Factors influencing shunt malfunction in patients with tuberculous meningitis

Sudheer Ambekar, Dwarakanath Srinivas, Paritosh Pandey, Somanna Sampath, Chandramouli Anandappa Bangalore, Devi B. Indira

Department of Neurosurgery, National Institute of Mental Health and Neurosciences, Bangalore, Karnataka, India

ABSTRACT

Background: Hydrocephalus secondary to tuberculous meningitis (TBM) is a challenging condition to treat. Though ventriculo-peritoneal (VP) shunt is an accepted modality of treatment for hydrocephalus in TBM, there is a high rate of complications associated with the same. **Objective:** The study was planned to evaluate various factors associated with shunt malfunction in patients undergoing VP shunt surgery for hydrocephalus due to TBM. **Materials and Methods:** A retrospective review of all the patients undergoing VP shunt and shunt revision for TBM between 2004 and 2008 was performed. 449 VP shunt surgeries were performed in 432 patients for hydrocephalus due to TBM. Among these 70 shunt revisions were performed in 53 patients. **Results:** Shunt malfunction rate in our series was 16.2%. High cerebrospinal fluid (CSF) protein concentration (>200 mg/dL) was associated with 5 times increased incidence of shunt malfunction. Patients with hyponatremia (Na^+ <130 mEq/dL) prior to surgery had a 3 times increased incidence of shunt malfunction ($P < 0.05$). Other factors such as duration of symptoms, presence of neurological deficits, Evan's index, third ventricular diameter, thickness of exudates, presence of infarcts, anemia, CSF cellularity and CSF glucose concentration were not associated with increased incidence of shunt malfunction. Analysis showed that shunt viability was longest in patients with normal serum sodium levels and CSF protein concentration less than 200 mg/dL and shortest in patients with low serum sodium and CSF protein concentration more than 200 mg/dL. **Conclusions:** Patients with pre-operative hyponatremia and high CSF protein concentration have a higher incidence of shunt malfunction and need to be followed-up closely.

Key words: Hydrocephalus, hyponatremia, shunt malfunction, tuberculous meningitis, ventriculo-peritoneal shunt

INTRODUCTION

Tuberculosis is one of the most common endemic infections encountered in developing countries, and with the advent of immunosuppression and population migration, is being increasingly reported from developed countries.[1] Central nervous system (CNS) tuberculosis is one of the most devastating forms of the disease with the greatest morbidity and mortality, although only about 5% of tuberculous infections affect the CNS.[2,3] Hydrocephalus is the most common complication of tuberculous meningitis (TBM) and is seen in 62-87% of patients.[4] In addition to anti-tuberculous therapy (ATT), cerebrospinal fluid (CSF) diversion procedures are often needed to treat hydrocephalus in patients with TBM. Ventriculo-peritoneal (VP) shunting is the most important modality of treatment of such patients. The incidence of shunt malfunction, though, has been reported to be higher in patients with tuberculosis. Sil and Chatterjee reported a shunt infection rate of 15.6% and a shunt revision rate of 43.8%, with 18.7% of patients requiring multiple shunt revisions.[5] Various factors have been implicated as a cause of the increased incidence of shunt malfunction, a high CSF protein concentration being the most common.[6,7] However, to date there has been no study analyzing the various clinical, radiological, biochemical and radiological factors associated with shunt malfunction in these patients. In the present study, we analyze various factors that may be associated with shunt malfunction in patients undergoing VP shunt for hydrocephalus secondary to TBM.

Access this article online	
Quick Response Code:	Website: www.ijns.in
	DOI: 10.4103/2277-9167.118121

AIM

The study was planned to evaluate various factors associated with shunt malfunction in patients undergoing VP shunt surgery for hydrocephalus due to TBM.

Address for correspondence: Dr. Dwarakanath Srinivas,
Department of Neurosurgery, National Institute of Mental Health and Neurosciences, Bangalore - 560 029, Karnataka, India.
E-mail: dwarakaneuro@yahoo.com

MATERIALS AND METHODS

This retrospective study was conducted at the National Institute of Mental Health and Neurosciences, Bangalore, India. All patients with TBM with hydrocephalus who presented with VP shunt malfunction and underwent shunt revision during 2004-2008 were included. These were included in the study Group I. Patients who underwent shunt revision for causes other than shunt blockage such as catheter malposition and infection were excluded from the study. Patients undergoing ventriculo-pleural shunt were excluded from the study. Age and sex matched controls were taken from patients who have undergone successful VP shunt surgery for TBM without any shunt malfunction during the same period. These patients were included in the study Group II (controls). All these patients underwent VP shunt (Ceredrain® HLL Lifecare Limited, Thiruvananthapuram, India) placement. The diagnosis of TBM was made by clinical symptoms, radiological findings and cytochemical analysis of the CSF obtained by lumbar puncture in all the patients [Table 1]. All patients were started on standard ATT (isoniazid, rifampicin, pyrazinamide and ethambutol) with steroids (dexamethasone) after the diagnosis. VP shunt was performed if there was associated hydrocephalus, along with clinical signs and symptoms of raised intracranial pressure. External ventricular drainage (EVD) was placed in the pre-operative period only in patients who had metabolic derangements such as severe hyponatremia and anemia which led to postponement of definitive surgery. Shunt surgery was, however, performed in most patients irrespective of the clinical grade once they were fit for general anesthesia. Only patients in very poor neurological state and those with extensive infarcts did not undergo shunt surgery. This is in accordance with a previous study from our institution, which demonstrated significant improvement following shunt surgery even in poor grade patients.[8] Shunt malfunction was diagnosed by clinical examination, computed tomography (CT) scan of the head and shunt tap whenever deemed necessary. Only patients with shunt malfunction due to shunt tube block was included in the study, whereas those with improper shunt position (ventricular catheter malposition and distal tube malposition) and shunt infection were excluded from the study. Patients with shunt infection were excluded from the study because the aim of the study was to analyze the characteristics specific to mechanical shunt malfunction in TBM. The variables analyzed were duration of symptoms, presence of focal neurological deficits, pre-operative clinical grade, hemoglobin concentration, serum sodium concentration, CSF cellularity, CSF glucose concentration, CSF protein concentration, Evan's index, third ventricular diameter, presence of periventricular lucency (PVL) (white matter hypointensity in periventricular region on CT scan) in the pre-operative scan, exudates thickness and the presence of infarcts in the pre-operative scan. Anemia was defined as a blood hemoglobin concentration less than 10 g% and hyponatremia was defined as a serum sodium concentration less than 130 mEq/dL.

Table 1: Criteria for diagnosis of tuberculous meningitis

Inclusion criteria
Duration of neurological symptoms >5 days
Headache
Focal neurological deficits or altered consciousness
Papilloedema
Lumbar CSF pleocytosis (>10 cells/dL) with lymphocyte predominance (>50%)
Lumbar CSF protein concentration (>100 mg/dL)
Lumbar CSF glucose concentration (<2.2 mM or CSF/plasma ratio <50%)
CT or MRI of brain showing communicating hydrocephalus
Exclusion criteria
Alternative diagnosis confirmed using gram stain, culture, NAAT, antigen test (e.g., *Cryptococcus*), serology (e.g., syphilis) or histopathology (e.g., lymphoma)
Presence of non-communicating hydrocephalus

CSF - Cerebrospinal fluid; CT - Computed tomography; MRI - Magnetic resonance imaging; NAAT - Nucleic acid amplification testing

Statistical analysis

Statistical analysis was performed with commercially available software (SPSS 16.0; SPSS, Inc.). Analysis was done using the independent samples *t*-test, Chi-square test and multivariate logistic regression. Kaplan-Meier graphs were plotted with shunt malfunction as the end point in each category of patients. The result was considered significant when $P<0.05$.

RESULTS

During the study period, 432 patients with TBM underwent VP shunt surgery for hydrocephalus. Among these 53 patients developed shunt malfunction due to shunt tube blockage. 17 cases of shunt malfunction were excluded from the study because their shunt malfunction was due to causes other than shunt tube blockage [Table 2]. The shunt malfunction rate in patients who underwent a pre-operative EVD placement was 12.7%. Of note, 49% of patients in the shunt malfunction group were in the pediatric age (up to 14 years). Follow-up in the shunt malfunction group ranged from 3 months to 6 years (mean 25.5 + months) and that in the control group ranged from 3 months to 5 years (mean 23.6 months). Overall, follow-up ranged from 3 months to 6 years (mean 24.6 months). A shunt

malfunction rate of 16.2% was observed in our series. Of the patients who had undergone successful shunt surgery for TBM without any shunt malfunction, 125 patients were selected as controls after matching for age and sex. The demographic profile of patients with shunt malfunction is depicted in Table 2.

Clinical parameters

The various clinical parameters studied between the two groups were duration of symptoms, pre-operative clinical grade as measured by Palur *et al*. grading[9] and presence of focal neurological deficits. The median duration of symptoms among patients in both groups was 1 month. EVD was inserted in 61 (34.3%) of the total 178 patients.

Table 2: Number of patients included in the study and their demographic profile

	Number of patients
Total no. of patients	432
No. of patients with shunt malfunction	53
No. of patients undergoing shunt revision	
Once	43
Twice	06
Three times	03
Six times	01
Total no. of shunt revisions	70
Ventricular end malposition	10
Shunt infection	03
Ventriculo-pleural shunt	02
Distal end malposition	01
Shunt over drainage causing subdural collection	01
Total no. of shunt revisions excluded from the study	17
Total no. of shunt revisions included in the study	53
Patients with shunt malfunction	
Number of males (%)	32 (60.4)
Number of females (%)	21 (39.6)
Number of patients in pediatric age (<14 years)	26 (49)
Age of patients	1-40 years
Mean age	15 years

There was no significant difference in any of the above mentioned variables between the two groups as evaluated by independent *t*-test [Table 3].

Radiological parameters

The various radiological parameters studied were Evan's index, diameter of the third ventricle, presence of PVL in the pre-operative CT scan, thickness and location of exudates and the presence of infarcts indicating vasculitis in the pre-operative scan. None of the studied variables were significantly different between the two study groups, indicating that shunt malfunction cannot be predicted based on these parameters. Thickness of basal exudates did not have any bearing on shunt function [Table 3]. Figure 1a shows the CT scans of a patient with TBM with hydrocephalus prior to shunt surgery, following VP shunting, prior to shunt revision and following shunt revision.

Laboratory parameters

The various parameters studied were blood hemoglobin concentration, pre-operative serum sodium concentration and the ventricular CSF composition of the patients, which included the cellularity, glucose and protein concentration.

The mean hemoglobin concentration in patients in the shunt malfunction group was compared with that of the patients in the control group. The difference was not significant [Table 3].

A high CSF protein concentration (>200 mg/dL) was noted in 40 (22.5%) patients. Patients were divided into two different groups based upon the CSF protein concentration (1) those with a protein concentration of <200 mg% and (2) those with a protein concentration of ≥200 mg%. The mean CSF protein concentration in the two groups was 309.85 mg/dL and 137.75 mg/dL respectively. The difference in the incidence

Table 3: Analysis of clinical, radiological and laboratory parameters

Variable	Group I (%)	Group II (%)	*P* value (%)
Mean duration of symptoms (days)	30	30	0.76
Number of patients in palur grade III/IV	49 (92.4)	111 (88.8)	0.70
Number of patients with focal CNS deficits	11 (20.8)	51 (33.6)	0.41
Mean evan's index	0.52	0.52	0.89
Mean third ventricular diameter (cm)	1.6	1.5	0.80
Mean thickness of exudates (mm)	2.5	2.7	0.56
Number of patients with infarcts on preoperative CT scan	31 (58.5)	30 (24)	0.97
Number of patients with PVL on preoperative CT scan	49 (92.4)	115 (92)	0.92
Mean CSF cell count	121	126	0.96
Mean CSF glucose concentration (mg/dL)	50	54	0.96
Presence of anemia	11	07	0.76

PVL - Periventricular lucency; CT - Computed tomography; CSF - Cerebrospinal fluid; CNS - Central nervous system

of shunt malfunction was studied between the two groups with independent samples test. High CSF protein concentration (≥200 mg/dL) was significantly associated with 5 times increased risk of development of shunt malfunction in these patients (P=0.004) [Figure 2]. On the other hand, CSF glucose concentration and CSF cellularity were not significantly different between the patients who had shunt tube block and those who did not [Table 3].

Hyponatremia in the pre-operative period was observed in 90 (60%) patients. The difference between the incidence of hyponatremia in the two groups was analyzed using the Chi-square test. Patients with hyponatremia had a 3 times higher incidence of shunt malfunction compared to those with normal sodium levels (P=0.003) [Figure 3]. This statistical significance was maintained in the multivariate analysis. Hence hyponatremia independently affects shunt function in patients with TBM.

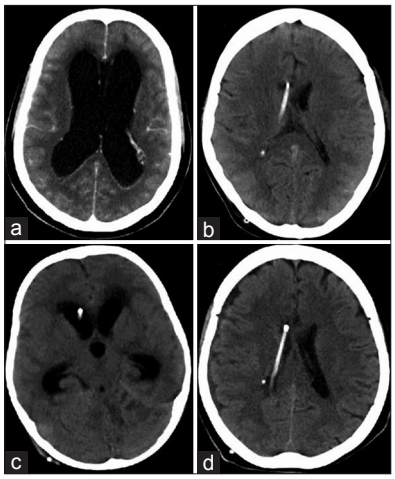

Figure 1: (a-d) Pre- and post-operative computed tomography scans of a 20-year-old lady with tuberculous meningitis and subsequent shunt malfunction

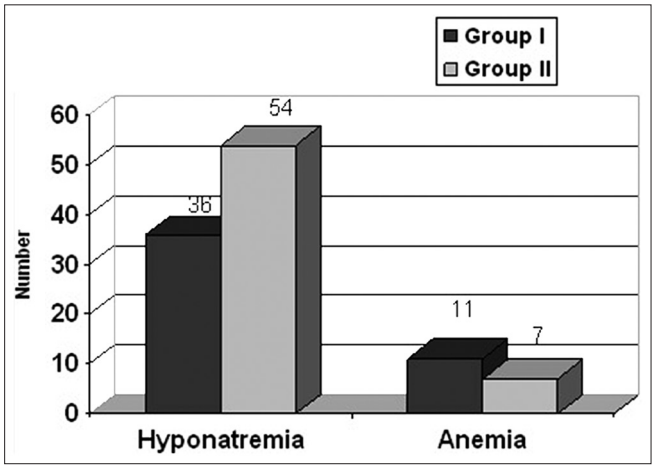

Figure 3: Analysis of hyponatremia and anemia with respect to shunt malfunction

Multivariate analysis was performed using logistic regression analysis taking into consideration all the above variables. Both high protein concentration and hyponatremia were independently associated with a higher incidence of shunt malfunction. Presence of both pre-operative hyponatremia and a high CSF protein concentration together had a cumulative effect and conferred a 9 times increased risk of developing shunt tube block when compared to those with a normal pre-operative serum sodium concentration and a CSF protein concentration less than 200 mg/dL (P<0.0001) [Table 3].

Duration to shunt malfunction

The duration to shunt malfunction was platted in various groups of patients with increasing CSF protein concentration and it was found that there is a significant decrease in duration to shunt malfunction in patients with CSF protein concentration greater than 200 mg/dL (P<0.05) [Figure 4]. The mean duration to shunt malfunction in patients with CSF protein less than 200 mg/dL was 608 days (standard deviation (SD) ±402) and that in patients with CSF protein greater than 200 mg/dL was 164 days (SD±18). Kaplan-Meier survival graph was plotted with shunt malfunction as the end point. Mean duration to shunt malfunction is

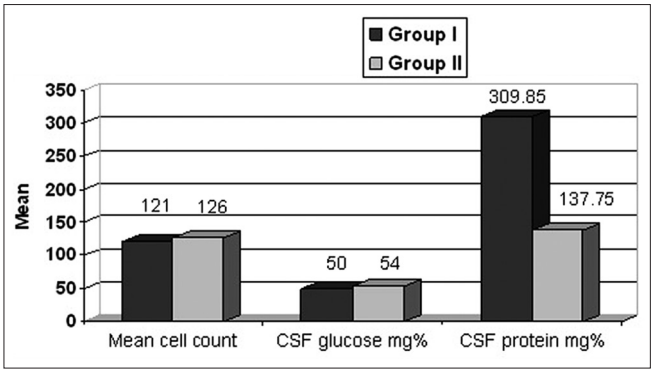

Figure 2: Analysis of cerebrospinal fluid parameters with respect to shunt malfunction

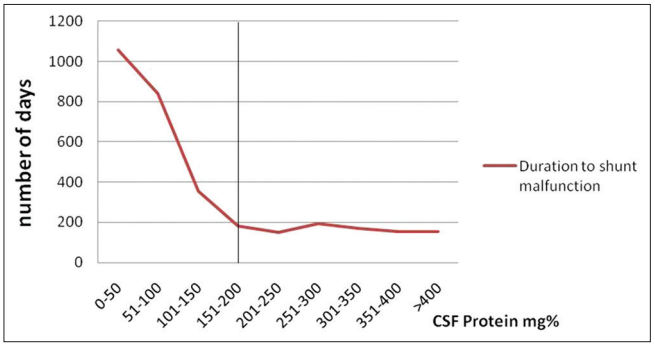

Figure 4: The number of days to shunt malfunction steadily decreases with increasing cerebrospinal fluid protein concentration

depicted in Table 4. Subgroup analysis revealed that the mean duration to shunt malfunction in patients with either CSF protein concentration ≥200 mg/dL or pre-operative hyponatremia or both is less than when these are not present. Figure 3 shows the survival curves in various groups of patients with respect to shunt function [Figure 5].

DISCUSSION

Various studies have reported a higher rate of complications following VP shunt surgery in patients with hydrocephalus due to TBM than in patients undergoing shunt surgery for other causes.[3] Shunt malfunction rates in various series ranges from 16% to 42.3%.[4,9,10] The rate of 16.2% of cases developing shunt malfunction in our study is in concordance with the above studies. Jain *et al*. in a study of 124 patients, concluded that the incidence of post-operative complications is significantly higher in undernourished patients.[11] None of the studies analyzed the factors associated with shunt malfunction.

Table 4: Interaction of CSF protein concentration and hyponatremia with duration to shunt malfunction

Category of patients	Mean duration to shunt malfunction (years)	95% confidence interval (years)	*P* value	Odds ratio
CSF protein<200 mg/dL without hyponatremia	10.4	8.5-12.3		1.0
CSF protein<200 mg/dL with hyponatremia	6.1	5.2-7.1	0.004	3.5
CSF protein>200 mg/dL without hyponatremia	5.4	3.5-7.3	0.007	5.0
CSF protein>200 mg/dL with hyponatremia	3.3	1.8-4.8	<0.0001	9.0

CSF - Cerebrospinal fluid

Our study analyzes the difference in various clinical, radiological and laboratory parameters between the patients who had shunt malfunction and those who had successful shunt surgery. Of the various parameters analyzed we noted that a high ventricular CSF protein concentration (>200 mg %) and hyponatremia (Na^+ <135 mEq/dL) are associated with higher risk of shunt malfunction.

CSF protein abnormalities are well documented in patients with TBM. The protein concentration is elevated in most patients with TBM with most series citing a median value of 150-200 mg/dL.[3,4] It is observed that the protein values tend to rise with sequential samples from untreated patients. Very high values are more commonly seen in patients with spinal block.[12] In our study, CSF proteins were elevated above 100 mg/dL in 149 (83.7%) patients. Guindi *et al*. analyzed the CSF electrophoretic pattern of 30 patients with TBM before and after starting ATT.[13] Their study revealed that the onset of disease is characterized by a rise in the alpha-1 and gamma globulin fractions and by a decrease in the beta and prealbumin fractions. These abnormalities were attributed to meningeal inflammation leading

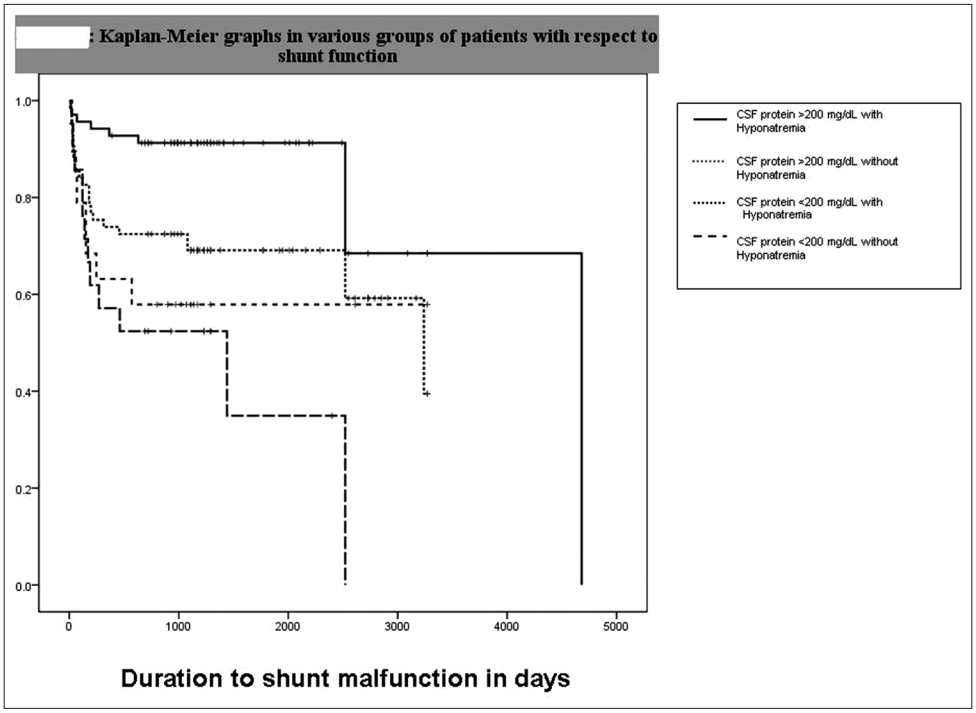

Figure 5: Kaplan-Meier graphs in various groups of patients with respect to shunt function and cerebrospinal fluid protein levels

to increased permeability. Mansour *et al*. propose unknown mechanisms in addition to simple diffusion process leading to increased protein concentration in the CSF.[14] These abnormalities in CSF electrophoretic pattern of various protein fractions may persist long after initiation of therapy. However, alpha 1 fraction and prealbumin tend to normalize after initiation of therapy. We hypothesize that these persistently elevated proteins have a potential to form a coagulum within the shunt tube causing block.[15]

Hyponatremia is commonly seen in patients with TBM. The reported incidence in various studies ranges from 10% to 65%.[16] In our study, hyponatremia was seen in 90 (50.6%) patients. 36 (57.9%) and 54 (43.2%) patients had hyponatremia in groups I and II respectively. Rapoport *et al*., in 1951, described a salt-losing state as a possible cause of hyponatremia in TBM and attributed this to renal tubule defect.[17] Since then, various mechanisms have been proposed to explain hyponatremia in these patients such as syndrome of inappropriate anti-diuretic hormone (SIADH) secretion, cerebral salt wasting and renal salt wasting due to mineralocorticoid deficiency secondary to tuberculous destruction of adrenals.[18]

In a study of 24 patients with TBM, Narotam *et al*. noted that the CSF cell counts and protein levels were higher in patients with hyponatremia than in patients with normal sodium levels.[19] This observation was attributed to a greater severity of the disease process in the former group of patients. Hyponatremia, by itself, is not associated with CSF protein abnormalities in the absence of any underlying disease. In our study, 74 (82.2) of patients with hyponatremia had an elevated CSF protein concentration whereas 67 (76%) of patients without hyponatremia had an elevated CSF protein concentration, although the difference was not significant ($P=0.55$). Whether hyponatremia is the cause or effect of this greater severity of the disease process in these patients remains to be answered. Ohta and Ito reported four patients with hyponatremia due to SIADH, which was related to inflammation.[20] They noted that intravenous and intraventricular administration of interleukin-1 in animals increased arginine vasopressin, atrial natriuretic peptide and adrenal corticotropic hormone levels. Pre-treatment with indomethacin attenuated this response. This study shows that inflammatory cytokines have a role in the development of hyponatremia due to SIADH (SIADH). The association of hyponatremia with CNS inflammation and high CSF protein concentrations in patients with TBM may account for the significantly high risk of shunt malfunction in these patients when compared to those without hyponatremia and CSF protein concentration less than 200 mg/dL. However, hyponatremia could have another unknown effect on shunt functioning as hyponatremia was independently associated with shunt malfunction on multivariate analysis.

In a recent study of 84 patients with TBM, of which 32 underwent shunt surgery for hydrocephalus, shunt malfunction was reported in only one patient at the end of 1 year.[15] The authors concluded that increased protein content with low molecular weighted proteins in CSF has no significant effect on the shunt function both clinically and radiologically and also leads to a decreased platelet and bacterial aggregation. The authors noted a return of CSF protein concentration to normal in all patients. However, Mansour *et al*. reported return of CSF protein concentration to normal range only in inactive phase of the disease and lower than the pre-operative level, but significantly elevated concentration in the subacute and chronic phases of the disease after initiation of treatment.[14] In our study, the median duration from shunt surgery to the development of malfunction was 10.2 months. This may explain the occurrence of shunt malfunction in our study. Even though some studies conclude that high protein content in the CSF only minimally changes its viscosity, the samples were obtained from a heterogenous group of patients with varied diagnoses and the components of proteins that were elevated were not studied.[6,7,21] Hence, applying these conclusions to a homogenous group of patients with TBM seems inappropriate.

Endoscopic third ventriculostomy (ETV) is emerging as a modality of treatment of hydrocephalus in patients with TBM with a success rate between 60% and 73%.[22,23] In a study by Chugh *et al*., longer history of duration of disease, lower stage of disease, longer pre-operative duration of ATT and absence of cisternal exudates were favorable factors associated with good outcome after ETV.[22] However, Jha *et al*. observed that only dense exudative adhesions in prepontine cistern negatively affected the outcome whereas, patients with soft, fluffy exudates had a good outcome.[24] In the same study, the authors also observed that patients with hyponatremia ($n=2$) and multisystem disease ($n=3$) had failed ETV, the reasons for which were not known. Larger studies are required to assess the outcome of ETV in this subset of patients with high CSF protein concentration and hyponatremia as against the outcome following VP shunt surgery.

Though our study is the largest so far in analyzing shunt malfunction in a homogenous group of patients with TBM, it has a few limitations. It is a retrospective study. The histopathological examination of blocked shunt tubes was not carried out to determine the material

causing shunt block. Nevertheless it gives us an insight into understanding shunt malfunction in these patients.

CONCLUSION

Patients with pre-operative hyponatremia and a CSF protein concentration of >200 mg/dL who undergo shunt surgery for hydrocephalus due to TBM have a high risk of developing shunt malfunction and hence have to be on close follow-up to detect and treat shunt malfunction at the earliest.

ACKNOWLEDGMENT

We gratefully acknowledge Dr. Mariyamma for her help in statistical analysis.

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How to cite this article: Ambekar S, Srinivas D, Pandey P, Sampath S, Bangalore CA, Indira DB. Factors influencing shunt malfunction in patients with tuberculous meningitis. Indian J Neurosurg 2013;2:175-81.

Source of Support: Nil, **Conflict of Interest:** None declared.