Original Article

Cerebrospinal fluid examination findings in infections of the brain and its meningeal coverings

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Abstract

Background*: Examination of the CSF is the most important diagnostic test in the management of patients with features of infection of the brain and its meningeal coverings.*

Objective*: To study the effectiveness of investigating the CSF in diagnosing infections of the brain and its meningeal coverings and treating such patients who are admitted in our tertiary care hospital.*

Methodology*: All patients admitted in Holy Family Red Crescent Medical College Hospital from July to December 2021 whose CSF was examined were included in the study. The course of the patients were followed till discharge, and the patients were followed up for 6 months after discharge. All the investigation reports were studied and their usefulness in reaching a specific diagnosis of these patients and their management were assessed.*

Result*: 12 patients met the criteria for inclusion in the study. Specific bacteriologic diagnosis was made by examination of CSF in one patient only in whom gram-ve intracellular diplocci were found suggestive of Meningococcal Meningitis. All the other CSF investigation reports helped as ancillary data in the management of these patients. All the 12 patients improved after treatment and left the hospital in stable condition.*

Conclusion*: Admission in a tertiary care hospital carries a good prognosis for patients suffering from the grave condition of infection in the brain and its meningeal coverings. In our patients CSF examination may help in reaching a specific diagnosis occasionally but mostly it provides ancillary data in reaching a diagnosis and in management of these patients.*

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Introduction

Bacterial meningitis causes approximately 318,000 deaths annually worldwide, resulting in an estimated 20,383 years of life lost. The incidence ranges from approximately 0.9 per 100 000 individuals per year in high-income countries to approximately 10 to 80 per 100 000 individuals per year in low income and middle-income countries. Mortality rates in adults and neonates with bacterial meningitis range from 6% to 54%.Mortality also varies from 10% in high-income countries to up to 58% in low-income countries. The risks of neurological sequelae, such as focal neurological deficits (eg, hemiparesis, cranial neuropathies), hearing loss, and memory impairment, also vary, from 9.4% in Europe to 25% in Africa.[1,2,3,4]

Bacterial meningitis is an acute medical emergency whose successful treatment requires highly bactericidal antibiotics. Many challenges have to be overcome to achieve optimal patient outcome. Firstly, the antibiotics must be able to penetrate the blood brain barrier and achieve significant bactericidal levels in the CSF. Finally bactericidal therapy produces lysis of the bacteria and these lytic products are highly inflammatory. To prevent damage from these lytic products adjunctive therapy have to be given to prevent neuronal death. These challenges are an extreme example of the different requirements for treating infections in different body sites.[5]

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Infections of the brain and its meningeal coverings require urgent specific diagnosis and choice of appropriate antibiotic treatment. For the diagnosis of the infection the most important investigation is the examination of the Cerebrospinal fluid and should be undertaken promptly before CSF is rendered sterile by broad-spectrum antibiotics.CSF culture is considered the gold standard for diagnosis of bacterial meningitis, yet it is only positive in 70–85% of persons with bacterial meningitis who have not received antimicrobial therapy prior to lumbar puncture.[6,7,8] Microbiological diagnostic tests such as culture, Gram stain, polymerase chain reaction, latex agglutination and immunochromatographic antigen testing can confirm the diagnosis of bacterial meningitis but, when negative, cannot rule out bacterial meningitis.[9] Gram stain is more rapid and has good specificity but sensitivity is poor (10–93% depending on the organism and whether or not antibiotics were given prior to CSF collection).[14,16]

This study was done to find out the CSF findings in patients presenting with features of infection of the brain and its meningeal coverings to assess the usefulness of this investigation in the specific diagnosis of such patients.

Materials and Method

This study was carried out in the Holy Family Red Crescent Medical College Hospital. Patients admitted in the different wards from July to December, 2021 and in whom Cerebro-Spinal Fluid examination was done were included in the study. CSF was collected by conventional lumbar puncture and examination of the CSF was done in the pathological laboratory of the hospital.

The CSF was first examined physically and the physical properties noted.

Then Gram stain and ZN staining was done to detect the presence of organisms including Mycobacteria.

Cytological examination was done to detect the type and number of different types of cells in the CSF.

Biochemical examination detected the presence of glucose and protein in the CSF and at the same time peripheral blood was collected and the Random blood sugar estimated.

CSF culture was done in all the patients. Culture for Mycobacteria was not done in any patient.

Amongst special investigations Gene Expert for detection of Mycobacteria and also PCR for Mycobacteria were done in some patients.

The patients were discharged after they improved. They were followed up once after one month and asked to report back again if they had any problem. 6 months after discharge the patients were contacted at the mobile number they provided and their condition noted.

Results

12 patients were included in the study.

Table I. Demographic Data of thePatients and their Chief Complaints.

Patient	Age (yrs)	Sex	Bed No	Address with Mobile number	Chief complaints
1.	18	F	SFG 2	Munshiganj	Low back pain for 10 days. Weakness both lower limbs - 3 days
2.	70	F	ICU 5	Brahmanbaria	Fever, cough, respiratory distress – 7 days. Disorientation – 2 days
3.	18	F	SC - C6	Cox's Bazaar	Fever, Headache – 17 days. Lower abdominal pain – 10 days
4.	19	F	ICU - 8	Brahmanbaria	Fever, headache for 4 days. Unconsciousness for 2 days.
5.	70	F	MF 9	Narsingdhi	Fever 3 days, Severe headache 1 day, Vomiting 3 times, Disoriented 7 hours
6.	50	F	MF 9	Noakhali	Fever for 15 days, Semiconscious for few hours.
7.	70	F	SC – 2/D	Narsingdhi	Fever for 4 days, Altered level of consciousness for 3 days

Table I. Cont'd

Patient	Age (yrs)	Sex	Bed No	Address with Mobile number	Chief complaints
8.	13	M	MM – 1/10	Cumilla 01843885261	Headache and Vertigo for 10 days, Vomiting for several episodes.
9.	40	F	314 C	Noakhali 01741048185	Fever for 3 days, Vomiting several episodes 1 day, Headache and generalized bodyache for 1 day.
10.	70	F	MF 10	East Rampura, Dhaka 01674862125	Fever for 20 days. Unconsciousness from 4 days back
11.	35	M	C - 227	BecharamDeuri, Dhaka01717067660	Unconsciousness for 8 hours, Convulsions for 3 episodes.
12.	55	M	MM - 3/8. ICU - 2A	Hobiganj, Sylhet 01722687898	Disorientation for 3 days. Headache and Fever for 1 day.

Table II. *Examination Findings of the Cerebro - Spinal Fluid (CSF)*

Patient	Physical Appearance			Cytological Report				Microbio-logical Report		Biochemical Report		Blood Sugar
	C	A	CS	Total WBC /cmm	N %	L %	RBCs /cmm	Gram Stain	Z N Stain	Glucose mmol/L	Pro tein Gm/L	mmol /L
1.	W	Cl	Nil	20	10	90	Nil	Nd	Nd	3.4	0.40	6.8
2.	W	Cl	Nil	50	10	90	Nil	Nd	Nd	9.0	0.48	17.8
3.	W	Cl	Nil	50	10	90	Nil	Nd	Nd	3.9	0.18	6.6
4.	W	Hazy	Nil	110	25	75	160	Nd	Nd	4.5	2.63	7.3
5.	W	Cl	Nil	60	15	85	40	Nd	Nd	6.8	1.88	12.7
6.	Red-dish	Hazy	Nil	30	30	70	950	Nd	Nd	3.8	1.03	6.1
7.	Red-dish	Hazy	Nil	100	10	90	Plenty	Nd	Nd	8.0	4.25	10.4
8.	W	Cl	Nil	620	75	25	100	Nd	Nd	4.3	1.72	7.8
9.	W	Cl	Nil	140	10	90	Nil	Nd	Nd	2.2	186.0	5.8
10.	W	Cl	Nil	100	20	80	20	Nd	Nd	2.4	2.1	6.1
11.	Straw	Hazy	++	300	90	10	100	Nd	Nd	3.4	3.0	10.1
12.	Red-dish	Hazy	Nil	200	20	80	600	Gram staining of smear shows some gram -ve diplococci within neutrophils, suggestive of meningococci	Nd	6.5	1.70	

C=Colour; A=Appearance; CS=Clot or Sediment; W=Watery; Cl=Clear N=Neutrophil; L= Lymphocytes; Nd=Not detected; Ng=No growth; PCR-M=Polymerase Chain Reaction for Mycobacteria; CSF Culture=CSF Cu; aom – after one month; ADL – Activities of Daily Living; Treatment=Trt.

Table III. Final Diagnosisand Result of Treatment

Patient	Special Reports	Clinical Diagnosis	Final Diagnosis	Follow up	Result of Treatment
1.	PCR -M: Nd	GBS	AMAN variety GBS	29.10.21 aom	Can walk with help. Some residual disability present
2.		Ischaemic Stroke with Lhp, DM, Encephalitis	Ischaemic Stroke with Lhp, DM	15.8.21 aom	Was improved with trt. Expired after 6 months - COVID
3.		Meningo-Encephalitis	TB brain.	15.8.21 aom	Continued anti TB trt for 2 yrs. Was improved but developed blindness
4.	CSF Cu -Ng. PCR -M: Nd	Viral Encephalitis	Viral Encephalitis	17.9.21 aom	Improved with trt. No residual disability
5.		Meningo Encephalitis DM, Hypt	Viral Encephalitis	17.9.21 aom.	Improved with residual disability. Can perform ADL with help.
6.	CSF Cu -Ng	Meningo Encephalitis	Meningo - Encephalitis	29.10.21 aom.	Improved.
7.	CSF Cu -Ng. Malignant cells-Absent	Encephalitis	Encephalitis	17.10.21 aom.	Improved with residual disability. Expired after 4 months at home, cause unknown
8.	MRI & MRV of Brain - NAD	Encephalitis Stroke.	Encephalitis	17.10.21 aom	Improved with normal activities
9.	CSF Cu-Ng.	Meningo-Encephalitis	Tubercular Meningitis	15.11.21 aom	Completely improved after full Anti-TB trt.
10.		Meningo-Encephalitis	Meningo - Encephalitis		Improved. Went off to Canada
11.	CSF Cu-Ng PCR -M: Nd	Meningo-Encephalitis	Meningitis	29.08.21 aom	Improved. No residual disability
12.	CSF Cu -Ng. PCR-M= Nd	Meningo-Encephalitis DM,CKD	Meningococ-cal Meningitis DM, CKD	20.10.21 aom	Improved & discharged. Expired suddenly after 25 days, cause unknown

C=Colour; A=Appearance; CS=Clot or Sediment; W=Watery; Cl=Clear N=Neutrophil; L= Lymphocytes; Nd=Not detected; Ng=No growth; PCR-M=Polymerase Chain Reaction for Mycobacteria; CSF Culture=CSF Cu; aom – after one month; ADL – Activities of Daily Living; Treatment=Trt; Lhp – Left Hemiparesis

Discussion

The Holy Family Red Crescent Medical College Hospital is a multi-disciplinary 720 bedded hospital situated in the heart of Dhaka City. It is one of the oldest high profile private hospital of Dhaka, established in the year 1954. Initially it was the choice institution for obtaining healthcare for the upper echelon of the society, but with the advent of the more posh private medical institutions, it has been relegated to the second division and now mostly caters to the need of the middle class people of the society. Apart from the major Medicine, Surgery, Gynae & Obstetrics, Pediatrics units, sub-specialty units are also available mostly for medicine.

In this study, all patients admitted in the Holy Family Red Crescent Medical College Hospitalfrom July to December 2021 and in whom cerebrospinal fluid examination was done were included. The patients

were followed up during their stay in the hospital and after discharge when they came for follow up mostly one month after discharge. 6 months after discharge the patient was contacted by the mobile number provided by them during hospitalization to know about the general condition of the patient.

Table I shows that 9 of the 12 patients (75%) were female. It is difficult to explain the preponderance of females in this study. 4 patients were below the age of 20 years and the other 8above 35 years, with 4 patients being 70 years old.

Physical Appearance of the CSF

Normal CSF is crystal clear. However, as few as 200 white blood cells (WBCs) per mm^3 or 400 red blood cells (RBCs) per mm^3 will cause CSF to appear turbid.[10] Xanthochromia is a yellow, orange, or pink discoloration of the CSF, most often caused by the lysis of RBCs resulting in hemoglobin breakdown to oxyhemoglobin, methemoglobin, and bilirubin. Discoloration begins after RBCs have been in spinal fluid for about two hours, and remains for two to four weeks.[11] In this study in 8 of the 12 patients the colour of the CSF was clear watery CSF. Out of these 8 patients 5 had WBCs ≤60, 1 had 620 and the other 2 had 100 and 110. Out of these 8 patients one had RBCs 160, another 100 and the other 2, 40 and 20, and the rest 4 had no RBCs. In 3 patients the colour was Reddish and in these patients the number of RBCs were 600, 950 and plenty. The appearance of CSF in 7 patients was crystal clear. Out of these 7 patients, 4 had no RBCs, while 2 patients had 20 and 40 RBCs and one had 100. The appearance of the CSF was Hazy in 5 patients. In all these 5 patients the number of RBCs were ≥100.

Cytological Examination of the CSF

Eighty-seven percent of patients with bacterial meningitis will have a WBC count higher than 1,000 per mm^3, while 99 percent will have more than 100 per mm^3. Having less than 100 WBCs per mm^3 is more common in patients with viral meningitis.[12]

In this study 5 patients had total WBCs < 100/cmmbut ≥20/cmmin the CSF, none of the patient had a WBC count > 1000/cmm^3 and 7 patients had a CSF count between 100 and 1000/cmm.

Peripheral blood in the CSF after a "traumatic tap" will result in an artificial increase in WBCs by one WBC for every 500 to 1,000 RBCs in the CSF. This correction factor is accurate as long as the peripheral WBC count is not extremely high or low. A traumatic tap occurs in approximately 20 percent of lumbar punctures.

The WBC count seen in normal adult CSF is comprised of approximately 70 percent lymphocytes and 30 percent monocytes. Occasionally, a solitary eosinophil or polymorphonucleocyte (PMN) will be seen in normal CSF.

Lymphocytosis is seen in viral, fungal, and tuberculous infections of the CNS, although a predominance of PMNs may be present in the early stages of these infections. CSF in bacterial meningitis is typically dominated by the presence of PMNs. However, more than 10 percent of bacterial meningitis cases will show a lymphocytic predominance, especially early in the clinical course and when there are fewer than 1,000 WBCs per mm^3.

In this study the lymphocyte count was 90% in 5 of the patients, and between 70 and 90 % in 5 patients. The other 2 had 10% and 20% lymphocytes. In one patient who was diagnosed as suffering from Meningococcal meningitis, there were 600 RBCs/cmm and 200 WBCs/cmm in the CSF out of which 80% were lymphocytes and 20% were neutrophils.

Microbiological Examination of the CSF

Gram stain is positive in 60 to 80 percent of untreated cases of bacterial meningitis and in 40 to 60 percent of partially treated cases. The sensitivity according to the causative organism ranges from 90 percent in pneumococcal or staphylococcal meningitis to less than 50 percent in Listeria meningitis. Hyphae can occasionally be seen in Candida or other fungal meningitis case.

Several factors influence the sensitivity of Gram stain. Laboratory techniques used to concentrate and stain CSF can greatly influence reliability. Cytocentrifugation increases the ability to detect bacteria.[13] Greater numbers of colony-forming units (CFU) per mm^3 of CSF increase the likelihood of a positive result. Staining will be positive in 25 percent of cases if fewer than 1,000 CFU per mm^3 are present, and in 75 percent of cases if more than 100,000 CFU per mm^3 are present. Lastly, the experience of laboratory personnel is very important. Up to 10 percent of initial Gram stains are misread.[14]

In this study no organisms were detected by gram staining in 11/12 patients. 10 patients had already started taking antibiotics 2 to 4 days before coming to

the hospital, which could have decreased the chances of detecting organisms by gram staining. In only one patient gram staining of the CSF showed some gram -ve diplococci within neutrophils, which was suggestive of meningococci. This patient was treated as a case of Meningococcal meningitis and the patient improved with treatment.

Acid-fast staining should be done if tuberculosis is clinically suspected. Only 37 percent of initial smears will be positive for acidfast bacilli. This result can be increased to 87 percent if four smears are done.[15] Sensitivity can also be increased by examining the CSF sediment.[16]

Acid-fast staining was also done in all the 12 patients in this study but no AFB was detected in any slide. 2 patients were diagnosed as Tubercular Meningitis and was cured with full course of anti-tuberculous treatment.

Biochemical Examination of the CSF

CSF Protein

The adult range of 18 to 58 mg per dL (0.18 to 0.58 g per L) is reached between six and 12 months of age.[17] Elevated CSF protein is seen in infections, intracranial hemorrhages, multiple sclerosis, Guillain Barré syndrome, malignancies, some endocrine abnormalities, certain medication use, and a variety of inflammatory conditions. Protein concentration is falsely elevated by the presence of RBCs in a traumatic tap situation. This can be corrected by subtracting 1 mg per dL (0.01 g per L) of protein for every 1,000 RBCs per cmm.[18] This correction is only accurate if the same tube is used for protein and cell counts.CSF protein levels do not fall in hypoproteinemia.

In this study, only 3 patients had CSF protein less than 0.58 gm/L. In these 3 patients the CSF was watery in colour and clear in appearance. RBCs were nil and WBCs were d" 50/cmm. The highest amount of protein detected in the CSF in this study was 4.25 gm/L and in this patient the colour of CSF was Reddish, appearance was Hazy, RBCs were plenty and WBCs were 100/cmm. In another patient the protein was 3 gm/L and in this patient the colour was straw, appearance was hazy, RBCs were 100 and WBCs were 300 and sediment was present ++. In the patient who had RBCs 950, and WBCs 30, the protein was 1.03 gm/L, and in the patient who had RBCs 600 and WBCs 200 the protein was 1.0 gm/L.

CSF Glucose

A true normal range cannot be given for CSF glucose. As a general rule, CSF glucose is about two thirds of the serum glucose measured during the preceding two to four hours in a normal adult. This ratio decreases with increasing serum glucose levels. CSF glucose levels generally do not go above 300 mg per dL (16.7 mmol per L) regardless of serum levels.[9]

CNS infections can cause lowered CSF glucose levels, although glucose levels are usually normal in viral infections. Normal glucose levels do not rule out infection, because up to 50 percent of patients who have bacterial meningitis will have normal CSF glucose levels.

Elevated level of glucose in the blood is the only cause of having an elevated CSF glucose level. There is no other pathologic process that causes CSF glucose levels to be elevated.

In the 12 patients of this study the CSF glucose was not markedly reduced in any patient. 2 patients had CSF glucose less than 2.5 mmol/L and the corresponding blood sugar was 5.8 and 6.1 in these two patients. One of them was diagnosed as Tubercular meningitis and the other as viral meningo-encephalitis. The highest CSF Glucose was 9 mmol/L in one patient and his corresponding blood sugar was 17.8 mmol/L. In another patient the CSF Glucose was 8 mmol/L and the corresponding blood sugar was 10.4 mmol/L. In most of the other patients the CSF Glucose was proportionately less than the corresponding blood sugar.

CSF Culture

Cultures done on 5 percent sheep blood agar and enriched chocolate agar remain the gold standards for diagnosing bacterial meningitis. Antibiotic treatment prior to lumbar puncture can decrease the sensitivity of culture, especially when given intravenously or intramuscularly.[19]

Mycobacterium tuberculosis is best grown using multiple large volume samples of CSF. At least 15 mL and preferably 40 to 50 mL of CSF are recommended. Culture is positive 56 percent of the time on the first sample, and improved to 83 percent of the time if four separate samples are cultured. These cultures often take up to six weeks to bepositive.[20]

In this study CSF culture was done in six patients, all of them were negative. All these patients had already started different broad-spectrum antibiotics before

coming to the hospital which could have decreased the CSF culture positivity.

CSF culture for Mycobacterium tuberculosis was not done for any patient in this study.

PCR Examination of the CSF

Polymerase chain reaction (PCR) has been a great advance in the diagnosis of meningitis. PCR has high sensitivity and specificity for many infections of the CNS, is fast, and can be done with small volumes of CSF. Although testing is expensive, there is a potential for cost savings by decreasing overall diagnostic testing and intervention. PCR has been especially useful in the diagnosis of viral meningitis,in which patients the sensitivity is 95 to 100 percent, and a sensitivity of 100 percent for herpes simplex virus type 1, Epstein-Barr virus, and enterovirus.

PCR has a sensitivity of 54 to 100 percent and a specificity of 94 to 100 percent for tuberculous meningitis, and could replace acid-fast bacillus smear and culture as the test of choice.[21] PCR is sensitive for acute neurosyphilis but not for more chronic forms. PCR also is being studied as a diagnostic tool for bacterial meningitis and other infections of the CNS.

In this study PCR for Mycobacteria was done in 4 patients out of the 12, and all of them were negative. In this study only one patient was diagnosed as Tubercular Meningitis but in that patient PCR was not done. In our country PCR is only done to diagnose Tuberculosis. PCR for diagnosis of Viral and other bacterial infections is generally not available in our country.

Conclusion:

In this study 12 patients whose CSF was studied were included. Final diagnosis of the patients was made on the basis of the clinical manifestations and the results of the tests done of the CSF. All the patients improved with treatment in the hospital and were discharged in a stable condition. At the follow-up after 6 months, 3 patients had died and 9 patients were alright. All the 3 patients had died at home and no exact cause of death could be ascertained. 1 patient died 25 days after discharge, one after 3 months and 1 after 6 months. Of the 9 patients who survived, four had residual disability though all of them could perform the activities of daily living independently.

This study shows that patients admitted with features suggestive of infection of the Central Nervous system or its covering membranes, had a good prognosis as all of them improved with treatment in the hospital and could be discharged in a stable condition. The examination and investigation of the CSF played a major part in the diagnosis of these patients. Thus examination of the CSF should be done at the earliest possible time after admission in a hospital so that a specific diagnosis can be made and the appropriate treatment started as soon as possible.

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