

SHORT REPORT

Substance P concentration and history of headache in relation to postlumbar puncture headache: towards prevention

Jeffrey W Clark, Glen D Solomon, Preenie deS Senanayake, Claudia Gallagher

Abstract

Medical treatment of postlumbar puncture headache (post-LP HA) is often difficult and ineffective. Prevention would be preferable to more invasive procedures, including blood patch. The aim was to determine the incidence of post-LP HA in two suspected high risk groups compared with the general outpatient population. Based on previous research, it was hypothesised that a low substance P concentration, or a history of chronic headache, or both would be associated with a higher risk of post-LP HA. A total of 310 randomly selected patients undergoing diagnostic lumbar puncture in the outpatient neurology clinic over 30 consecutive months were studied. Follow up was by headache questionnaire or phone survey after diagnostic lumbar puncture. Substance P was measured by radioimmunoassay on a subset of 102 samples of CSF. The overall incidence of post-LP HA was 38%. Patients with a measured substance P value < 1.3 pg/ml were three times as likely to have post-LP HA than those with a higher value. A history of chronic or recurrent headache was reported by 57% of those who developed post-LP HA. This group was also three times as likely to experience post-LP HA as those who did not have chronic headaches.

(*J Neurol Neurosurg Psychiatry* 1996;60:681-683)

Keywords: substance P; headache; lumbar puncture

Headache is a common and often severe complication of lumbar puncture not yet readily preventable or predictable.¹⁻⁵ Simple therapeutic interventions including intravenous hydration and vasoactive medications have afforded limited success.^{4 6 7} Epidural blood and saline patches are effective, but are invasive and can cause complications.^{8 9} Use of a very small gauge needle may be helpful, but other preventative manoeuvres such as remaining supine for up to 24 hours after the procedure, copious oral fluid intake, and prophylactic blood patch have proved futile.^{3 4 8-15}

Established risk factors for developing post-

lumbar puncture headache (post-LP HA) include a small body mass, female sex, age less than 40 years, and use of a large gauge spinal needle by the clinician.¹⁰⁻¹⁵ A history of headache reported one week before the procedure can serve as a valuable predictor.⁴ Also, research has suggested that those who experience post-LP HA may have significantly lower baseline (resting) substance P concentrations.¹⁶ The post-LP HA in this group may be related to a combination of factors including a hypersensitivity to substance P or a receptor mediated phenomenon (low resting substance P concentrations with receptor up regulation).

We hypothesised that a low CSF substance P concentration (< 1.3 pg/ml) or a history of chronic headache would identify those at high risk for developing post-LP HA. To test this hypothesis, we studied 310 patients (randomised daily) undergoing diagnostic lumbar puncture over a 30 month period.

Methods

Headache questionnaires were distributed to 310 patients undergoing diagnostic lumbar puncture in the outpatient neurology clinic after informed consent to participate in this study was obtained. Lumbar puncture was requested before this by independent clinicians for clinical reasons not directly associated with the research. Information obtained from the questionnaire included: (a) the incidence, quality, and severity of the postural (post-LP) headache after the procedure, and (b) history of chronic or recurrent headache. Those who did not return their questionnaires by mail were phoned to verbally obtain this information. Responses were received from 266 of the 310 patients. Reasons for not responding included inability to comprehend the questions (language barrier or dementia), change of address, disconnected phone, and death.

None of the patients were undergoing intrathecal treatment or systemic chemotherapy. All were ambulatory, and none were under evaluation for intractable/recurrent headache or pseudotumour cerebri. The average age was 56 (range 23 to 79) years. There were 162 women and 104 men.

Lumbar puncture was performed with a 20 gauge 3.5 inch spinal needle. Patients were

Department of
Neurology, Scott &
White Clinic, Temple,
Texas, USA
J W Clark

Headache Center,
The Cleveland Clinic
Foundation,
Cleveland, Ohio, USA
G D Solomon

Neurovascular
Research Center, The
Cleveland Clinic
Foundation,
Cleveland, Ohio, USA
P Senanayake

Department of
Neurology, The
Cleveland Clinic
Foundation,
Cleveland, Ohio, USA
C Gallagher

Correspondence to:
Dr Jeffrey W Clark,
Department of Neurology,
Scott & White Clinic, 2401
South 31st Street, Temple,
Texas 76508, USA.

Received 13 November 1995
and in revised form
22 January 1996
Accepted 23 February 1996

Comparison between the sexes, those with and without chronic headache and those with high or low substance P in CSF

	Women (n = 162)	Men (n = 104)	Chronic headache		Substance P	
			Yes (n = 88)	No (n = 178)	Low (n = 54)	High (n = 37)
Post-LPHA (No (%))	64 (39)	38 (37)	50 (57)	53 (30)	26 (48)	9 (24)
Odds ratio	—		3.09		2.9	

instructed to remain supine for one hour after the procedure in the clinic, and for a further six hours at home. The CSF was collected into sterile tubes with aprotinin added (500 kU per ml of CSF added, 2 ml of CSF per patient). The tubes were immediately frozen at -20°C until analysis. Substance P in CSF was quantified by radioimmunoassay under controlled conditions as described by McGregor and Bloom (see below) in 102 randomly selected members of the entire group of 310.¹⁷ Responses to the headache questionnaire were available for 91 of these. Technicians performing the assay were blinded to the results of the questionnaire.

For radioimmunoassay, duplicate 50, 100, and 200 μl aliquots of the reconstituted sample of CSF were transferred to prechilled (4°C) tubes containing 450, 400, and 300 μl assay buffer, respectively. A 100 μl aliquot of ^{125}I -substance P (^{125}I Bolton-Hunter labelled substance P; Amersham, Chicago) containing 6000 counts was added to each tube, followed by a 100 μl aliquot of antiserum (Arnel Products, NY; ca No 17). After a 48 hour incubation at 4°C bound and free substance P were separated by the addition of a suspension of charcoal (1 ml). The suspension contained per 100 ml assay buffer, 0.8 g activated charcoal (untreated powder, 100–400 mesh, Sigma Chemical Co, St Louis, MO), and 0.08 g dextran (clinical grade, Sigma). The assay tubes were then centrifuged (2200 rpm, 20 minutes, 4°C), and the supernatant liquid was decanted. The bound ^{125}I -substance P in the supernatant liquid was measured with a gamma counter (Apex Micromedic Systems, Inc, Huntsville, AL). Synthetic substance P (Bachem No PSUB 10) was used as a standard in serial dilutions of 1–400 pg/tube.

Results

Post-LP HA was reported by 39% of the women and 37% of the men (102 of 266 patients). The frequency of post-LP HA in these two groups was not statistically different ($\chi^2 = 0.24$; $P > 0.05$; table).

A history of chronic or recurrent headache was reported by 88 patients (33%). Fifty of these experienced post-LP HA (57%). This group was three times as likely to develop post-LP HA than those without a history of chronic headache (odds ratio 3.1; 95% confidence interval (95% CI) 1.8–5.3 ($\chi^2 = 18.1$; $P < 0.0001$; table)).

Assay results for substance P in CSF were available for 91 of the questionnaire responders. In this group, 35 reported post-LP HA. The average value in the post-LP HA group was 0.895 (SD 0.718) pg/ml and the average

was 1.421 (SD 1.796) pg/ml in the group without post-LP HA. The substance P concentration was low (< 1.3) pg/ml in 26 of the 35 who developed post-LP HA (74%). Conversely, 48% of those with a low substance P value reported post-LP HA compared with 24% of those with a high value. Those with a low substance P concentration were three times as likely to develop post-LP HA (odds ratio 2.9; 95% CI 1.1–7.3 ($\chi^2 = 5.3$; $P < 0.05$; table)).

Discussion

Headache is a common and debilitating complication of lumbar puncture.^{1–3,11} The headache is severe in many cases, and protracted in some.^{1,2,13} Comments received from patients participating in this study reflected the emotion associated with this condition. Many took the time to write full page letters about their experience.

Therapeutic options include analgesics, intravenous fluids, caffeine, and epidural blood patch.^{2,3,6–9} Most medical remedies provide limited relief, and blood patch requires a repeat procedure. The most reliable method for alleviating post-LP HA pain is to remain supine.^{2,3,12} However, many patients are forced to do so for days, which can be disabling. Prolonged supine positioning is also associated with an increased incidence of gastrointestinal symptoms.¹⁵ Because medical treatment is of limited success, prevention may be the best option. To this end, we have identified two risk factors which will simplify the design of future studies and our understanding of post-LP HA.

The general incidence of post-LP HA in our clinic is consistent with that reported by others.^{1,4,15} Low concentrations of substance P in CSF proved to be a sensitive marker for post-LP HA. This may represent a hypersensitivity (receptor mediated) phenomenon as previously outlined.¹⁶ As research has also shown that substance P concentrations in CSF correlate with serum concentrations, measurement of substance P in serum before lumbar puncture may have utility.¹⁸ This may identify a subset of patients who are more likely to respond to medications which have an effect on substance P concentrations (including prazosin, captopril, spantide, and capsaicin). These medications may be used in trials to prevent post-LP HA in this particular high risk group.^{19–22}

We also found that a history of chronic or recurrent headache is associated with post-LP HA. These patients were three times as likely to develop post-LP HA as those without chronic or recurrent headache. One study

identified a history of recent headache (within seven days) as a risk factor for post-LP HA.⁴ Many patients must wait several weeks to schedule a spinal tap, and most studies require advanced planning. Therefore, a positive history of chronic headache may prove more useful in predicting post-LP HA. This information will also help to simplify the design of long term prophylactic treatment trials.

- 1 Tourtellotte WW, Haerer AF, Heller GL, Sommers JE. *Post lumbar puncture headache*. Springfield, IL: Charles C Thomas, 1964.
- 2 Gielen M. Post dural puncture headache (PDPH): a review. *Reg Anaesth* 1989; 14:101-6.
- 3 Raskin NH. Lumbar puncture headache: a review. *Headache* 1990;30:197-200.
- 4 Kuntz KM, Kokmen E, Stevens JC, Miller P, Offord KP, Ho MM. Post lumbar puncture headaches: experience in 501 consecutive procedures. *Neurology* 1992;42:1884-7.
- 5 Lybecker H, Moller JT, May O, Nielsen HK. Incidence and prediction of postdural puncture headache: a prospective study of 1021 spinal anesthetics. *Anesth Analg* 1990;70:389-94.
- 6 Sechzer PH, Abel L. Post-spinal anesthesia headache treated with caffeine. *Curr Ther Res* 1978;24:307-12.
- 7 Fuerstein TJ, Zeides A. Theophylline relieves headache following lumbar puncture. *Klin Wochenschr* 1986;64:216-8.
- 8 Crawford JS. Experiences with epidural blood patch. *Anaesthesia* 1980;35:513-5.
- 9 Berrettini WH, Simmons-Alling S, Nurnberger JI. Epidural blood patch does not prevent headache after lumbar puncture. *Lancet* 1987;i:856-7.
- 10 Tourtellotte WW, Henderson WG, Tucker RP, et al. A randomized double-blind clinical trial comparing the 22 versus 26 gauge needle in the production of the post lumbar puncture syndrome in normal individuals. *Headache* 1972;12:73-78.
- 11 Vandam LD, Dripps RD. Long term follow up of patients who received 10,098 spinal anesthetics. *JAMA* 1956; 161:586-91.
- 12 Vilming ST, Shrader H, Monstad I. Post lumbar puncture headaches: the significance of body posture. *Cephalalgia* 1988;8:75-78.
- 13 Cook PT, Davies JM, Beavis RE. Bed rest and postlumbar puncture headache: the effectiveness of 24 hours' recumbency in reducing the incidence of postlumbar puncture headache. *Anaesthesia* 1989;44:389-91.
- 14 Handler C, Smith FR, Perkin GD, Rose FC. Posture and lumbar puncture headache: a controlled trial in 50 patients. *J R Soc Med* 1982;75:404-7.
- 15 Vilming ST, Shrader H, Monstad I. The significance of age, sex, and cerebrospinal fluid pressure in post lumbar headache. *Cephalalgia* 1989;9:99-106.
- 16 Solomon GD, Clark JW, Kunkel R. The role of denervation hypersensitivity to SP in the etiology of post lumbar puncture headache. *Headache* 1995; 35:25-8.
- 17 McGregor GP, Bloom SR. Radioimmunoassay of substance P and its stability in tissue. *Life Sci* 1983;32: 655-62.
- 18 Clark JW, Senanayake P, Solomon GD, Gallagher C. Substance P: correlation of CSF and plasma levels. *Headache* 1994;34:261-4.
- 19 Burks TF, Buck SH, Miller MS. Mechanisms of depletion of substance P by capsaicin. *Fed Proc* 1985;44:2531-4.
- 20 Delgado-Sygmunt TJ, Arbab MA, Edvinsson L, Jansen I, Svendgaard NA. Prevention of cerebral vasospasm in the rat by depletion or inhibition of substance P in conducting vessels. *J Neurosurg* 1990;72:917-25.
- 21 Rouissi N, Nantel F, Drapeau G, Rhaleb N, Dion S, Regoli D. Inhibitors of peptidases: how they influence the biological activities of substance P, neurokinins, kinins and angiotensins in isolated vessels. *Pharmacology* 1990;40: 185-95.
- 22 Faulhaber HD, Oehme R, Baumann J, Enderlein R, Rostock RG, Naumann E. Substance P in human essential hypertension. *J Cardiovasc Pharmacol* 1987;10:S172-6.

NEUROLOGICAL STAMP

Karl Rokitansky (1804-78)

Rokitansky was a Czech who studied philosophy at the University of Prague and later moved to Vienna to study medicine. He was one of the greatest of the gross descriptive pathologists and was able to base his lifelong study of disease on more than 30 000 necropsies personally performed over 40 years. Rokitansky was professor of pathology in Vienna for 30 years from 1844 and was one of the chief founders of the new Vienna School. His *Handbuch der pathologischen Anatomie (1842-46)* was based on many thousands of necropsies. Among his special contributions were treatise on diseases of the arteries and defects of the heart. He was the first to detect bacteria in the lesions of malignant endocarditis. Other contributions include studies on goitre, acute yellow atrophy of the liver (also known as Rokitansky's disease), polycystic tumour of the ovaries, acute dilatation of the stomach, and perforating gastric ulcer and he recognised the association of intracranial lesions with erosions of the gastric mucosa. He also described spondylolisthesis and spondylitic deformity of the spine. At first he was an adherent of the humoral theory of disease but was bitterly opposed by Virchow, the founder of modern cellular pathology. Later Rokitansky accepted Virchow's view.

He was a genial and witty man. Of his four sons, two became physicians and the other two concert singers which led him to remark that they were of two classes, the healers and howlers: *Die Einen heilen, die Anderen heulen*.



He was honoured in the set of stamps issued by Austria in 1937 showing great doctors (Stanley Gibbons 817, Scott B158).

L F HAAS