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RESEARCH ARTICLE

# CLINICAL AND PROGNOSTIC APPROACH TOWARDS PYOGENIC MENINGITIS- A PROSPECTIVE STUDY FROM KASHMIR INDIA

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**ABSTRACT**

**Background:-**Despite the availability of potent antibiotics the mortality rate of Pyogenic Meningitis (PM) remains significantly high in India. Clinical triad of head, fever and neck stiffness forms the core presentation of PM. However, the reports on sensitivity of this clinical triad among PM patients and association of various prognostic factors towards PM is not conclusive in the study population.
**Aim:-**The current study was aimed to assess the sensitivity of clinical triad and role of various prognostic markers among PM subjects.
**Materials and Methods:-**The study was conducted at Sher-i-Kashmir Institute of Medical Science, Srinagar from 2014-2016. All cases of acquired bacterial meningitis who fulfilled the inclusion criteria were included in the study. In total 70 cases were recruited in the current study. Outcome of cases was classified as unfavorable and favorable on the basis of Glasgow Scale. Glasgow outcome scale (GOS) of 1-4 was classified as unfavorable and Glasgow Coma scale (GCS) of >14 as favorable.
**Results:-**The majority of cases belonged to young and middle age groups (21-40 years) with 37±15.4 years as mean age of presentation. Headache 91.4 % and fever 87.1% were most common symptom. Sensitivity of the triad of fever, neck stiffness and altered mental status was 45.7%. Focal neurological deficit was found in 31.4% of cases while as cranial Nerve Palsy (CNP) was found in 19.8% of cases with cranial nerve 6 palsy being most prevalent. Altered mental status indicated by GCS<14 was found in 60.5% of cases.
Higher counts in blood culture and CSF gram staining was positive in 7.1% of cases. Total leukocyte, differential leukocyte counts and protein levels associated with unfavorable outcome in CSF were statistically significant ($P < 0.05$).
**Conclusion:-**Acute PM is disease of young adults. Cases with GCS >14 has 0% unfavorable outcome. CSF leucocyte count, Gram staining and culture has significant impact on the outcome of patient with PM.



## INTRODUCTION

Pyogenic meningitis (PM) remains a major cause of mortality and long term neurological deficits worldwide. In spite of the recent management of acute bacterial meningitis, the mortality rate remains significantly high, particularly in developing countries (1-4). There is need for periodic review of bacterial meningitis globally since the pathogens responsible for infection vary with time, geography and patient's age (3, 5). Most epidemiological data from developed world have reported, *Haemophilusinfluenzae*, *Streptococcus pneumoniae*, *Neisseria meningitides*as the three most common pathogens responsible for acute pyogenic meningitis (6, 7), although the frequency of gram negative bacteria has increased over time (8). Mortality is 3 to 7% for meningitis due to *H. influenza*, *N meningitides* and 20% for *S. Pneumonia* (9). However, in some studies, mortality due to *H. influenza* has decreased due to decrease in incidence of *H. influenza meningitis* (10-12). Predisposing factors for acute bacterial meningitis include otitis media, sinusitis pneumonia, and endocarditis, head injury, neurological procedures, immune deficiency as HIV, infection, diabetes mellitus, alcoholism, Cerebrospinal Fluid (CSF) leak and low score on Glasgow coma scale (GCS) (13, 14).

PM can present as either acute illness that progresses rapidly in a few hours or as a sub-acute infection that progresses over several days. The sensitivity of classic triad of fever, neck stiffness and altered mental status is low but almost all patients present with two of four symptoms of headache, fever, neck stiffness and altered mental status (15). Other clinical features which will be present are rash in meningococcal meningitis,

focal neurological deficit (33%), cranial nerve palsy (CNP) of $3^{rd}$ , $4^{th}$ , $6^{th}$aphasia, hemi paresis, papilledema (16). Alteration in mental status occurs in 69% of patient and can vary from lethargy to coma (17). Seizures occur as a part of initial presentation of bacterial meningitis or during the course of illness in 20-40% of patients (3). Nuchal rigidity occurs in 70% of adult cases of bacterial meningitis (18, 19).

Blood tests for markers of inflammation such as complete blood count, blood cultures and C-reactive protein are the common and routine test for diagnosing a suspected subject for meningitis (14). The most important test in identifying or ruling out meningitis is analysis of raised intracranial pressure or a mass lesion, for which a computed tomography (CT) or magnetic resonance imaging (MRI) scan is recommended (20, 21).

Bacterial meningitis remains one of the major neurological problems in Kashmir particularly among adults. Despite the availability of potent antibiotics the mortality rate remains significantly high. Clinical triad of head, fever and neck stiffness forms the core presentation of PM. However, the reports on sensitivity of this clinical triad among PM patients and association of various prognostic factors towards PM is not conclusive in the study population.

Therefore, the current study is warranted in this part of the world to determine the clinical and prognostic markers of PM.

## MATERIAL AND METHODS

The study was a prospective observational and hospital based study. It was conducted at Sher-i-Kashmir Institute of Medical Science (SKIMS), Srinagar from Aug.2014 to Jul.2016in the Department of Neurology. The study protocol was approved by the Institution alethics committee of Sheri Kashmir Institute of Medical Sciences (SKIMS), Srinagar. Similarly, the written and verbal consent was obtained from the study subjects. All cases of community acquired bacterial meningitis (CABM) with age more than 15 years, presenting with symptoms and signs of meningitis who fulfilled the inclusion criteria were included in the study. After fulfilling the inclusion criteria 70 subjects with PM were taken for the current study. Various clinical, laboratory and radiological parameters were assessed. In the current study commutated tomography (CT) was done in all cases, however, magnetic resonance imaging (MRI) was done only for those subjects were the etiology could not be revealed by CT. All the cases were clinically assessed at the time of admission and discharge.

***Inclusion criteria of patients:*** All the patients fulfilled the following criteria's were considered as cases of PM. Presence of any two of the below mentioned criteria's were also considered as subjects.

- Fever, headache, neck stiffness, vomiting, altered sensorium, focal neurological deficit.
- CSF analysis: turbid in gross appearance, peliocytosis with cells mostly neutrophils, >100 cells/mm3, protein >45mg/dl, sugar <40 mg/dl or <40% of blood sugar, serum glucose ratio <(0.4).
- Demonstration of bacterial agent in gram staining with clinical features of meningeal inflammation.
- Demonstration of pathogen in CSF, with history of acute disease and clinical findings of meningeal inflammation or.
- Demonstration of bacterial pathogen in blood culture, history of acute disease with features of meningeal inflammation.

***Exclusion criteria:*** The main exclusion criteria for subject selection in our study were:

- Subjects with <16 yearsage
- Nosocomial or hospital acquired meningitis
- Tubercular not meeting the above diagnostic criteria.
- Fungal, viral and other causes of meningitis.
- Subjects who refused to participate.

After taking care of inclusion and exclusion criteria, 70 subjects were finally included in the current study

***Outcome of cases***

All patients underwent neurological examination at discharge and outcome was classified as unfavorable and favorable on the basis of Glasgow Scale. Glasgow outcome scale (GOS) of 1-4 is unfavorable and 5 are favorable. Similarly, Glasgow Coma scale (GCS) of >14 was considered favorable (22).

In our study, CSF analysis was an important diagnostic aid. Lumber puncture was performed in all patients, interval between admission and lumber puncture was not recorded. CSF was sent for analysis and was analyzed for total leucocytes count, differential leucocytes count, sugar level, protein concentration CSF was also sent for Gram staining and culture during our study.

***Score:*** All patients underwent neurological examination at discharge and outcome was classified as unfavorable and favorable on the basis of well validated instrument with good inter observer agreement i.e.by GOS and GCS.

***Score***

1. Indicates deaths.
2. Vegetative state (unable to interact with environment).
3. Severe disability (unable to live independent).
4. Moderate disability (living independent but unable to return to work).
5. Mild or no disability.

***Statistical Analysis:-***All the statistical analysis were done using Stata software, version 12 (StataCorp., College Station, TX, USA). The data collected are presented as percentage incidence or mean ± standard deviation. The data association and difference in means were analyzed using Person's Chi-square test. Two-sided P-values <0.05 were considered as statistically significant.

## RESULTS

Age and gender wise distribution of subjects is presented in Table1. The majority of cases belonged to young and middle age groups (21 to 40 years). The mean age of presentation was 37±15.4 years and males slightly outnumbered females. Out of these 41 cases (58.6%) were males and 29 (41.4%) were females with male: female ratio of 1.4:1 ($P$= 0.501).

General characteristics of the study participants with PM are represented in Table2. Most common symptom was headache 64 (91.4%) followed by fever 61 (87.1%). Neck stiffness was found in 81.4%. Altered mental status was found in 60% of cases. Sensitivity of triad of fever, neck stiffness and altered mental status was noted in 32 (45.7%) of participants.

**Table1** Age and gender distribution of the studied subjects

| Age (Yrs.) | Male N (%) | FemaleN (%) | Total N (%) | *P*value |
|---|---|---|---|---|
| Mean ±SD | 38.0±17.0 | 35.5±13.0 | 37.0±15.4 | |
| 16-20 | 07 (17.1) | 04 (13.8) | 11 (15.7) | |
| 21 to 30 | 10 (24.4) | 06 (20.7) | 16 (22.9) | |
| 31 to 40 | 08 (19.5) | 10 (34.5) | 18 (25.7) | 0.501 |
| 41 to 50 | 05(12.2) | 05 (17.2) | 10 (25.7) | |
| >50 | 11(26.8) | 04 (13.8) | 15 (21.4) | |

Seizures were found in 12.8% of cases. 31.4% of patient's showed focal neurologic deficit on admission (Hemiparesis=18.6%; monoparesis= 7.1% and dysphasia =5.7%).CNP was found in 11(19.8%) of cases with 6$^{th}$CNP (5.7%) as most common followed by combination of 3$^{rd}$, 4$^{th}$, and 6$^{th}$CNP in 2.9%. Isolated 8$^{th}$CNP was found in 1.4% of cases (Table 2).

**Table 2** General characteristics of studied subjects with pyogenic meningitis (2014-16).

| Variable | N | %age |
|---|---|---|
| **Common symptom** | | |
| Fever | 61 | 87.1 |
| Neck Stiffness | 57 | 81.4 |
| Altered Mental Status | 42 | 60.0 |
| Headache | 64 | 91.4 |
| Fever+ neck stiffness +altered mental status | 32 | 45.7 |
| 2 of 4 | 68 | 97.1 |
| Vomiting | 40 | 57.14 |
| Seizures | 09 | 12.8 |
| **Focal Neurological deficit** | | |
| Hemiparesis | 13 | 18.6 |
| Monoparesis | 05 | 7.1 |
| Dysphasia | 04 | 5.7 |
| **Cranial Nerve Palsy** | | |
| 6$^{th}$ | 04 | 5.7 |
| 8$^{th}$ | 01 | 1.4 |
| 3$^{th}$ | 02 | 2.9 |
| 4$^{th}$ | 02 | 2.9 |
| 3$^{th}$ + 4$^{th}$ +6$^{th}$ | 02 | 2.9 |

Altered mental status indicated by GCS< 14 was found in 60.5% of cases. 57 cases recovered fully at discharge with GOS score of 5. At discharge, 10% of cases (7/70) were having unfavorable outcome with 4 cases having moderate disability with GOS score of 4 and 3 (Table3).

**Table 3** Glasgow comma and outcome scale at admission among the studied subjects

| Glasgow scale | N | % | *P* value |
|---|---|---|---|
| **GCS** | | | |
| <14 | 42 | 60.0 | 0.024 |
| >14 | 28 | 40.0 | |
| Mean ± SD | 13.5± 1.4 (10,15) | | |
| **GOS** | | | |
| 1 | 6 | 8.6 | |
| 2 | 0 | 0 | |
| 3 | 3 | 4.3 | |
| 4 | 4 | 5.7 | |

GCS= Glasgow comma Scale; GOC= Glasgow outcome scale; Chi-square test was used to calculate the P-Value

Table4 and Table 5 represent the clinical parameters of subjects and their outcome on the basis of their favorable and unfavorable association with PM. Blood culture, CSF gram staining and CSF culture positive was present in 7.1% participating subjects.

Comparison of outcome of cases with relation to different parametersis presented in Table5. Higher counts in blood were significantly associated with unfavorable outcome ($p$<0. 01).

**Table4** Clinical parameters of the pyogenic meningitis in study subjects

| Parameters | Mean/N (SD) | %age |
|---|---|---|
| TLC | 10.3 ±4.1 | |
| DLC | 73.3 ± 11.7 | |
| Platelet | 26.7 ± 11.7 | |
| Blood Sugar | 141.2 ± 52.0 | |
| CSF (Protein) | 123.9 ± 18.1 | |
| CSF (sugar) | 71.8 ± 20.4 | |
| Blood Culture | 05 | 7.1 |
| CSF (gram staining) | 05 | 7.1 |
| CSF (Culture) | 05 | 7.1 |

TLC = total leukocyte count; DLC =differential leukocyte count; CSF= cerebrospinal spinal fluid

**Table 5** Comparison of outcome of cases with relation to different parameters

| | Outcome | | |
|---|---|---|---|
| **Parameters** | **Favorable (SD)** | **Unfavorable(SD)** | ***P* value** |
| TLC (blood) | 9.7 ± 3.8 | 15.7±2.4 | 0.000 |
| DLC | 71.9±11.5 | 85.7±4.6 | 0.002 |
| Blood Sugar | 124.0 ± 17.0 | 123.3± 27.9 | 0.987 |
| CSF (TLC) | 610.6 ± 497.8 | 1307.1±596.7 | 0.001 |
| CSF (DLC) | 81.2± 11.3 | 94.3 ± 2.8 | 0.003 |
| CSF (Sugar) | 33.5 ± 5.5 | 29.7± 6.6 | 0.095 |
| CSF (Protein) | 70.0±19.2 | 88.1± 25.3 | 0.025 |

**Table 6** Frequency distribution of various CSF Parameters

| Variable | Number | %age |
|---|---|---|
| CSF (TLC) | 100 to 200 | 12.9 |
| | 201 to 500 | 35.7 |
| | 501 to 1000 | 32.9 |
| | >1000 | 18.6 |
| CSF (DLC) | 50 to 80 | 32.9 |
| | 81 to 90 | 41.4 |
| | >90 | 25.7 |
| | <20 | 2.9 |
| CSF (Sugar) | 20 to 40 | 90.0 |
| | >40 | 7.1 |
| CSF (Protein) | 45 to 100 | 85.7 |
| | 100 to 500 | 14.3 |

**Table 7** Relations of PM parameters with GCS at admission with outcome

| GCS at Admission | Favorable | Unfavorable |
|---|---|---|
| <14 | 83.3 | 16.7 |
| ≥14 | 100.0 | 0.0 |
| Blood culture | | |
| Positive | 40.0 | 60.0 |
| Negative | 93.8 | 6.2 |
| CSF Gram staining | | |
| Positive | 20.0 | 80.0 |
| Negative | 95.4 | 4.6 |
| CSF Culture | | |
| Positive | 20.0 | 80.0 |
| Negative | 95.4 | 4.6 |
| CSF TLC | | |
| 100 to 200 | 100.0 | 0.0 |
| 201 to 500 | 96.0 | 4.0 |
| 501 to 1000 | 91.3 | 8.7 |
| >1000 | 69.2 | 30.8 |
| CSF DLC – P | | |
| 50 to 80 | 100.0 | 0.0 |
| 81 to 90 | 96.6 | 3.4 |
| >90 | 66.7 | 33.3 |
| CSF sugar | | |
| < 20 | 50.0 | 50.0 |
| 20 to 40 | 92.1 | 7.9 |
| >40 | 80.0 | 20.0 |
| CSF protein | | |
| 45 to 100 | 93.3 | 6.7 |
| 100 to 500 | 70.0 | 30.0 |

Higher % age of neutrophils was associated with higher chances of unfavorable outcome with $p$=<0. 01. Neither, blood sugar nor sugar levels in CSF could reach the statistical significant value ($P$>0.05).

Total leukocyte count (TLC) and differential leukocyte count (DLC) in CSF, which was associated with unfavorable outcome was statistically significant ($p$<0.01). Similarly, unfavorable CSF protein levels were statistically significant among PM patients ($P$= 0.025).

cases Gram Negative organism was isolated. The same was true with Gram staining, same 03 cases were reported to have shown Gram positive organism (*streptococcus pneumonia*) while other 02 have shown gram negative organism (*klebsella pneumonia* and *E. coli*). Others have not shown any organism, thus correlation between Gram staining and culture was found to be 100% (Table8).

**Table 8** Univariate analysis of predictors of mortality of acute bacterial meningitis

| Variable | | Outcome | | | | |
|---|---|---|---|---|---|---|
| | | Favorable | | Unfavorable | | *P* value |
| | | n | %age | n | %age | |
| Age (Yr) | 16≤ 20 | 11 | 100.0 | 0 | 0.0 | 0.00 |
| | 21 to 30 | 16 | 100.0 | 0 | 0.0 | |
| | 31 to 40 | 17 | 94.4 | 1 | 5.6 | |
| | 41 to 50 | 10 | 100.0 | 0 | 0.0 | |
| | > 50 | 09 | 60.0 | 6 | 40.0 | |
| | mean ± SD | 34.5 ± 13.6 (17, 65) | | 59.4 ± 12.7 (33,70) | | |
| Gender | Male | 36 | 87.8 | 05 | 12.2 | 0.470 |
| | Female | 27 | 93.1 | 02 | 6.9 | |
| Triad | Present | 27 | 84.4 | 05 | 15.6 | 0.153 |
| | Absent | 36 | 94.736 | 02 | 5.26 | |
| GCS at admission | < 14 | 35 | 83.3 | 07 | 16.7 | 0.024 |
| | ≥ 14 | 28 | 100.0 | 00 | 0.0 | |
| CNP | Present | 06 | 83.4 | 01 | 16.6 | 0.735 |
| | Absent | 57 | 90.5 | 6 | 9.5 | |
| Blood culture | Absent | 7 | 70.0 | 3 | 30.0 | 0.000 |
| | Positive | 2 | 40.0 | 3 | 60.0 | |
| | Negative | 61 | 93.8 | 4 | 6.2 | |
| CSF (Gram staining) | Positive | 1 | 20.0 | 4 | 80.0 | 0.000 |
| | Negative | 62 | 95.4 | 3 | 4.6 | |
| CSF (culture) | Positive | 1 | 20.0 | 4 | 80.0 | 0.000 |
| | Negative | 62 | 95.4 | 3 | 4.6 | |

The details of CSF among the study participants is given in Table6.CSF leucocytes count was found to have significant prognostic correlation with the outcome ($P$ = <0.01) out of 12.9% cases, who had CSF cell count between 100-200, favorable outcome was found in 100% of cases, while out of 35.7% of cases, who had cell count between 200-500, only 4% has unfavorable outcome 18.6% of cases had cell count above 1000, among these 30.8% had unfavorable outcome. Most common cells in CSF were neutrophils. Higher the percentage of neutrophils, higher the %age of unfavorable outcome. 32.9% of cases had neutrophils in the range of 50 - 80%, 41.4% had 81- 90% and 25.7% of cases had neutrophils greater than 90% cases with neutrophils in the range of 50-80% unfavorable outcome was found in 0% of cases.

CSF protein was found to have statically significant value with the outcome.

Relations of PM parameters with GCS at admission with outcome among study subjects is provided in Table7. Cases with CSF protein concentration >100 mg/dl, 30% had unfavorable outcome while cases with protein concentration < 100 mg/dl, unfavorable outcome was found in only 6.7 % of cases.CSF sugar has also prognostic correlation with outcome but does not reach the statistically significant value. Cases with sugar concentration < 20 mg/dl unfavorable outcome was found in 50 of cases with sugar concentration between 20 -40 mg/dl, unfavorable outcome was found in 7.9% of cases only.

***CSF Gram staining and culture:*** Out of 70 cases, blood culture was positive in only 5 cases. Most common organism found was *streptococcus pneumonia* and was isolated in 3 cases (60%).While in one case, *klebsella pneumonia* was isolated and in another *E. coli* was found. Thus in 40% of

## DISCUSSION

In our study, a total number of 70 cases with a diagnosis of CABM were registered. Males slightly outnumbered females with ratio of male: females = 1.4:1. Majority of cases were in the age group of 21-40 years. The median age of presentation for males was 35 years. This age and sex distribution of our cases was in accordance to previous studies (11, 23).

In our study classic symptom and signs of bacterial meningitis were present in a large proportion of cases. Fever, neck stiffness, altered mental status individually and the triad of fever, neck stiffness and altered mental status in combination was noted in maximum number of cases in the current study which was completely in agreement with previous reports (15, 17). In the current study we noted that triad of fever, neck stiffness and altered mental status was more likely to be present with culture positive meningitis. These results are in compliance to those observed by van de beek *et al* and other studies (17, 24, 25). In their study triad of fever was present in only 44% of cases; however 95% had at least two of the four symptoms of headache, fever neck stiffness and altered mental status.

On admission patient's focal neurologic deficit clinical symptoms were same as observed previously (26), similarly CNP of 3$^{rd}$, 4$^{th}$, 6$^{th}$and8$^{th}$nerve noted in the study subjects is repeated elsewhere (27, 28). The mental status of the participating subjects was described as GCS and GOS scale as observed in previous reports (29-31).

Similar to earlier studies, we observed significant prognostic correlation between CSF leucocytes count, protein and sugar levels with the patient outcome ($P$ = <0.01) (32-34).

The result regarding Gram staining and culture were not consistent with the most of the studies conducted in developed countries where the isolation rate was high (35). Abdeldaim GM *et al* conducted a study in which they reported maximum isolation of *streptococcus pneumonia* from cerebrospinal fluid and blood cultures (9). Similarly studies conducted in India showed variable isolation rate. Study conducted by R. Mani *et al* reported isolation rate of 73.8% with *streptococcus pneumoniae* as the predominant pathogen in 61.8% of cases followed by *Haemophillus influenza* and *Neisseria meningitides* accounting for 1.8% and 1% respectively(36). Another study from A. Sonavane *et al* reported isolation rate of 0.55% with *pseudomonas aeruginosa* as the predominant organism (23.25%) followed by *Klebsella*, *Acinetobacter* species (37, 38). In our study positive Gram staining and culture had direct relation with the outcome. Among 5 cases, which were culture positive, 4 expired while 1 survived with mild disability at discharge i.e., 80% culture positive cases were having unfavorable outcome and 20% have favorable outcome.

The low sample size and empirical antibiotic therapy in some patients before CSF examination was the main limitation of our study however to the best of our knowledge the study was first of its kind in our tertiary care hospital among PM patients.

## CONCLUSION

From this study, we concluded that sensitivity of triad of fever, neck stiffness and altered mental status was low as 45.7%. The factors which have prognostic implication included GCS at admission less than 14, age above 50 years, Higher CSF leukocyte count, Positive CSF gram staining and culture.

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