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Factors predicting response to the first epidural blood patch in spontaneous intracranial hypotension

Jr-Wei Wu,[1,*] Shu-Shya Hseu,[2,3,*] Jong-Ling Fuh,[1,3] Jiing-Feng Lirng,[3,4] Yen-Feng Wang,[1,3] Wei-Ta Chen,[1,3] Shih-Pin Chen[1,3] and Shuu-Jiun Wang[1,3,5]

*These authors contributed equally to this work.

Spontaneous intracranial hypotension results from cerebrospinal fluid leakage. Currently, the treatment of choice for spontaneous intracranial hypotension is the epidural blood patch, which has a variable response rate and no clear outcome predictors. This study aimed to identify predictors for response rate of a first targeted epidural blood patch in patients with spontaneous intracranial hypotension. We reviewed cases of patients with spontaneous intracranial hypotension who received targeted epidural blood patch at our hospital between 1 January 2007 and 1 July 2014. The outcome measure was first epidural blood patch response. We analysed demographics, clinical manifestations, neuroimaging findings (non-contrast heavily T_2-weighted magnetic resonance myelography and brain magnetic resonance imaging), and blood volume as potential outcome predictors. Significant predictors were tested and a decision tree was used to construct a predictive model. In total, 150 patients with spontaneous intracranial hypotension were included for final analyses. Their overall first targeted epidural blood patch response rate was 58.7%. Among patients with a greater injected blood volume ($\geq$22.5 versus $<$22.5 ml), the response rate was higher (67.9% versus 47.0%, $P = 0.01$). In brain and spinal magnetic resonance imaging studies, significant predictors included anterior epidural cerebrospinal fluid collection length (<8 versus ≥ 8 segments; 72.5% versus 37.3%, odds ratio = 4.4, 95% confidence interval: 2.2–8.9, $P < 0.001$) and midbrain-pons angle ($\geq 40^\circ$ versus $<40^\circ$; 71.3% versus 37.5%, odds ratio = 4.1, 95% confidence interval 2.1–8.3, $P < 0.001$). Decision tree analyses showed that patients with anterior epidural CSF collection involving <8 segments and an injected blood volume $\geq$22.5 ml had an 80.0% response rate. Patients with anterior epidural cerebrospinal fluid collection involving ≥ 8 segments and a midbrain-pons angle $<40^\circ$ had a 21.2% response rate. These three variables predicted first epidural blood patch response in 71.3% of patients. Brain and spinal neuroimaging findings and epidural blood patch blood volume can be used to predict targeted first epidural blood patch response in patients with spontaneous intracranial hypotension.

1 Department of Neurology, Neurological Institute, Taipei Veterans General Hospital, No. 201, Sec. 2, Shi-Pai Road, Taipei, 11217, Taiwan
2 Department of Anaesthesiology, Taipei Veterans General Hospital, No. 201, Sec. 2, Shi-Pai Road, Taipei, 11217, Taiwan
3 Faculty of Medicine, National Yang-Ming University School of Medicine, No. 155, Sec. 2, Li-Nong Street, Taipei, 11217, Taiwan
4 Department of Radiology, Taipei Veterans General Hospital, No. 201, Sec. 2, Shi-Pai Road, Taipei, 11217, Taiwan
5 Brain Research Center, National Yang-Ming University, No. 155, Sec. 2, Li-Nong Street, Taipei, 11217, Taiwan

Correspondence to: Shuu-Jiun Wang, M.D.,
Department of Neurology, Neurological Institute,
Taipei Veterans General Hospital, No. 201, Sec. 2,
Shi-Pai Rd, Taipei, Taiwan, 11217
E-mail: sjwang@vghtpe.gov.tw

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Abbreviations: EBP = epidural blood patch; MRM = magnetic resonance myelography; SIH = spontaneous intracranial hypotension

Introduction

Spontaneous intracranial hypotension (SIH), also termed CSF hypovolaemia, results from CSF leakage from the spinal column (Mokri, 2013). The hallmark symptom of SIH is protracted and disabling orthostatic headache (i.e. worsens when upright, improves upon lying down). According to the International Classification of Headache Disorders (ICHD), 3rd edition, beta version, SIH diagnosis requires measurement of low CSF pressure (<60 mm CSF) and/or evidence of CSF leak on neuroimaging (Headache Classification Committee of the International Headache Society, 2013). Diagnostics for suspected SIH include lumbar puncture, radioisotope cisternography, computed tomography myelography, and magnetic resonance myelography (MRM) (Wang *et al.*, 2009; Headache Classification Committee of the International Headache Society, 2013; Mokri, 2013). Brain neuroimaging findings described for SIH include diffuse pachymeningeal enhancement (Pannullo *et al.*, 1993), venous distention (Baryshnik and Farb, 2004; Farb *et al.*, 2007), brain sagging (Pannullo *et al.*, 1993), enlarged pituitary gland (Mokri and Atkinson, 2000), and subdural fluid accumulation (Reich *et al.*, 1993; Lin *et al.*, 2002). Spinal neuroimaging findings described for SIH include periradicular leaks, epidural CSF collection, and high cervical (C1–2 to C2–3) retrospinal CSF collection (Schievink *et al.*, 2004; Tsai *et al.*, 2007; Wang *et al.*, 2009). At present, these findings are used for diagnosis, but not outcome prediction.

Treatment for SIH includes bed rest, caffeine, theophylline, intravenous fluid infusion, epidural blood patch (EBP), epidural fibrin glue injection, and surgical repair (Mokri, 2013; Ducros and Biousse, 2015). The EBP, introduced by Gormley in 1960 for post-dural puncture headache treatment, is the current treatment of choice for SIH (DiGiovanni and Dunbar, 1970; Schievink, 2006; Ducros and Biousse, 2015). The immediate effect of EBP is volume replacement by compression of the dural membrane, and the delayed effect is fibrosis or scar formation on the dural tear (Mokri, 2013). Several factors may influence EBP response rates, such as bed-rest duration, bed-rest position (e.g. flat versus Trendelenburg position), and whether the EBP was targeted or blind (Mokri, 2013).

First-EBP response rates in SIH patients are variable, ranging from 36% to 90% with different injection methods and blood volumes (Sencakova *et al.*, 2001; Berroir *et al.*, 2004; Ferrante *et al.*, 2010). EBP response predictors are lacking, and there are no standard EBP methods for SIH due to the small sample sizes of previous studies (15–56 patients) and a dearth of neuroimaging data analysis. The aims of this study were to identify whether demographics, clinical profiles, the injected blood volume or the brain and spinal neuroimaging findings could predict the response to the first targeted EBP in patients with SIH.

Materials and methods

Demographics and clinical profiles

Consecutive patients with SIH who were admitted to the Neurology ward of Taipei Veterans General Hospital between 1 January 2007 and 1 July 2014 were recruited. Diagnoses were made according to the ICHD 2nd edition criteria (Headache Classification Committee of the International Headache Society, 2004) for headache attributable to SIH (7·2·3), except for criterion D (headache resolution within 72 h of EBP) because some patients' headaches did not resolve within 72 h. Age, sex, body mass index (BMI), disease duration, hospital course data, history of pre-morbid headache, headache features (orthostatic headache, thunderclap headache, and cough headache), headache intensity [11 point (0–10) numeric rating scale], and associated phenomena (nausea, vomiting, photophobia, hearing impairment, tinnitus, vertigo, diplopia) were collected from medical records (Fig. 1).

Neuroimaging

Heavily T_2-weighted non-contrast MRM was performed with a phased-array spine coil on a 1.5 T superconducting system (Signa HD or Signa Excite twin, GE Medical Systems) without using intrathecal gadolinium as described previously (Wang *et al.*, 2009, 2015). The following signs were recorded (Fig. 2): periradicular leaks, epidural CSF collections, high cervical (C1–2 to C2–3) retrospinal CSF collections (Wang *et al.*, 2009, 2015; Watanabe *et al.*, 2009). In addition, we also measured 'anterior' epidural fluid collections (Watanabe *et al.*, 2009) and posterior epidural fluid collections separately. The anterior epidural fluid collection was defined as the epidural fluid collections at the anterior epidural space (surrounded by dura, posterior longitudinal ligament, and the periosteum of the vertebral body) (Newell *et al.*, 1999; Loughenbury *et al.*, 2006). The posterior epidural fluid collection was defined as the epidural fluid collections presented at posterior epidural space (surrounded by dura and ligamentum flavum) (Newell *et al.*, 1999; Loughenbury *et al.*, 2006). We used vertebral segment(s) to measure the lengths of total, anterior and posterior epidural fluid collections as well as the periradicular leaks.

The following brain MRI signs of SIH were recorded: diffuse pachymeningeal enhancement (Pannullo *et al.*, 1993), venous distention of the lateral sinus (Baryshnik and Farb, 2004; Farb *et al.*, 2007), brain sagging (Fishman and Dillon, 1993), iter descent below the incisural line (>2 mm) (Pannullo *et al.*, 1993; Reich *et al.*, 1993; Savoiardo *et al.*, 2007), enlarged pituitary gland (Mokri and Atkinson., 2000), subdural fluid

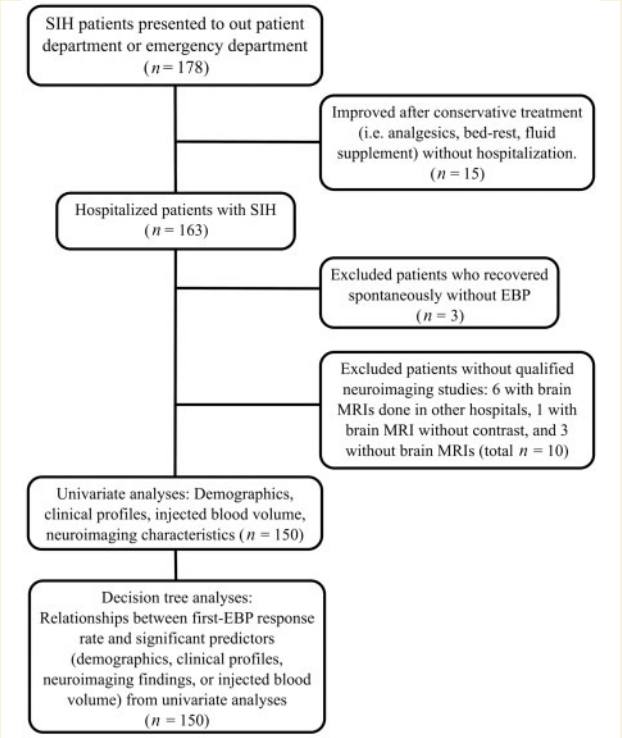

Figure 1 Schematic patient flow chart.

collection (Lin *et al.*, 2002; Schievink *et al.*, 2005), and midline shift. We also measured the midbrain-pons angle as a continuous variable of diencephalic-mesencephalic deformity severity (Fig. 3B and E) (Shah *et al.*, 2013). The midbrain-pons angle was defined as the angle between the line tangential to the anterior margin of the midbrain and the line tangential to the superior margin of pons on sagittal midline of brain MRI with a good interobserver reliability in 29 patients with SIH (kappa coefficient = 0.62) (Shah *et al.*, 2013). The Shah *et al.* (2013) study showed that the mean midbrain-pons angle of SIH patients were sharper compared to that of normal controls (41.2° versus 65°) (Shah *et al.*, 2013); therefore, in this study, we used 40° as a cut-off value. The angle between the vein of Galen and straight sinus (vG/SS angle) was measured as an index of downward stretching (Fig. 3C and F) (Savoiardo *et al.*, 2007). All imaging findings were interpreted by an experienced neuroradiologist (J.F.L) as in our previous studies (Tsai *et al.*, 2007; Wang *et al.*, 2009, 2015).

Epidural blood patch

Periradicular leaks revealed by MRM were considered a direct sign of leakage for targeted EBP (Yoo *et al.*, 2008; Wang *et al.*, 2009). In patients without periradicular leaks, we selected the level(s) with the most prominent epidural fluid collection for EBP injection. EBP was performed in aseptic conditions by an experienced anaesthesiologist (S.S.H) with an 18-gauge epidural Tuohy needle via a midline approach with the patient in a lateral recumbent position. Autologous blood was injected slowly until onset of radicular pain, headache, nausea, or maximum, 55 ml. After the procedure, patients lay in the supine position for at least 2 h. If complete recovery did not occur within 2 days, an additional targeted EBP was performed.

Treatment response

A good response was defined as complete remission of symptoms within 48 h after the first EBP, persisting for at least 3 months. A poor response was defined as persistent symptoms or only partial relief after the first EBP, with at least one additional EBP being needed. The outcome measure was first-EBP response.

Statistics

Relationships were analysed between response rate and demographics, clinical profiles, neuroimaging findings, and injected blood volume. Relationships among categorical and continuous variables were analysed using chi-square, Fisher's exact, linear-by-linear association, or *t*-tests as appropriate. Significant variables were examined by a classification and regression tree (CRT), a non-parametric, binary decision tree used to estimate bivariate cut-off values for maximal sensitivity and specificity (Breiman *et al.*, 1984). The terminal subgroups of all CRT split points contained at least 25 patients. We used rounded values for MRI measurements. The significant variables were used to construct a decision tree based on the exhaustive 'Chi-squared Automatic Interaction Detection' (CHAID) algorithm (Kass, 1980) with the following adjustments: $\geqslant 30$ and $\geqslant 25$ cases per parent node and child node, respectively; automatic maximum tree depth; Pearson's χ^2 statistic; significance for splitting nodes set at <0.05 with Bonferroni correction; and 10-fold cross-validation. For all analyses, results were considered significant when $P < 0.05$. All statistical analyses were conducted with IBM SPSS (version 22·0).

Ethics

The study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital (2015-08-001BC).

Results

Patients

From 1 January 2007 to 1 July 2014, 178 patients who were diagnosed with SIH presented to our outpatient clinics or emergency department. Fifteen patients improved after conservative treatment, that is, analgesics, bed-rest, and fluid supplement without hospitalization. A total of 163 SIH patients (51 males and 112 females) were admitted to our hospital during the study period (Fig. 1). Of the 163 hospitalized patients, three patients' symptoms recovered spontaneously without further treatment. Among them, 150 (Table 1) who received at least one targeted EBP were enrolled into the final analyses of this study. The overall response rate of the first targeted EBP was 58.7% (88/150). Among the remaining 62 patients, 50 (33.3%) responded to the second EBP and nine (6.0%)

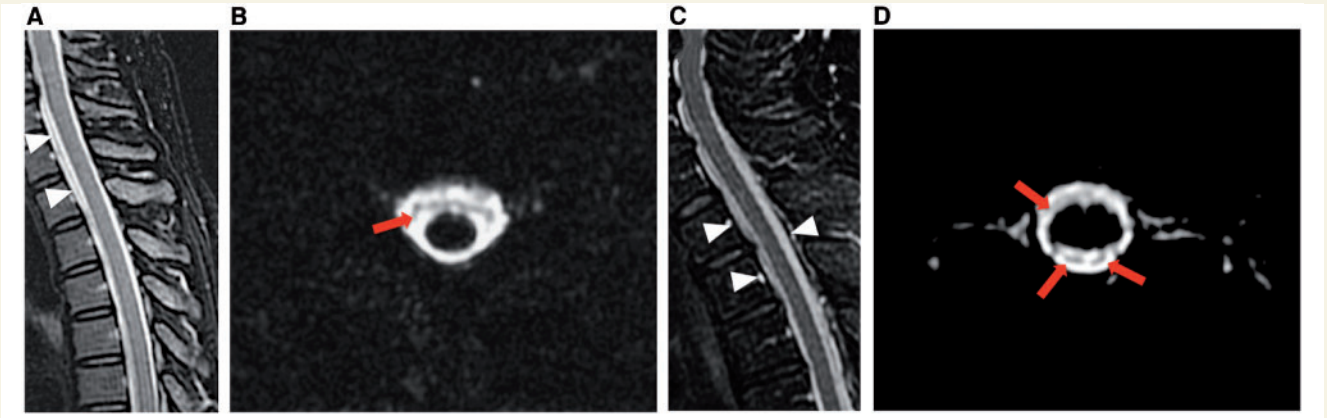

Figure 2 Images of epidural CSF collection. One patient (**A** and **B**) had substantial anterior epidural CSF collection. (**A**) Sagittal MRI of the cervical and thoracic spine showing the anterior epidural CSF collection (arrowhead). (**B**) Axial MRM showing anterior epidural CSF collection beyond the dura (arrow). Another patient (**C** and **D**) had both anterior and posterior epidural CSF collection. (**C**) Sagittal MRI of the cervical and thoracic spine showing anterior and posterior epidural CSF collection (arrowhead). (**D**) Axial MRM showing epidural CSF collection located outside of the dura (arrow).

responded to the third EBP. Three patients failed to respond after three EBPs, of whom, one (0.7%) responded to the fourth EBP and the other two (1.3%) who did not receive the fourth EBP remained symptomatic. Of the 150 patients enrolled into the final analysis, their mean age was 39.6 ± 9.5 years (range, 24–67), mean hospitalization duration 9.2 ± 8.7 days (range, 1–53), and mean onset-diagnosis interval 45.1 ± 94.1 days (range 1–749, median 20).

Demographics and clinical profiles

First EBP response rate was not associated with age, sex, BMI, onset-diagnosis interval, history of pre-morbid headaches, headache features, headache intensity, or associated phenomena (Table 1).

Injected blood volume of epidural blood patch

First EBP response rate increased with increasing blood injection volume across six 10-ml intervals ($P = 0.039$; Supplementary Table 1). The response rate was higher when blood injection volume was >22.5 ml ($n = 84$, 67.9%) compared with <22.5 ml ($n = 66$, 47.0%) [$P = 0.01$; odds ratio (OR) = 2.4, 95% confidence interval (CI) 1.2–4.6, Supplementary Table 1].

Neuroimaging

Among brain MRI findings in our patients, the most common abnormalities were an enlarged pituitary gland ($n = 134$, 89.3%), venous distention ($n = 124$, 82.7%), and diffuse pachymeningeal enhancement ($n = 103$, 68.7%). Subdural fluid collection (haematoma/effusion) was observed in 39 patients (26.0%) and 11 of them received surgery for subdural haematoma. In spinal MRM, CSF leakage sites occurred most commonly in upper thoracic levels (Supplementary Fig. 1). There was no difference in the response rates between the two methods for determination of EBP injection sites [periradicular leaks and most prominent epidural fluid collection; 57.7% (75/130) versus 65.0% (13/20); $P = 0.537$]. First EBP response rates are reported by spinal level in Table 1.

Most of the brain MRI signs for SIH were not associated with the response rate, including vG/SS angle (Table 1) (Savoiardo *et al.*, 2007). However, the midbrain-pons angle was wider in responders than in non-responders (45.9° ± 15.7° versus 34.1° ± 20.0°, $P < 0.001$). We subdivided the midbrain-pons angle using a cut-off value of 40° (mean value of midbrain-pons angle = 41.1°, cut-off value derived from CRT analysis = 42.6°). The response rate was higher (71.3%; 67/94) in patients with a midbrain-pons angle ⩾40° than in those (37.5%; 21/56) with an angle <40° ($P < 0.001$; OR = 4.1, 95% CI 2.1–8.3). Most of the MRM signs of CSF leakage (i.e. length of epidural CSF collection, length of posterior epidural CSF collection, length of periradicular leaks, and presence/absence of high cervical restrospinal CSF collections) did not associate with the outcome (Table 1). Anterior epidural CSF collections involved fewer segments in responders than in non-responders (5.5 ± 4.3 versus 9.1 ± 5.0, $P < 0.001$) (Table 1). We subdivided the length of anterior epidural CSF collections using a cut-off value of eight segments (best cut-off value derived from CRT analysis = 7.5 segments). The response rate was higher in patients with <8 segments involved (72.5%, 66/91) than in patients with ⩾8 segments involved (37.3%, 22/59; $P < 0.001$; OR = 4.4, 95% CI 2.2–8.9).

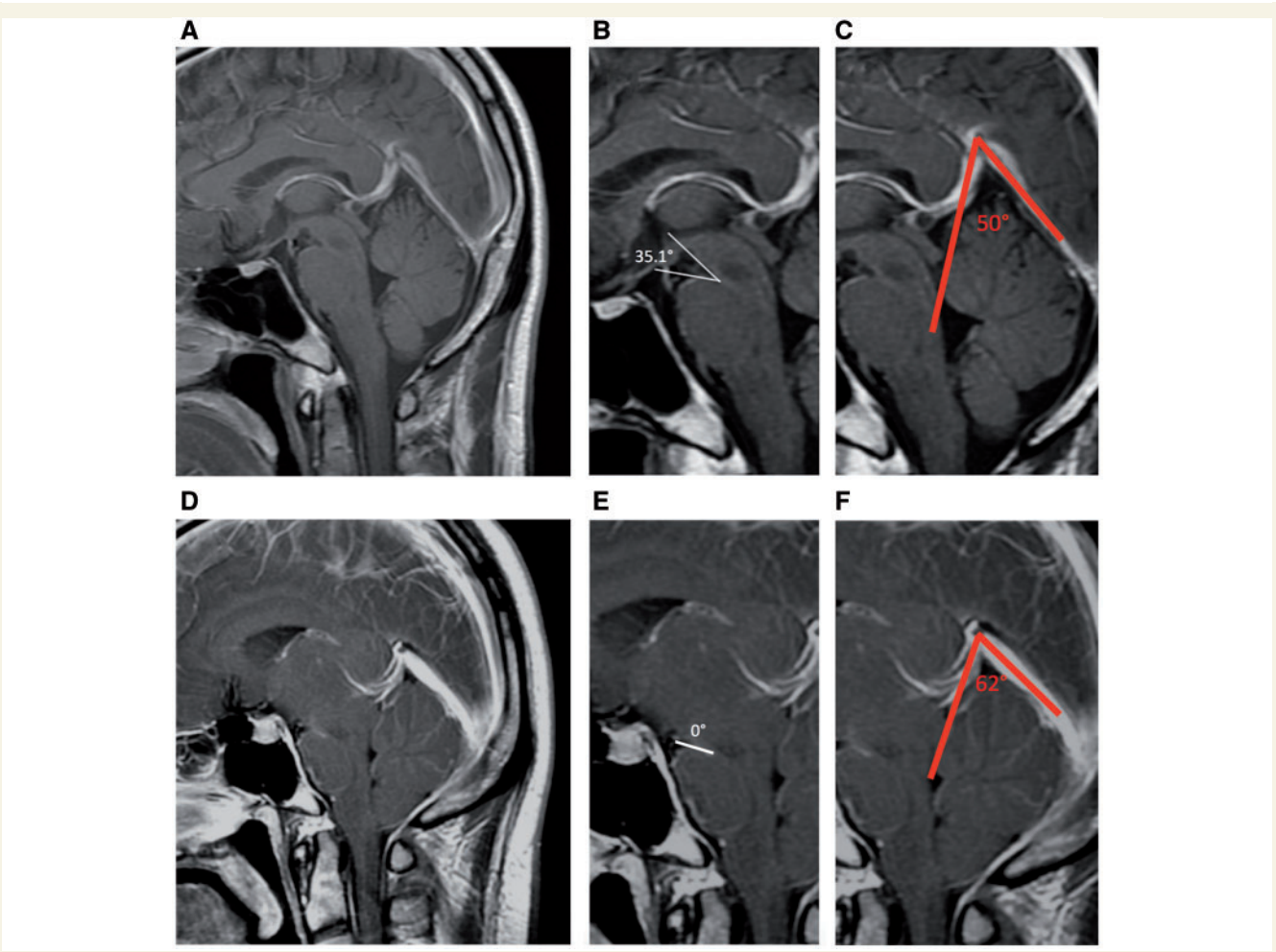

Figure 3 Brain MRI images and measurement of anatomical angles. One patient is shown in **A–C** and a second patient is shown in **D–F**. Midbrain-pons angles are shown in (**B**) and (**E**), which was defined as the angle between the line tangential to the anterior margin of the midbrain and the line tangential to the superior margin of pons based on the midline sagittal view of brain MRI; note the more severe diencephalic-mesencephalic deformity with a 'closed' midbrain-pons angle in the second patient (**E**). The patients' corresponding vG/SS angles (index of downward stretching) are shown in **C** and **F**.

Decision tree analyses for response predictors

A decision tree model constructed based on the most significant data-splitting factors with the exhausted CHAID method (Fig. 3) had an overall classification accuracy of 71.3% ($n = 150$) by using three significant variables obtained above. The variable that best predicted outcome was the length of anterior epidural CSF collection (level 1). In patients with <8 such segments, the best predictor for a good response was blood volume $\geqslant 22.5$ ml (level 2). In patients with $\geqslant 8$ such segments, the best predictor was midbrain-pons angle (level 2). Additional EBPs were needed in patients with midbrain-pons angles $<40^{\circ}$ (2.0 ± 0.6 versus 1.5 ± 0.7 EBPs, $P = 0.007$). Patients with both anterior epidural CSF collection <8 segments and a blood volume $\geqslant 22.5$ ml had a 3.8-fold higher (80.0% versus 21.2%) response rate than patients with anterior epidural CSF collection $\geqslant 8$ segments and a midbrain-pons angle $<40^{\circ}$ (Fig. 4).

Discussion

The main finding of this study was that the length of anterior epidural CSF collection, severity of diencephalic-mesencephalic deformity, and blood volume injected were three major predictors of targeted EBP treatment response. Our study has several strengths. First, the sample size was larger than in previous SIH studies regarding treatment efficacy (Sencakova *et al.*, 2001; Berroir *et al.*, 2004; Ferrante *et al.*, 2010; Horikoshi *et al.*, 2010; Cho *et al.*, 2011). Second, we considered

Table 1 Demographics, clinical features, neuroimaging findings, and first EBP response rate in SIH patients

Factors All patients	Total patients (*n* = 150)	Responders (*n* = 88)	Non-responders (*n* = 62)	*P**
Age (years)	39.6 ± 9.5	40.4 ± 9.6	38.4 ± 9.3	0.220
Sex				
Male	46 (30.7%)	27 (30.7%)	19 (30.6%)	0.996
Female	104 (69.3%)	61 (69.3%)	43 (69.4%)	
Onset-diagnosis interval, days	45.1 ± 94.1	41.2 ± 79.4	50.6 ± 112.2	0.547
Body mass index	23.0 ± 4.0	22.7 ± 3.6	23.4 ± 4.5	0.272
History of premorbid headaches	22 (14.7%)	12 (13.6%)	10 (16.1%)	0.671
Headache features				
Orthostatic headache	150 (100%)	88 (100%)	62 (100%)	
Thunderclap headache	2 (1.3%)	1 (1.1%)	1 (1.6%)	1.000
Cough headache	3 (2%)	2 (2.3%)	1 (1.6%)	1.000
Headache intensity (0–10)	8.3 ± 2.1	8.2 ± 2.3	8.5 ± 1.8	0.408
Associated phenomena				
Nausea	110 (73.3%)	62 (70.5%)	48 (77.4%)	0.342
Vomiting	72 (48.0%)	41 (46.6%)	31 (50.0%)	0.681
Photophobia	32 (21.3%)	18 (20.5%)	14 (22.6%)	0.453
Hearing impairment	31 (20.7%)	16 (18.2%)	15 (24.2%)	0.371
Tinnitus	62 (41.3%)	31 (35.2%)	31 (50.0%)	0.07
Vertigo	3 (2.0%)	2 (2.3%)	1 (1.6%)	1.000
Diplopia	1 (0.7%)	1 (1.1%)	0 (0.0%)	1.000
Level of CSF leakage[a]				
Cervical	7 (4.7%)	5 (5.7%)	2 (3.2%)	0.366
Thoracic	127 (84.7%)	76 (86.4%)	51 (82.3%)	
Lumbar	16 (10.7%)	7 (8.0%)	9 (14.5%)	
Brain MRI signs				
Diffuse pachymeningeal enhancement	103 (68.7%)	58 (65.9%)	45 (72.6%)	0.386
Venous distension of the lateral sinus	124 (82.7%)	71 (80.7%)	53 (85.5%)	0.444
Brain sagging	62 (41.3%)	32 (36.4%)	30 (48.4%)	0.141
Iter >2 mm below incisural line	99 (66.0%)	57 (64.8%)	42 (67.7%)	0.705
Enlarged pituitary gland	134 (89.3%)	76 (86.4%)	58 (93.5%)	0.160
Subdural fluid collection	39 (26.0%)	20 (22.7%)	19 (30.6%)	0.276
Midline shift, subdural fluid collection	15 (10.0%)	10 (11.4%)	5 (8.1%)	0.507
vG/SS angle G/SS angle, degree, mean ± SD)	63.5° ± 25.0	63.0° ± 25.7	64.3° ± 24.1	0.742
Midbrain-pons angle	41.1° ± 18.5	45.9° ± 15.7	34.1° ± 20.0	<0.001
⩾40°	94 (62.7%)	67 (76.1%)	27 (43.5%)	<0.001
<40°	56 (37.3%)	21 (23.9%)	35 (56.5%)	
MRM signs				
Epidural CSF collection	145 (96.7%)	83 (94.3%)	62 (100.0%)	0.056
Length (vertebral segments)	15.1 ± 5.3	14.6 ± 5.8	15.7 ± 4.3	0.174
Anterior epidural CSF collection	141 (94.0%)	80 (90.9%)	61 (98.4%)	0.058
Length (vertebral segments)	7.0 ± 4.9	5.5 ± 4.3	9.1 ± 5.0	<0.001
Posterior epidural CSF collection	145 (96.7%)	84 (95.5%)	61 (98.4%)	0.324
Length (vertebral segments)	12.7 ± 5.1	12.3 ± 5.7	13.2 ± 4.1	0.270
Periradicular leaks	130 (86.7%)	75 (85.2%)	55 (88.7%)	0.537
Length (vertebral segments)	3.1 ± 3.2	3.3 ± 3.5	2.8 ± 2.5	0.379
High cervical (C1–2 to C2–3) retrospinal CSF collections	34 (22.7%)	16 (18.2%)	18 (29.0%)	0.118
Injection site determination				
Periradicular leaks	130 (86.7%)	75 (85.2%)	55 (88.7%)	0.537
Most prominent epidural fluid collection	20 (13.3%)	13 (14.8%)	7 (11.3%)	

Data are number (%) or mean (SD).

*Student's *t*-test for continuous variables and chi-square or Fisher's exact tests for categorical variables, comparisons between responders and non-responders.

[a]Visibility of periradicular leaks in MRM was considered a direct sign of CSF leakage (Yoo *et al.*, 2008; Wang *et al.*, 2009).

both brain and spinal magnetic resonance findings, which were interpreted by the same neuroradiologist and well-validated by our previous studies (Lin *et al.*, 2002; Tsai *et al.*, 2007; Wang *et al.*, 2009, 2015). Third, except for differing blood volumes across cases, we used a consistent targeted EBP technique in our hospital, making analysis of this variable possible (Wang *et al.*, 2009, 2015).

Neuroimaging predictors for epidural blood patch response rate

In spinal MRM, possibly due to the ceiling effect, the total length of epidural CSF collection might not reflect the severity of CSF leakage in patients with SIH. In contrast, the length of anterior epidural CSF collection was more useful as a predictor. Because MRI was performed supinely, anterior collection may better reflect the amount or severity of epidural CSF leakage. The mean midbrain-pons angle (41.1° ± 18.5°) in our SIH patients was similar to that (41.2° ± 17.4°) in the study of Shah *et al.* (2013), validating the reliability of this measurement. In fact, midbrain-pons angle narrowing might reflect brain sagging severity (Shah *et al.*, 2013), which is different from the other MRI findings due to the Monro-Kellie doctrine (e.g. venous distension sign, diffuse pachymeningeal enhancement, and pituitary hyperaemia) (Mokri, 2001). Savoiardo *et al.* (2007) used the vG/SS angle to reflect severity of transtentorial brain sagging and brain swelling. However, this latter angle was not associated with the response in our study.

In MRM, anterior epidural CSF collection involving $\geqslant 8$ segments could be considered a criterion for severe spinal CSF leakage in patients with SIH. In brain MRI, we defined severe diencephalic-mesencephalic deformity as midbrain-pons angle $\leqslant 40°$. Hence, in patients with severe spinal CSF leakage (anterior epidural CSF collections $\geqslant 8$ segments), severity of diencephalic-mesencephalic deformity can serve as a prognostic predictor. Downward stretching of the brainstem may indicate cerebral decompensation due to severe spinal CSF leakage and thus be suggestive of a poor prognosis.

Optimal blood volume for epidural blood patch

We found that a larger blood volume for EBP was associated with a higher success rate. In subgroup analysis, this effect was more pronounced in patients with less severe spinal CSF leaks (epidural CSF collection < 8 segments). In patients with anterior epidural CSF collection affecting $\geqslant 8$ segments, injected blood volume was not predictive of outcome, and most (62.7%) required an additional EBP.

The association between injected blood volume and treatment outcome has been studied previously in post-dural puncture headache, but not in SIH (Brownridge, 1983; Crawford, 1980; Safa–Tisseront *et al.*, 2001). Compared with patients with post-dural puncture headache, SIH patients are more severe clinically and more likely to have multiple leakage sites (Cohen-Gadol *et al.*, 2006; Wang *et al.*, 2009). In patients with post-dural puncture headache, the EBP response rate was 75% with an injected blood volume $\leqslant 10$ ml (Brownridge, 1983) and 93–98% with a volume > 20 ml (Crawford, 1980). Likewise, in SIH patients, we found that a larger blood injection volume associated with a higher response rate. A larger blood volume should displace more CSF from the extradural space, providing more compressive force on the dural sac and thereby reducing the compartment volumes (Mokri, 2013). Additionally, a greater blood volume should facilitate spreading of blood across segments, compressing dural defects at multiple levels (Szeinfeld *et al.*, 1986; Cho *et al.*, 2011). For those with more severe leakage, even blood volumes $\geqslant 22.5$ ml may not provide sufficient compression. Further increasing the blood volume might improve efficacy, but also might cause intolerable radicular pains, nausea, and headaches. Therefore, repeated EBPs may be a necessity in these patients.

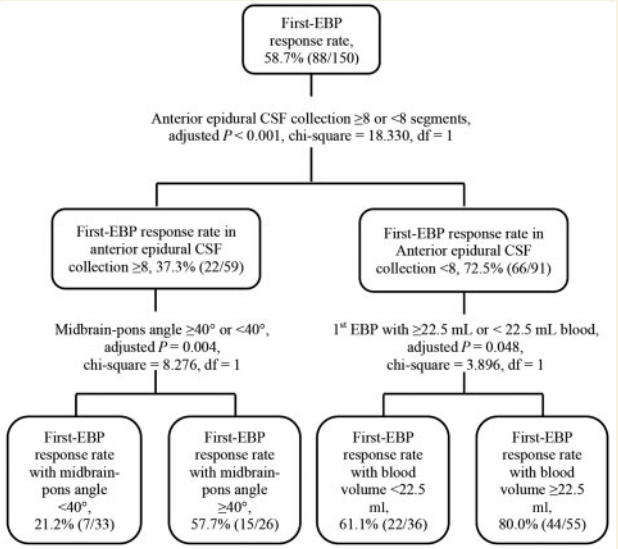

Figure 4 Decision tree analyses for response predictors. Predictors associated with first EBP response rate were used to construct a decision tree based on the exhaustive CHAID algorithm with the following adjustments: $\geqslant 30$ and $\geqslant 25$ cases per parent node and child node, respectively; automatic maximum tree depth; Pearson's χ^2 statistic; significance level for splitting nodes set at < 0.05 with Bonferroni correction; and 10-fold cross-validation.

Table 2 summarizes recent studies on the treatment response to the first targeted EBP in patients with SIH. Of note, targeted EBP resulted in a higher response rate than blind EBP in a controlled study (Cho *et al.*, 2011). However, the response rates for targeted EBP varied, ranging from 36% in Sencakova *et al.* (2001) to 87% in Cho *et al.* (2011) with similar blood amount (10–15 ml). The reasons accounting for this discrepancy are not known. Different disease severity should be considered. Our study demonstrated that larger blood volume was associated with a higher response rate. Therefore, the technique that may facilitate spreading of the injected blood within the epidural space (i.e. larger blood amount) may have a chance to improve the response rates.

Predicting first epidural blood patch response rate in patients with spontaneous intracranial hypotension

Based on the decision tree analyses for targeted EBP treatment of our patients with SIH, only three variables could

Table 2 Recent studies on the response rates of targeted EBP in patients with SIH

EBP technique(s)	Study location, citation	*n*	EPB injected blood volume, ml	Bed rest duration after EBP	First-EBP response rate
Targeted	Taiwan (present study)	150	⩾22.5	>2 h	67.9% (57/84)
			<22.5	>2 h	47.0% (31/66)
	USA Sencakova *et al.* (2001)	25	15–20 (mean, 17)	2 h	36% (9/25)
	Korea Targeted EBP group (Cho *et al.*, 2011)	31	10–15	24–48 h	87% (27/31)

provide a high accuracy (71.3%) in predicting the response. Patients with less severe spinal CSF leakage, i.e. anterior epidural fluid collection <8 segments, had a 72.5% response rate. Of them, injected blood volume of EBP ⩾22.5 ml would result in 80.0% response rate. Conversely, in patients with severe spinal CSF leakage (>8 segments), the treatment outcome depended on severity of the diencephalic-mesencephalic deformity but not injected blood volume. In this group of patients, repeating EBP with a tolerable blood volume is recommended because a single 'tolerable' EBP may not provide adequate compression for potentially multiple dural defects.

Limitations

This study has limitations. First, the study was of a retrospective design. However, our group have studied this topic for a long time and used similar protocols for neuroimaging diagnoses and treatment in SIH patients (Lin *et al.*, 2002; Tsai *et al.*, 2007; Fuh *et al.*, 2008; Wang *et al.*, 2009, 2015). Therefore, we recruited a sizeable number of patients to analyse the predicting factors for treatment outcomes. Second, SIH patients may recover spontaneously; therefore, without a control group, it is unclear what percentage of EBP-treated patients in our study would indeed recover spontaneously. Third, the amount of injected blood volume was determined by the occurrence of radicular pain, headache, or nausea, which might have different underlying causes and might have influenced the clinical outcomes. Fourth, it should be cautious to extrapolate our results to other SIH populations because our participants might represent a more severe subgroup of SIH. Our hospital is a tertiary hospital as well as a medical centre. In addition, SIH patients who failed conservative treatment were likely to be admitted to our hospital for EBP because this is an in-patient procedure in our hospital. In fact, high percentages of epidural fluid collection (96.7%) and periradicular leaks (86.7%) reflected the severity of our patients (Wang *et al.*, 2009; Watanabe *et al.*, 2009). Fifth, not all headache features were collected by this study such as residual headache in recumbence or migraine diagnoses, which might be contributory to the outcomes of EBP.

Conclusions

This study showed that both brain and spinal neuroimaging findings and EBP blood volume are predictive factors for first-EBP response. Future studies are warranted to replicate our study results.

Supplementary material

Supplementary material is available at *Brain* online.

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