Dural puncture and activated protein C resistance: risk factors for cerebral venous sinus thrombosis

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Abstract

***Objectives*—Dural puncture is regarded a safe procedure when contraindications are carefully excluded and has so far not been recognised as a risk factor for cerebral venous sinus thrombosis (CVST). Five patients are described with CVST after dural puncture in the presence of additional risk factors.**

***Methods*—In four out of five patients complete investigations for thrombophilia were performed at least one month after withdrawal of oral anticoagulation.**

***Results*—In three out of four patients tested, activated protein C (APC) resistance due to heterozygous coagulation factor V R506Q mutation (factor V Leiden) was found. One patient was using oral contraceptives as a circumstantial risk factor and three had had spinal anaesthesia for surgical procedures. Family history of venous thromboembolism was negative in all patients. Retrospective evaluation of 66 patients with CVST disclosed that dural puncture was the fourth most common risk factor (8%) possibly contributing to thrombosis.**

***Conclusion*—Dural puncture may constitute an additional risk factor for CVST especially in patients with APC resistance or surgery. In such patients a thrombophilia screen is indicated.**

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Keywords: Cerebral venous sinus thrombosis; dural puncture; activated protein C resistance; factor V R506Q mutation

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Lumbar puncture is generally regarded as a safe procedure when appropriate indications and contraindications are respected. Postdural puncture headache is the most common complication and is estimated to occur in 0.4% to 70% with most reports giving incidences of 15%–30%, depending on technique, age of patients, and size of needle.[1 2]

Overall risk of disabling or persistent symptoms—defined as severe headaches lasting longer than seven days, cranial nerve palsies, major exacerbation of pre-existing neurological disease, prolonged backache, aseptic meningitis, and nerve root or peripheral nerve injuries—has been estimated at between 0.1% and 0.5% in a review on complications after spinal anaesthesia.[3] High risk patients with papilloedema have an incidence of serious complications of about 1.2%.[4] Severe side effects of lumbar puncture, which include brainstem herniation, infection, subdural haemorrhage or effusion, and subarachnoid haemorrhage are considered to be rare.[1 2 5]

Cerebral venous sinus thrombosis (CVST) has a myriad of predisposing conditions which are often associated.[6–9] We report five cases of a hitherto unrecognised possible causal association: dural puncture. The common clinical picture was severe, progressive postdural puncture headache, changing from positional to continuous headache shortly before focal neurological signs arose. In three out of four patients investigated for thrombophilia we found a defect in the anticoagulant response to activated protein C (APC resistance)[10] due to the heterozygous factor V R506Q mutation (factor V Leiden).[11]

Subjects and methods

CASE REPORTS

Patient 1

This healthy 30 year old woman underwent surgical knee joint exploration under peridural anaesthesia. Postoperatively subcutaneous low dose unfractionated heparin (3×5000 IU/day) was started. On the second postoperative day she developed severe postural headache, thought to be due to accidental dural puncture during anaesthesia. The headache progressed over the next days and lost its positional component. Two days later a progressive right sided hemisyndrome evolved. Subsequently, the patient became somnolent and focal epileptic seizures of the right arm were found. As the patient became comatose a few days later a transfer to the intensive care unit for intubation was necessary. The patient was afebrile. Neurological examination showed meningism and a tetraspastic syndrome. Cerebrospinal fluid was xanthochromic with raised opening pressure and showed pleocytosis (33 mononuclear cells/µl and raised protein (0.9 g/l, normal value < 0.48 g/l). Brain CT disclosed extensive thrombosis of superior sagittal sinus and straight sinus associated with haemorrhagic infarction in both hemispheres. EEG was diffusely slowed. There was no clinical improvement under therapeutic anticoagulation with intravenous unfractionated heparin and the patient died two weeks after the initial event. Only brain necropsy was performed and

confirmed extensive CVST. No oral contraceptives were taken, she did not smoke, and family history for thrombosis was negative. Retrospective collection of data showed a haemoglobin concentration of 14.3 g/dl, a leucocyte count of 17.5×10^9/l with a left shift in the differential count, a sedimentation rate (Westergren) of 32 mm, and a serum creatinine of 62 μmol/l.

Patient 2

This healthy 23 year old man underwent surgical knee joint exploration. Peridural anaesthesia after several attempted punctures was unsuccessful and general anaesthesia had to be performed. Accidental dural puncture was suspected. Postoperative subcutaneous low dose unfractionated heparin (3×5000 IU/day) was given. Two days later headache with a postural component developed. Over the next week the headache intensified, lost its positional character, became continuous, and was accompanied by nausea and vomiting. Generalised epileptic seizures occurred twice. The patient was afebrile and somnolent, with a left sided sensorimotor hemisyndrome. His CSF was bloody with raised opening pressure, and pleocytosis (30 mononuclear cells/μl) and raised protein (1.2 g/l) were noted. Brain CT showed a small subcortical hypodensity in the right hemisphere and venous thrombosis of the superior sagittal sinus was suggested. This was confirmed by cerebral angiography showing thrombosis of the superior sagittal sinus and draining superior cortical veins. Treatment was initiated with continuous intravenous high dose heparin. Nevertheless, pulmonary embolism confirmed by intravenous digital subtraction angiography occurred. Over the next week, his mental status rapidly improved whereas hemiparesis persisted. Oral anticoagulation with phenprocoumon was maintained for six months. Clinical follow up three years later showed disabling residual left sided hemiparesis. Rare focal epileptic seizures occurred despite antiepileptic treatment. Brain CT at this point showed unchanged subcortical hypodensity of the right hemisphere. He did not smoke and family history for thrombosis was negative.

Patient 3

A 26 year old woman was admitted because of suspected left sided optic neuritis. Her CSF and cerebral MRI were normal. Visual evoked potentials were delayed and reduced in amplitude on the left side. She was treated with intravenous high dose methylprednisolone (0.5 g/day) and her vision rapidly improved. Four days after diagnostic lumbar puncture typical postlumbar puncture headache developed. Two days later the headache intensified, lost its positional component, and became throbbing and persistent. Serial generalised epileptic seizures occurred and the patient became somnolent. She was afebrile with a triparesis (both arms, right leg) and motor aphasia. Brain CT showed thrombosis of the superior sagittal sinus with bilateral, partially haemorrhagic venous infarctions. Thrombosis was confirmed by cerebral angiography (fig 1). Lumbar puncture disclosed a bloody CSF and raised opening pressure, cell count (28 mononuclear cells/μl), and protein (1.3 g/l). EEG was slowed with intermittent bifrontal delta wave activity and no epileptiform discharges. Anticoagulation was established with continuous intravenous high dose unfractionated heparin. As serial epileptic seizures continued despite antiepileptic drug treatment the patient had to be transferred to the intensive care unit and for several days there was no clinical improvement. Cerebral MRI one week after diagnosis of sinus thrombosis documented a minimally recanalised superior sagittal sinus with multifocal haemorrhagic and non-haemorrhagic infarctions (fig 2 and 3A). Over the next week there was almost complete remission of the neurological and neuropsychological deficits. Epileptic seizures did not occur any more. Oral anticoagulation with phenprocoumon was stopped after seven months, when clinical follow up showed the patient to have completely recovered. Control MRI documented almost entire recanalisation of superior sagittal sinus (fig 3B) and residual bilateral infarctions.

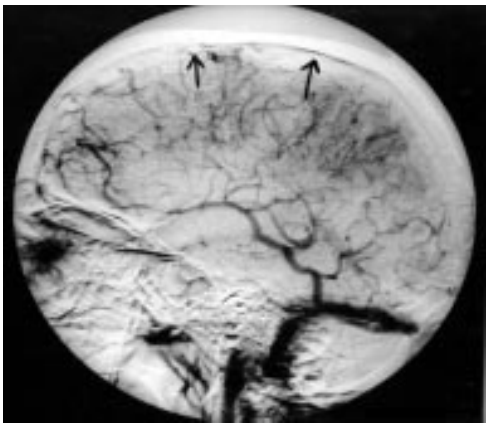

Figure 1 Digital subtraction angiography of patient 3, lateral view of the venous phase. There is extensive thrombosis of the superior sagittal sinus and connecting cortical veins. Arrows show filling defects.

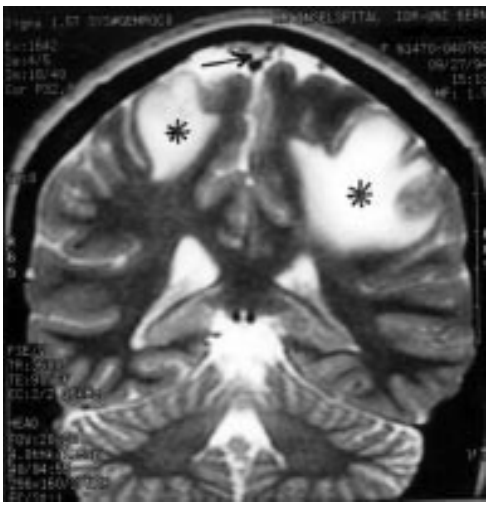

Figure 2 MRI one week after diagnosis of venous thrombosis. The coronal T2 weighted image shows multiple hyperintensive infarction areas (*). There is only minimal flow (hypointense area) in the superior sagittal sinus (arrow).

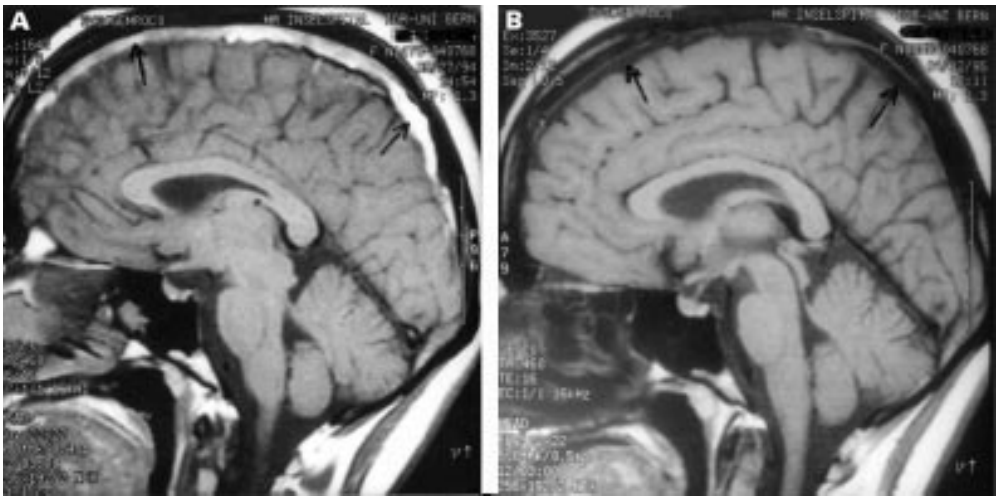

Figure 3 (A) Non-enhanced sagittal section one week after diagnosis of venous thrombosis shows extensive hyperintense signal in the superior sagittal sinus (arrows) in this T1 weighted image indicating venous occlusion. (B) Control examination seven months after picture A. The T1 weighted sagittal midline section shows regular flow void in the superior sagittal sinus corresponding to almost complete recanalisation (arrows).

EEG was normal and antiepileptic treatment slowly tapered. During three years preceding the event the patient had used a third generation oral contraceptive (Minulet) containing 0.075 mg gestodene and 0.03 mg ethinyl oestradiol. She did not smoke and family history for thrombosis was negative.

Patient 4

A 40 year old man had renal calculus lithotripsy under peridural anaesthesia. Two days later he developed typical postdural puncture headache. Over the next week headache lost its positional component, pain intensity increased, and nausea and vomiting developed. Subsequently, a right sided hemisyndrome with aphasia and two generalised epileptic seizures occurred. His CSF was bloody, opening pressure, cell count (pleocytosis of 54 cells/μl), and protein (1.2 g/l) were raised. Cerebral angiography confirmed the findings of CT of the brain with thrombosis of the superior sagittal sinus, transverse sinus, and partially straight sinus. Treatment with intravenous continuous high dose heparin and phenytoin was established. Within 10 days there was almost complete remission of neurological and neuropsychological deficits. Cerebral MRI at this time showed unchanged sinus venous thrombosis. Clinical follow up three months later confirmed complete recuperation. Control cerebral MRI was normal with complete recanalisation of the superior sagittal, transverse, and straight sinus. Oral anticoagulation with phenprocoumon was stopped and replaced by antiplatelet drugs for six months. Antiepileptic drugs were slowly tapered. He smoked one pack of cigarettes a day and family history for thrombosis was negative.

Patient 5

A 46 year old woman had lumbar myelography for evaluation of shooting pains in the left leg without sensorimotor deficits starting 12 days earlier. Two days later, she was dismissed as no lumbar disc herniation was found and CSF analysis was normal. However, due to moderate headache in the sitting and standing position, she spent most of the next few days in bed. One day before a second admission to our hospital, she awoke with severe headache, now persisting also in the supine position and increasing during the day despite analgesic medication. In the evening she had a focal epileptic seizure with secondary generalisation and was admitted to a local hospital, where a slight left sided sensorimotor hemisyndrome was found. The patient was afebrile and routine blood tests were normal. Early in the morning two further generalised epileptic seizures occurred and the patient was transferred to our department. She was afebrile, somnolent, disoriented, with meningism, exaggerated tendon reflexes, and bilateral extensor plantar response. Her CSF was clear, and opening pressure, cell count (11 cells/μl), and protein (1.2 g/l) were raised. Emergency CT of the brain showed thrombosis of the superior sagittal sinus and diffuse brain swelling which was later confirmed by MRI disclosing additional thrombosis of the straight sinus. Treatment with intravenous continuous high dose heparin and phenytoin was established. The next day headache decreased in intensity and she was fully oriented. Within seven days there was complete remission of neurological findings. Follow up MRI confirmed complete sinus recanalisation six months later. Oral anticoagulation with phenprocoumon was stopped after a year. The patient was a smoker (three packs of cigarettes a day) and had been treated for arterial hypertension during the past 11 years. Personal and family history for thrombosis was negative.

LABORATORY INVESTIGATIONS

Laboratory tests were performed no earlier than a month after stopping oral anticoagulation. After obtaining 5 ml blood in EDTA for a whole blood count and 5 ml blood without anticoagulant for chemical analysis, 2×9 ml blood samples were drawn into two plastic

Testing for coagulation and thrombophilia indices in four patients with postdural puncture cerebral venous sinus thrombosis

Index (units; normal values)	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*
Platelets ($\times 10^{-9}$/l; 125-320)	158	237	243	327
Factor V:C (%; 70-130)	79	99	112	150
Factor II:C (%; 70-130)	ND	79	100	132
Factor VII:C (%; 70-130)	ND	106	64	189
Factor X:C (%; 70-130)	ND	85	112	156
Fibrinogen (g/l; 1.5-3.0)	1.7	2.4	2.1	2.8
TAT-complex (µg/l; ≤ 4.1)	< 2	3.2	2.6	2.8
aPTT (s; 40-60)	47	51	30	40
Antithrombin III activity (%; 80-120)	106	105	98	123
Plasminogen activity (%; 70-130)	112	81	109	88
Protein C activity:				
aPTT method (%; 65-135)	73	96	96	131
Chromogenic substrate (%; 65-135)	ND	91	108	153
Protein S free antigen (%)*	83‡	70†	134‡	100†
Protein S total antigen (%)*	113‡	88†	136‡	136†
Euglobulin clot lysis test (min):				
Before venous occlusion (> 240)	> 240	ND	> 240	> 240
After venous occlusion (≤ 100)	173	ND	> 240	> 240
APC resistance:				
Basal aPTT (s)	33.6	37.9	34.5	27.4
Ratio (2.02-3.73)	2.04	2.09	1.93	2.40
Factor V R506Q (FV Leiden)	Heterozygous	Heterozygous	Heterozygous	Normal

ND = not done; * Protein S has different normal values for women † (free antigen 55%-120%, total antigen 65%-118%) and men ‡ (free antigen 67%-153%, total antigen 73%-134%).

syringes (Monovette®, Sarstedt, Nümbrecht, Germany), each containing 1 ml 0.106 M trisodium citrate as anticoagulant. Plasma was prepared as described[12] and assayed directly or first stored at −70°C. Samples were tested for a broad range of haematological indices using conventional methods as described earlier[12]: thromboplastin time (Quick), kaolin based activated partial thromboplastin time (aPTT), thrombin time, fibrinogen, factors II:C, V:C, VII:C, and X:C, antithrombin III heparin cofactor activity (Coatest® AT III, Chromogenix, Mölndal, Sweden), plasminogen activity (Coatest® Plasminogen, Chromogenix), protein C activity (aPTT method and chromogenic substrate method, kits from Behring, Marburg, Germany), total and free protein S antigen (Asserachrom® Protein S, Stago, Asnières, France), thrombin-antithrombin III (TAT) complex (Enzygnost®-TAT, Behring), and IgG and IgM anticardiolipin antibodies.

Euglobulin clot lysis time before and after 10 minutes of venous occlusion was determined.

The APC resistance was measured using the Coatest® APC resistance kit (Chromogenix) according to the method of Dahlbäck *et al*[10] and the Fibrintimer two channel coagulation analyser (Behring). The normal range for the aPTT ratio—that is, aPTT with added APC/aPTT without APC—had previously been evaluated in 200 healthy subjects as 2.02 to 3.73 in our laboratory.[12] Factor V genotype at nucleotide position 1691 was determined by DNA analysis employing the method described by Zöller *et al*.[13] Briefly, DNA was extracted from white blood cells. The DNA fragment containing the potential mutation site was amplified by polymerase chain reaction and then digested by the restriction enzyme Mnl I.

Results

In the four tested patients (one patient died before testing was possible) thromboplastin time, thrombin time, aPTT (excluding a lupus anticoagulant), and anticardiolipin antibodies (IgM and IgG) were normal. The systematic testing for thrombophilia (table) disclosed a heterozygous factor V R506Q mutation associated with hereditary APC resistance in three (patients 2, 3, and 4) out of four. Moreover, a reduced (patient 2) or lacking (patients 4 and 5) stimulation of the fibrinolytic system was disclosed by the euglobulin lysis test after venous occlusion.

Discussion

We have identified five patients with a common clinical pattern of initially typical positional postdural puncture headache progressing within a week to intensive continuous headache associated with focal neurological deficits which could be assigned to CVST. We could not identify conditions usually associated with CVST such as postpartum state, malignancy, vasculitis, infection, dehydration, or hyperviscosity. Two patients (1 and 2) had had recent minor surgery and patient 4 lithotripsy of kidney stones, which may induce a transient prothrombotic state. Interestingly, patients 1 and 2 received prophylactic postoperative low dose unfractionated heparin (3 × 5000 IU/day), which was not able to prevent development of CVST. In these patients, surgery itself and not only dural puncture may be a relevant prothrombotic risk factor. However, to our knowledge, surgery alone so far has not been established as a risk factor for CVST.

Whether women in labour under peridural anaesthesia are at increased risk for developing postpartum CVST has not been studied so far. Neither are studies available examining incidence of CVST in surgery performed under peridural anaesthesia compared with general anaesthesia. Patient 3 was taking concurrent oral contraceptives, which are well known risk factors.[8 9 14] No patient had headache or other neurological signs and symptoms suggestive of CVST before dural puncture, and in one (patient 3) predural puncture MRI was normal.

In three of the five patients dural puncture is not finally established as they had attempted peridural anaesthesia (PDA). However, the circumstances (several attempted punctures), the temporal relation, and the almost pathognomonic positional quality of the ensuing headache are strong arguments for accidental dural puncture.[15 16] Such headache is not known to follow uncomplicated PDA. On the other hand headache is the most prominent symptom of accidental dural puncture and occurs in up to 90% of patients.[15–17] Accidental dural puncture on attempted PDA is reported to occur in 2% to 3% (range 0.2%-7%).[15–18]

The continuously evolving headache and the close temporal association of dural puncture and CVST suggest causality. This possible serious complication of dural puncture has only been mentioned in a few case reports,[19–22] without discussion of a causal relation.

Three of the four patients tested had hereditary APC resistance due to the factor V R506Q mutation (FV Leiden) recently shown to be the most common coagulation abnormality associated with CVST.[23 24] This finding, however, is not unanimously confirmed.[25] In a retrospective

case-control study the prevalence of APC resistance was 20% in 25 patients with CVST and only 2.7% in healthy controls matched for sex and age.[23] The intake of oral contraceptives as an established risk factor for thrombosis was not different in the two groups. The single point mutation in the factor V gene that replaces arginine by glutamine at position 506 (R506Q) in the factor V protein[11] is a common defect in the general white population with a prevalence of about 2%–15%.[26 27] The mutation abolishes an APC cleavage site in the heavy chain of factor Va, thus leading to impaired regulation of FVa.

In all three tested patients we found an impaired or lacking fibrinolytic response to venous occlusion, which is a common abnormality described in patients with a history of deep vein thrombosis.[28] However, a causal relation between impaired fibrinolysis and venous thromboembolism is uncertain[29] and its clinical importance in CVST is not known.

Is there a plausible explanation as to how dural puncture could contribute to the pathogenesis of CVST? It is known that sampling and continued loss of CSF after dural puncture result in decreased volume and pressure of the CSF compartment.[30] This can trigger two processes. Firstly, a downward pulling or stretching or "rostrocaudal sagging" effect is exerted on the intracranial contents due to the negative spinal-cranial pressure gradient. This "sagging" effect has recently been well documented in MRI studies,[31 32] in which reversible rostrocaudal brain descent of up to 14 mm was measured in patients with intracranial hypotension.[32] It is self evident that this may, in the presence of increased intracerebral pressure with partial or complete obstruction of CSF pathways, lead to brain herniation and subsequent death.[2] Even in the absence of raised intracerebral pressure and in the presence of free CSF communications, cranial nerves, vessels, dura, and brain parenchyma may be injured by stretching, leading to the complications of acquired Chiari I malformation,[31–33] sixth nerve palsy, subdural haematoma or hygroma,[2] and very rarely to subarachnoid haemorrhage.[5]

The second process triggered by decreased CSF pressure is cerebral venous vasodilatation with resultant stasis. This has been directly seen in animals through a cranial window.[34] In humans, MRI studies provide further indirect evidence. Two separate reports of patients with intracranial hypotension postulate underlying venous vasodilatation as the cause of meningeal enhancement and subdural effusions.[32 35]

Vasodilatation is thought to arise because of the abnormal pressure gradient between cerebral vasculature and CSF space. As veins are thin walled and within certain limits passively adjust to pressures in and around them, it is likely that a negative pressure on the outside of the vein wall will result in dilatation.[31] In addition, a sudden decrease in CSF volume is proposed to further propagate vasodilatation via activation of vascular adenosine receptors.[31 36]

It follows that two of the three pathogenetic factors for thrombosis according to Virchow's classic triad may be induced by dural puncture:

- Traumatic damage of the fragile venous endothelial lining due to stretching of the cerebral vessels by a negative spinal-cranial pressure gradient
- Stasis of blood flow via venous vasodilatation which is further aggravated by impaired venous drainage due to the recumbent position maintained after lumbar puncture.

The possibility of an additional procoagulant stimulus due to the postoperative states in patients 1, 2, and 4 needs to be considered as even minor operations are known to activate coagulation. Whether this is sufficient to result in cerebral venous thrombosis on its own is doubtful as experiments have shown that a procoagulant stimulus will only consistently lead to venous thrombosis when venous stasis—the most important factor in the pathogenesis of venous thrombosis—is superimposed.[37] It is also important to note that in two patients undergoing minor surgery (1 and 2), prophylactic low dose heparin did not prevent the development of thrombosis. We propose that dural puncture may be an additional risk factor for the development of cerebral venous thrombosis.

To estimate the importance of dural puncture as a risk factor for CVST, we retrospectively reviewed all documented cases of cerebral venous thrombosis in the Department of Neurology. Sixty six patients were identified for the past 26 years. The most frequent underlying risk factor was ethinyl oestradiol medication in 19 out of 44 women (43%), followed by migraine (14%) and diverse underlying diseases (18%). The fourth most frequent risk factor was preceding dural puncture (five patients, 8%), whereas in 28% no established risk factor was found. Among the five patients with postdural puncture CVST, APC resistance was found in three out of four tested patients. The fifth one died before we were able to test for thrombophilia. CVST is often caused by the presence of a combination of predisposing factors.[7–9] We realise that this is a biased group due to the selection bias of our tertiary referral centre. Nevertheless, we wonder whether the association between dural puncture and cerebral venous thrombosis has not until now been overlooked, and whether patients affected by hereditary or acquired thrombophilia undergoing surgery under peridural anaesthesia complicated by accidental dural puncture are at especially high risk for this complication.

Thus the main message of this report is to draw attention to the possibility of CVST in patients complaining of headache after dural punctures (lumbar puncture, myelography, or epidural or spinal anaesthesia) especially if the headache loses its positional character. In such patients screening for thrombophilia is indicated.

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