as motoneurons, nociceptive sensory neurons and dopaminergic neurons. Intrathecal GDNF has prevented and reversed pain behaviours in an animal model of neuropathic pain[2] and, when co-administered with grafts of Schwann cells, enhances axonal regeneration and myelination following spinal cord injury.[3]

The recent study of this group showed a relationship between the cerebrospinal fluid (CSF) levels of neuroimmune mediators and reported pain in patients with a functioning spinal cord stimulator implanted for the relief of pain arising from Failed Back Surgery Syndrome (FBSS).[4] The study showed that CSF concentrations of vascular endothelial growth factor and brain-derived neurotrophic factor were correlated with reported pain but not with stimulation parameters. The control group consisted of matched patients with spinal lumbar facet joint osteoarthritis. In this control group, who did not have a functioning spinal cord stimulator implanted, concentrations of GDNF in CSF had a significant positive relationship with the mental health component of the Short Form-36 (SF-36) health survey (Figure 1). The analysis of the CSF samples from the patients with FBSS and a functioning spinal cord stimulator was subsequently repeated to evaluate if there was a relationship between GDNF, pain and stimulation parameters.

SUBJECTS AND METHODS

Subjects

Nine patients with a spinal cord stimulator (Synergy or Restore, Medtronic, Minneapolis, MN, USA) implanted for the relief of pain associated with FBSS consented to participate in this study. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research. Written consent was obtained from all participants.

Study protocol

Patients were instructed to turn their stimulator off at midnight and to attend for CSF sampling between 08:00 and 10:00 h the following day. The SCS parameters that each patient had been using to achieve satisfactory analgesia were recorded. A SF-36 was administered to assess quality of life and a Brief Pain Inventory to assess reported pain and pain relief in the preceding 24 h.

Methods

A lumbar puncture was performed aseptically with a 25-G Whitacre needle under radiological guidance to minimize the risk of damaging the stimulator leads. Control subjects were patients with chronic arthritic lumbar back pain who were matched for age, gender and SF-36 score. Concentrations of GDNF in CSF were measured by multiplex chemiluminescent immunoassay kits (Aushon Biosystems, Billerica, MA, USA). The detection limit, as reported by the manufacturer, was 1.5 pg ml^{-1} for GDNF. Samples were assayed in duplicate.

[1]Department of Physiology, Trinity College Dublin, Dublin, Ireland and [2]Department of Pain Medicine, St. James's Hospital, Dublin, Ireland
Correspondence: Dr KF McCarthy, Department of Anaesthesia, Great Ormond Street Hospital, London WC1N 3JH, UK.
E-mail: kfinmccarthy@gmail.com
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Data analysis

Data are reported as the mean ± standard deviation unless otherwise indicated.

Correlations between SCS parameters and CSF protein levels were performed by Spearman's ranked correlation co-efficient. The difference in median CSF concentrations of protein compared with matched controls was tested with a Wilcoxon matched-pairs signed rank test. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

The six men and three women (Table 1) ranged in age from 26 to 68 years (mean 47 ± 13.7 years) were included in the study. SF-36 scores ranged from 28 to 75 (mean 50.4 ± 17.2). SCS parameters ranged from pulse widths of 210 −360 μs (mean 282 ± 46 μs), frequencies of 40–100 Hz (mean 73 ± 20 Hz) and amplitudes of 3–7.4 V (mean 4 ± 1.4 V). Median concentrations of GDNF in CSF were significantly higher in patients with FBSS than matched controls ($P = 0.002$; Figure 2). Concentrations of GDNF in CSF correlated positively with SCS frequency (Spearman rank correlation $r = 0.7365$, $P = 0.029$; Figure 3).

DISCUSSION

Several limitations existed in this study: small sample size and observational nature. However, this is a preliminary finding that suggests that, compared with arthritic low back pain, concentrations of GDNF in CSF are elevated in a neuropathic pain syndrome such as FBSS and that levels correlate with the frequency of SCS that provides pain relief in these patients. Little is known about the mechanism of action of SCS, even in conditions known to respond well. There can be non-response rate of up to 30% and diminution in effect over time in responders, which are not explained by changes in γ-amino butyric acid.[5]

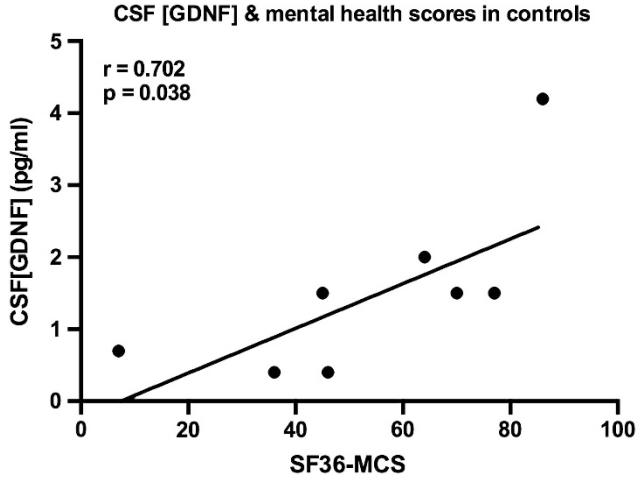

Figure 1 Correlation between fluid concentrations of glial cell-derived neurotrophic factor (GDNF) in cerebrospinal fluid (CSF) of control patients with osteoarthritic back pain and mental health component score of the Short Form-36 Health Survey (SF-36-MCS), $N = 9$, assayed in duplicate. Spearman's ranked correlation co-efficient, $r = 0.702$, $P = 0.038$.

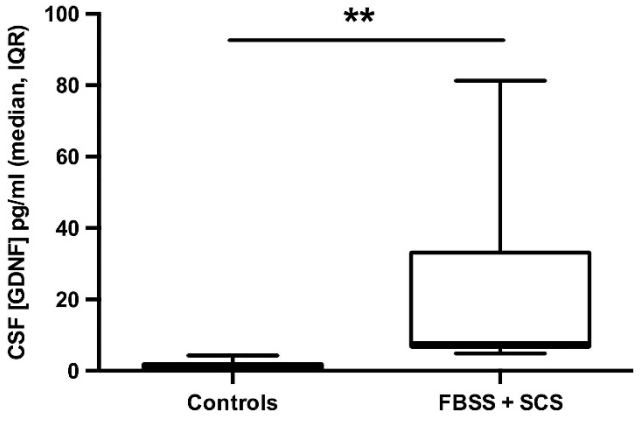

Figure 2 Differences in median concentrations of glial cell-derived neurotrophic factor (GDNF) in cerebrospinal fluid of patients with Failed Back Surgery Syndrome (FBSS) and a functioning spinal cord stimulator (SCS) vs matched controls with osteoarthritic back pain, $N = 9$. Wilcoxon Matched Pairs Signed-rank Test, $P = 0.002$.

Table 1 Clinical characteristics and stimulation parameters of patients

CSF GDNF (pg ml^{-1})	*Frequency (Hz)*	*Volts (V)*	*Pulse width (μs)*	*SF-36 score*	*Worst pain: BPI Q5*	*Pain relief: BPI Q8*	*Age (years)*	*Gender*
4.9	40	3	360	62	2	70	61	M
6.1	60	4.5	310	33	6	70	68	M
7.5	60	3	310	56	2	75	49	F
7.6	100	3.2	240	75	3	70	57	F
7.7	60	4	300	34	1	80	49	F
17.9	80	4	210	70	5	50	26	M
19.6	80	7.4	240	56	8	70	33	M
46.7	80	3	300	28	3	40	41	M
81.3	100	4.5	270	40	5	65	38	M

Abbreviations: BPI, Brief Pain Inventory; CSF, cerebrospinal fluid; F, Female; GDNF, glial cell-derived neurotrophic factor; M, Male; SF-36, Short Form-(36).

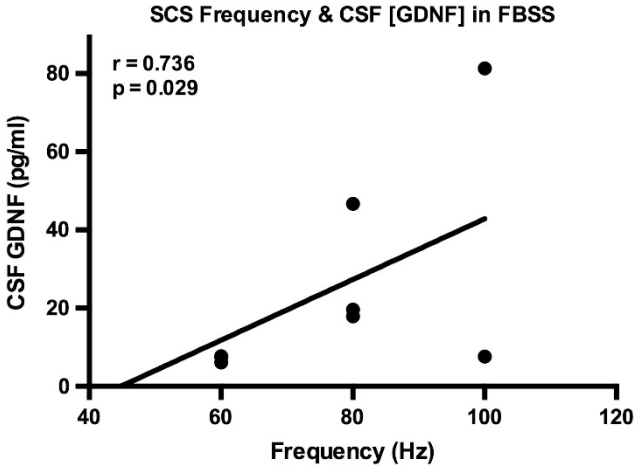

Figure 3 Correlation between concentration of glial cell-derived neurotrophic factor (GDNF) in cerebrospinal fluid (CSF) and SCS frequency in Hertz (Hz), $N = 9$, assayed in duplicate. Spearman's ranked correlation co-efficient, $r = 0.736$, $P = 0.029$.

One of the major roles of GDNF is in supporting the survival of motor and dopaminergic neurons. The clinical availability of GDNF as a therapy for Parkinson's and motor dysfunction has been hampered by side effects and the need for an intracerebral-ventricular mode of delivery. If there is a relationship between GDNF and SCS frequency, then it may be bi-directional and SCS might represent a means of modulating endogenous GDNF, thereby attenuating some of the side effects and avoiding the need for a more invasive delivery system. Although lumbosacral stimulation can induce standing and rhythmic locomotor-like stepping movements in animal models, there is a recent report of a patient with a clinically motor complete cervical injury who regained voluntary control of leg movement, but only in the presence of epidural stimulation.[6] Standing and movement were facilitated by two different frequencies of stimulation and the emergence of supraspinal control of lower limb movement was accompanied by improvements in mood and bladder activity. Although speculative, a modulation of GDNF could account for the improvements in mood, locomotor and bladder function.

In conclusion, it appears that lumbosacral SCS is emerging as a means of augmenting or facilitating rehabilitation after spinal cord injury. The results in this study suggest a relationship between SCS frequency and GDNF level that may underlie the efficacy of SCS.

CONFLICT OF INTEREST

Dr McCarthy has no potential conflict of interest to declare. Dr McCrory has received research grant support from Medtronic Inc. Neither author has a commercial interest in the material presented in this article.

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