

# Outbreak analysis of meningococcal meningitis: A case series from a tertiary care hospital in Eastern India



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## ABSTRACT

In a span of 4 months, there were 7 cases of meningococcal meningitis who presented with diagnostic dilemma and also a few atypical manifestations. A retrospective data analysis was carried out in children diagnosed with meningococcal meningitis who were admitted from October 2022 to January 2023. There were 7 confirmed cases of *Neisseria meningitidis* infections during the study period. The median age of presentation was 6 years (range: 4.5 months–9 years) with four males and three females. All the children presented with fever, but none had signs of meningeal irritation as such. Routine blood and cerebrospinal fluid (CSF) analysis were also near normal. Reverse transcriptase polymerase chain reaction (RT-PCR) for *N. meningitidis* was positive in the CSF samples of all the seven cases. All of the patients recovered completely, except that there were residues of neurodeficit in one patient. In endemic areas, pediatricians should have a low threshold of suspicion for *N. meningitidis* in children presenting with signs and symptoms involving the central nervous system and consider an RT-PCR of the CSF sample even if routine blood and CSF studies are near normal.

**Key words:** Cerebrospinal fluid reverse transcriptase polymerase chain reaction; *Neisseria meningitidis*; Outbreak

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## INTRODUCTION

*Neisseria meningitidis*, a Gram-negative diplococci, is notorious for causing life-threatening septicemia called meningococemia and meningitis.<sup>1</sup> Clinical spectrum of meningococcal disease varies widely and progresses very rapidly. A nonspecific prodrome consisting of fever, irritability, lethargy, maculopapular/petechial rash (seen in 10% cases) is followed by signs and symptoms of meningeal irritation (stiff neck, headache, photophobia and impaired sensorium) and/or signs of shock (tachycardia, tachypnea, cyanosis, oliguria, hypotension) that can progress over a matter of hours to death.<sup>2</sup> Characteristic meningococcal rash may not appear early in the course, thereby delaying the diagnosis.

*N. meningitidis* is a commensal of the upper airways, which serves as the only reservoir for the bacteria. Whether or not overt disease will manifest in a carrier of *N. meningitidis* is dependent on microbial, environmental, and host genetic and behavioral factors.<sup>3</sup> Humans get infected when they come in contact with the infected respiratory secretions.

The organism has the capacity to cause both epidemic and endemic infections with large number of individuals getting infected within a short span of time.

We present seven patients from our tertiary care center, in a span of four months, whose routine blood and cerebrospinal fluid (CSF) examinations were near normal,

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but CSF reverse transcriptase polymerase chain reaction (RT-PCR) was positive for *N. meningitidis*.

## CASE SERIES

We carried out a retrospective analysis of the children diagnosed with *N. meningitidis* at a tertiary care institute in Eastern India from October 2022 to January 2023. All patients underwent thorough clinical examination with special emphasis on neurological assessment, followed by basic blood biochemistry, CSF routine analysis, blood and CSF culture (aerobic and anaerobic), CSF RT-PCR, and neuroimaging.

### Cases 1, 2, and 3

The following three cases were that of a 4.5 month old male, 1 year 1 month old male, and 1 year 2 months old female, respectively. All the three cases presented with high-grade fever and convulsions. Their blood workup, neuroimaging, and CSF analysis were normal. Blood and CSF culture grew no organism. However, CSF RT-PCR showed the presence of *N. meningitidis*. All the three cases presented with high-grade fever and convulsions. Their blood workup, neuroimaging, and CSF analysis were normal. Blood and CSF culture grew no organism. However, CSF RT-PCR showed the presence of *N. meningitidis*.

### Case 4 and 7

Both cases had fever and severe headache with one of them being drowsy with altered sensorium on presentation. On examination, neck rigidity, Kernig's and Brudzinski's signs were negative. As severe headache persisted in both the patients, neuroimaging followed by CSF analysis was done both of which were normal. CSF RT-PCR isolated the diplococci for both the patients. CSF RT-PCR here also isolated the diplococci.

### Case 5

A 7-year-old boy presented with a history of fever, gait abnormality (ataxic gait), and sudden onset aphasia. This was a rather unique presentation. On examination, signs pertaining to cerebellar involvement (dysmetria, pendular knee jerk, and dysdiadochokinesis) were present. Signs of meningeal irritation like neck stiffness, Kernig's and Brudzinski's signs were absent. Even though neuroimaging and CSF analysis were normal, the CSF RT-PCR was positive for *N. meningitidis*. Residual neurological deficit (aphasia persisted post treatment) was present in only this patient. He also had an abnormal Brainstem Auditory Evoked Response (BAER) (high-intensity hearing threshold with peripheral conduction abnormality in right auditory pathway). However, aphasia could not be explained by the BAER findings *per se*. On further follow-up after 2 months, the child was able to speak with difficulty.

### Case 6

This was an 8-year-old girl who had presented with fever, generalized tonic-clonic convulsions, and typical petechial rash with focal necrotic areas. Positive contact history (in sibling) was elicited. Her Glasgow coma scale was poor, and she presented to the emergency in a state of shock and she required ventilatory support. Her CSF culture grew the Gram-negative diplococci and the CSF RT-PCR was also positive for the same.

The individual patient details are outlined in Table 1.

## DISCUSSION

Meningitis requires prompt diagnosis and management. The gold standard for the diagnosis of acute bacterial meningitis is the demonstration of viable bacteria in the CSF by staining and culture.<sup>4</sup> However, due to pre-treatment with antibiotics that causes sterilization of CSF within 2 h.<sup>5,6</sup> and delayed CSF plating on the culture media, the culture may often come negative. Furthermore, financial constraints, lack of laboratory facilities, and lack of laboratory expertise in detecting *N. meningitidis* and lack of available techniques apart from Gram stain and culture were also identified as hindrance to successful *N. meningitidis* identification.<sup>7-9</sup> Use of PCR techniques increases the chances of detection of *N. meningitidis*, particularly in patients who have received antibiotics.<sup>7</sup> Wagner et al. described the utility of multiplex RT-PCR in diagnosing meningitis when the CSF culture was negative.<sup>10</sup> RT-PCR does not require viable cells; hence, its diagnostic efficacy is less affected by antibiotic treatment. Several studies that have compared the yield from bacterial culture with PCR have found that 30–50% of culture-negative CSF specimens are positive according to PCR.<sup>11,12</sup> Guiducci et al., in their study, demonstrated that PCR was 3.5 times (blood) or 3.1 times (CSF) more sensitive than culture in achieving a laboratory diagnosis of invasive meningococcal disease.<sup>13</sup> As a complement to classical bacteriological CSF culture, the RT-PCR assay proved to be valuable by improving the rapidity and accuracy of the diagnosis of bacterial meningitis, especially in culture-negative samples.<sup>14</sup> Reyes et al. studied 99 CSF samples, 90 from children with fever and negative CSF culture, and 9 from positive CSF culture patients. Their multiplex PCR protocol had a sensitivity of 89%, specificity of 100%, positive predictive value 100%, and negative predictive value 99%.<sup>15</sup> In our study, 6 out of 7 patients were only discovered to have had meningococcal meningitis following a positive RT-PCR on the CSF samples. The real burden of acute bacterial meningitis is often seriously underestimated because of the poor performance of culture sampling, which has always been the primary method of surveillance. Nhantumbo et al., in their study, found that

Table 1: Description summary of patients

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age	4.5 month	1 year 1 month	1 year 2 months	6 year	7 year	8 year	9 year
Location	Rural	Urban	Urban	Urban	Urban	Urban	Urban
Sex	Male	Male	Female	Female	Male	Female	Male
Duration of illness before hospitalization (days)	2	1	1	4	5	4	3
Fever	+	+	+	+	+	+	+
Headache	-	-	-	+ severe	-	-	+ severe
Neck stiffness	-	-	-	-	-	-	-
Rash	-	-	-	-	-	+	-
Convulsion	+, tonic posturing and up rolling of eyes.	4 episodes of focal seizures	2 episodes of tonic clonic seizures	-	-	1 episode of tonic clonic seizures.	-
Other symptoms	-	-	-	-	Abnormal gait	Drowsy + (sibling)	-
Contact history	-	-	-	-	-	Not given.	-
Meningococcal Vaccination status	Not given	Not given	Not given	Not given	Not given.	Not given.	Not given.
Prior treatment with antibiotic	-	-	-	-	-	Oral acyclovir	-
Place of admission	General ward	General ward	PICU	General ward	General ward	PICU	General ward
Features of shock	-	-	-	-	-	+	-
CNS examination	Normal	Normal	Post ictal drowsiness present	Normal	Ataxic gait, dysmetria, dysdiadochokinesis Pendular knee jerk, no signs of meningeal irritation	GCS 8/15, Altered sensorium, tachycardia, poor peripheral pulses, BP at 50 <sup>th</sup> centile.	Drowsy with altered sensorium No signs of meningeal irritation.
Blood investigation							
Hemoglobin (g/dl)	9.8	11.6	11	12	11.9	12	13
Total leucocyte count (cummm)	7000	6100	12600	9000	14500	16500	9000
Neutrophil (%)	30	23	80	56	74	74	46
Lymphocyte (%)	63	72	15	42	23	24	54
C-reactive protein (normal<6 mg/L)	20	5	12.9	34	22	90	<1
CSF examination							
Glucose (mg/dl)	68	70	48	63	55	94	59
Protein (mg/dl)	25	10	20	18	37.4	15.3	46
Cell count (cummm)	<5	<5	10	75	75	25	10
Cell type	Mono nuclear	Mono Nuclear	Mono nuclear	Mono nuclear (92%)	Mono nuclear cells (94%) Gram negative diplococci found in both staining and culture.	Mono nuclear	Mono nuclear
Gram stain	-	-	-	-	-	-	-
Culture	-	-	-	-	+	-	-
RT-PCR for <i>N. meningitidis</i>	+	+	+	+	+	+	+
MRI brain findings	Normal.	Normal	Normal.	Normal.	Normal	Normal	Normal.

(Contd...)

**Table 1: (Continued)**

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Treatment <sup>#</sup>	Levetiracetam Ceftriaxone	Levetiracetam Ceftriaxone Acyclovir	Levetiracetam Ceftriaxone	Ceftriaxone	Ceftriaxone	Levetiracetam Ceftriaxone Acyclovir Required	Ceftriaxone, Acyclovir Levetiracetam
Ventilatory support	-	-	-	-	-	-	-
Duration of hospital stay (days)	9	9	8	1	9	12	10
Outcome	Survived	Survived	Survived	Survived	Survived	Survived	Survived
BAER	Normal	Normal	Normal	Normal	High intensity hearing threshold with peripheral conduction abnormality in right auditory pathway.	Normal	Normal
Household prophylaxis	Given	Given	Given	Given	Given	Given	Given
Follow up	NS	NS	NS	NS	Aphasia	NS	NS

PICU: Pediatric intensive care unit, GCS: Glasgow coma scale, RT-PCR: Reverse transcriptase polymerase chain reaction, BAER: Brainstem Auditory Evoked Response, NS: Not significant. #Treatment includes empirical and specific therapy

bacterial pathogens causing meningitis were detected by CSF PCR in 52.3% (193/369) of CSF samples, while only 7.3% (27/369) of CSF samples were culture positive. This represents a seven-fold increase in the detection rate.<sup>16</sup>

*N. meningitidis* may present with atypical signs and symptoms and, therefore, pose a diagnostic challenge for the physician. Atypical presentation was reported by Rashad et al., in their study, where they reported two adult patients: one presenting with pneumonia and the other presenting with gastroenteritis.<sup>1</sup> The findings indicated that the most prevalent atypical presentations include acute gastrointestinal symptoms, septic arthritis, and bacterial pneumonia or severe upper respiratory tract infection, especially epiglottitis.<sup>17,18</sup> Aphasia, as was seen in our patient, has been rarely described in the literature. Damásio et al., in their study, described aphasia in a 17-year-old boy who suffered from meningococcal meningitis.<sup>19</sup> In all of our cases, the signs of meningitis like neck rigidity, Kernigs Brudzinski, photophobia, and vomiting were absent. Although the presence of rash is a distinctive feature of meningococcal infection, it is present in only <7% of cases.<sup>20</sup> In our study also, only one patient presented with petechial rash with focal necrotic areas. Bacterial meningitis often results in a neutrophil predominant CSF pleocytosis. However, in our study, surprisingly, all of the 7 cases had a lymphocyte predominant CSF pleocytosis though they did not receive any prior antibiotic treatment. This rare phenomenon was also noticed by Powers in his study,<sup>21</sup> where he noted lymphocytosis in the CSF in 13% of cases of acute bacterial meningitis when the CSF cell count was <1000/cumm. Arevalo et al., in their study, found that CSF lymphocytosis to be associated with mild degrees of CSF pleocytosis.<sup>22</sup> CSF Gram stain and culture were more frequently negative than in patients who had polymorphonuclear predominant CSF. CSF lymphocytosis denotes earlier stage of the disease where the small bacterial load in the CSF results in majority of Gram stain and culture becoming negative. Furthermore, except in one patient, the routine CSF culture and blood culture were negative. CSF glucose may be normal in almost 50% of cases with bacterial meningitis.<sup>23</sup> In our cases, 6 out of 7 patients had normal CSF glucose. Hearing impairment is common after bacterial meningitis. BAER was done in all the 7 patients. BAER in one of our patients showed high-intensity hearing threshold with peripheral conduction abnormality in the right auditory pathway. Kutz et al., in their study, found decreased CSF glucose as the most consistent predictor of hearing loss.<sup>24,25</sup> Possibly, the low CSF glucose directly damages the cochlear neuroepithelium.<sup>26</sup> In our study, the patient with abnormal BAER, however, did not have very low CSF glucose (CSF glucose was 55 mg/dL). Repeated follow-up BAER is required, especially if the initial test results are abnormal. Rodenburg-Vlot et al.,<sup>27</sup> in their study,

found two such patients with unilateral hearing loss who later also developed hearing loss in the contralateral ear, which had normal hearing initially.

Vaccination is the mainstay to control meningococcal disease apart from chemoprophylaxis to the close contacts. None of the 7 cases in our study were immunized. MenACWY-DT (Menactra) has been licensed in India. Two doses are recommended at 9 months and 12 months with catch up to 18 years and a single dose above 2 years age. The other conjugate vaccine MenACWY-CRM (Menveo) is recommended only as a single dose above 2 years of age. The vaccine is essential in the following: immunocompromised individuals, people suffering from functional or anatomical asplenia/hyposplenia, and chronic systemic diseases, individuals travelling to countries in the African meningitis belt, Hajj pilgrims and laboratory personnel. Chemoprophylaxis should be administered in close contacts of patients and during outbreaks (even  $\geq 3$  months of age and/or close household contacts).<sup>28</sup>

We had offered chemoprophylaxis to all the close contacts of our patients in the form of single-dose ceftriaxone injection (125 mg IM below 15 years and 250 mg IM above 15 years) or single-dose oral ciprofloxacin (20 mg/kg maximum dose 500 mg). Fortunately, none of the contacts were affected with the disease.

## CONCLUSION

In endemic areas, pediatricians should have a low threshold of suspicion for *N. meningitidis* in children presenting with signs and symptoms involving the central nervous system or who present in shock even before the skin manifestation is evident. It is not essential that signs of meningeal irritation will be present in all patients as was seen in our study. Even the CSF studies may be near normal and the cultures may be negative without use of prior antibiotics as seen in our cases. RT-PCR of CSF sample can help us clinch the diagnosis in such doubtful cases. Vaccination and chemoprophylaxis will help prevent outbreak of this deadly disease.

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**PK-** Concept and design, manuscript preparation; **SP-** Revision of manuscript and lab investigation analysis; **BD-** Design, preparation and revision of manuscript and treating physician; **SK-** Referral physician; **SB-** Referral physician; **RK-** Treating physician; **HD-** Treating physician; **AM-** Referral physician; **DS-** Resident-in-charge.

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