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Predisposing conditions and outcome in adult patients with recurrent pneumococcal meningitis

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Abstract

Introduction: Recurrent pneumococcal meningitis is a relatively rare condition associated with predisposing factors. The objective of the study was to evaluate the characteristics and predisposing factors for recurrent pneumococcal meningitis in adults and compare them to patients with non-recurrent meningitis. *Methods*: A retrospective record review was performed of all patients hospitalized for pneumococcal meningitis in a large tertiary referral center, during a 10-year period. *Results:* We identified a total of 194 pneumococcal meningitis episodes in 182 patients. Thirty-eight (20%) meningitis episodes in 26 patients were recurrent. Anatomical defects and/or CSF leakage were present in 55% of recurrent pneumococcal meningitis vs. 10% of non-recurrent episodes ($p<0.001$). Impaired immune response was encountered in 41% non-recurrent meningitis vs 24% of recurrent episodes ($p=0.02$). Median age in patients with recurrent meningitis was 29 years, while patients with non-recurrent meningitis had a median age of 57 years ($p<0.001$). The in-hospital mortality was 3% in patients with recurrent meningitis vs 27% in patients with non-recurrent meningitis ($p<0.001$). An unfavorable outcome was more likely to occur in patients with advanced age and an impaired immune status.
Conclusions: Patients with recurrent pneumococcal meningitis were younger, had less comorbidities and a better outcome.

Keywords: Bacterial meningitis, recurrent; pneumococcal, CSF leak

INTRODUCTION

Recurrent bacterial meningitis is defined as two or more episodes of meningitis caused by the same organism and occurring at least 3 weeks after completion of therapy for the initial episode, or at least two episodes caused by different organisms irrespective of the time interval between the episodes. Thus, recurrent bacterial meningitis is differentiated from relapse in which the initial infection is persisting.[1] The incidence of bacterial recurrent meningitis was estimated at 5-6% of the community-acquired meningitis.[2,3] More than half of cases are due to *Streptococcus pneumoniae*, followed by *Neisseria meningitidis,* which causes one quarter of the episodes.[1]

S. pneumoniae is the leading cause of acute bacterial meningitis in adults, with a mortality of 15–34%.[2] It is the most frequently isolated organism in conditions associated with abnormal cerebrospinal fluid (CSF) flow or cranial bone defects, and in patients with underlying congenital or acquired immunodeficiency.[2-4] Recurrent pneumococcal meningitis is not a common occurrence but it is a challenging condition and requires further investigations to identify predisposing factors in order to prevent further episodes and improve the overall outcomes. Although better described in children, there are only few studies on recurrent meningitis in adults. Predisposing conditions associated with recurrent bacterial meningitis can be divided into chronic parameningeal infections and congenital or acquired anatomical defects and immunodeficiencies.

The objective of this study was to analyze the underlying predisposing conditions and in-hospital mortality of adult patients with recurrent pneumococcal meningitis and compare them to non-recurrent cases during a 10 year-period.

METHODS

We conducted a retrospective record review of all patients hospitalized between January 2005

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and December 2015 for pneumococcal meningitis at the National Institute of Infectious Diseases "Prof. Dr. Matei Bals" from Bucharest, Romania, a large referral hospital specialized in infectious diseases. Electronic medical records were searched for patients diagnosed with meningitis during the study period. The patient files were retrieved and cases of pneumococcal meningitis were selected. The diagnosis of pneumococcal meningitis was established based on the presence of clinical signs and symptoms of meningitis and the detection of *S. pneumoniae* from CSF or blood samples in combination with cerebrospinal fluid abnormalities (pleocytosis, elevated protein levels and decreased CSF/serum glucose ratio < 0.5). Microbiological confirmation of pneumococcal infection was made based on typical morphology on Gram-stain, a positive CSF latex agglutination reaction, and/or a positive culture for *S. pneumoniae* (CSF or blood culture). Recurrent pneumococcal meningitis was defined as at least two pneumococcal meningitis episodes occurring at least 4 weeks after the completion of treatment for the initial episode followed by full recovery. We excluded relapsing meningitis resulting from treatment failure (defined as the persistence of the initial infection) or healthcare associated infections (such as following neurosurgery, otorhino-laryngological interventions or other forms of cranial or maxillofacial surgery).

We recorded data on socio-demographic status, clinical features, predisposing conditions associated with pneumococcal meningitis and in-hospital mortality. Patient records were evaluated for the presence of any of the following diagnoses: otitis, mastoiditis, sinusitis, pneumonia, endocarditis, inner ear abnormalities, congenital skull base defects, head injury/basal skull fracture, CSF fistulas or conditions associated with immunodeficiency (diabetes mellitus, alcohol abuse, end-stage liver disease, advanced chronic kidney disease, malignancy, malnutrition, splenectomy, autoimmune disorders or immunosuppressive therapy). Immunosuppressive drugs were considered: glucocorticosteroids at a higher cumulative dose of 700 mg or prednisone at a higher dose than 20 mg/day, chemotherapy drugs, monoclonal antibodies, or drugs acting on immunophilins. There was no follow-up of patients after discharge and therefore no data on long-term sequelae was available.

We analyzed data using the Statistical Package for Social Sciences (SPSS version 21, IBM Corp., Armonk, NY, USA). Dichotomous variables were compared by the Chi-squared test. Continuous variables were compared by the Mann-Whitney U test and $p < 0.05$ was considered significant.

RESULTS

We identified a total of 194 pneumococcal meningitis episodes in 182 patients diagnosed and treated in our institution between January 2005 and December 2015. Thirty-eight (20%) episodes of recurrent meningitis were recorded in 26 patients and 156 (80%) episodes of non-recurrent meningitis. Sixteen (8.8%) out of 182 patients with recurrent meningitis experienced two episodes, 5 patients (2.7%) had three episodes and there were 5 patients with four, five, seven, 11 and 40 prior recurrent episodes. We included in this analysis only episodes considered as "recurrent meningitis" according to the aforementioned definition and occurring during the study period.

The demographic characteristics of our patients and the underlying conditions predisposing to recurrent or non-recurrent pneumococcal meningitis are shown in Table 1.

Bone defects and/or CSF leakage in recurrent and non-recurrent pneumococcal meningitis groups were: inner ear abnormalities in one case in both groups, congenital skull base defects in 8 (21%) versus and 3 (2%) cases, head injury/basal skull fracture in 4 (11%) and 5 (3%) cases, CSF fistulas in 8 (21%) and 6 (4%) of cases, respectively. Hematogenous spread from a primary infectious site was observed only in patients from the non-recurrent meningitis group: 10 (71%) cases with lower respiratory tract infections and 4 (29%) cases with endocarditis. Other predisposing factors in patients with non-recurrent meningitis were immunodeficiency (in most cases acquired). Other conditions associated with an increased risk of pneumococcal meningitis in patients with recurrent and non-recurrent meningitis: diabetes mellitus in 1 (3%) and 31 (20%) cases, alcohol abuse in 2 (5%) and 14 (9%) cases, end-stage liver disease in 0 and 7 (4%) cases, malignancy in 2 (5%) and 7 (4%) cases, malnutrition in 1 (3%) and 4 (3%) cases, splenectomy in 0 and 1 (1%) case, immunosuppressive therapy in 0 and 2 (1%) cases respectively (1 patient was on anti-TNF therapy and the other received 60 mg of prednisone/day). Overall, conditions associated with an impaired immune response were present in 70 patients (38%).

The median time from onset of disease until admission was 2.5 days (IQR 1.5-3.2) in the recurrent meningitis groups versus 2.4 days

Table 1: Characteristics of patients with recurrent and non-recurrent pneumococcal meningitis

	Recurrent meningitis N=38	Non-recurrent meningitis N=156	p value OR (95% CI)
Age, median (IQR)	29 (21-47)	57 (38-65)	**< 0.001**
Male gender, n (%)	19 (50)	90 (58)	0.2 1.3 (0.6-2.7)
Bone defects and/or CSF leakage, n (%)	21 (55)	15 (10)	**< 0.001** 14.4 (6.2-33.4)
Sinusitis, n (%)	7 (18)	18 (12)	0.19 1.7 (0.6-4.5)
Otitis/ mastoiditis, n (%)	2 (5)	47 (30)	**0.003** 0.2 (0.05-0.68)
Hematogenous spread, n (%)	0	14 (9)	**0.04** 0.9 (0.8-0.95)
Impaired immune response, n (%)	8 (21)	62 (40)	**0.02** 0.4 (0.1-0.9)

CSF cerebrospinal fluid, IQR interquartile range, OR odds ratio.

(IQR:1.8-3.6) in the non-recurrent meningitis group ($p = 0.8$). Focal neurological deficits were represented by pyramidal signs and cranial nerve palsies. Seizures were found in 5 cases in the recurrent meningitis group (13%) and in 7 cases (5%) in the non-recurrent meningitis group ($p = 0.06$; OR 3.6, 95% CI: 0.9-14.1). Impaired consciousness on admission was seen in 15 cases (39%) in the recurrent meningitis group versus 64 cases (41 %) in the other group ($p = 0.6$; OR 0.78, 95% CI: 0.26-2.28).

In hospital mortality was 27% in the non-recurrent meningitis group versus 3% in the recurrent meningitis group ($p< 0.001$; OR 0.07, 95% CI: 0.01-0.5). Risk factors associated with in-hospital mortality in both groups are shown in Table 2.

DISCUSSION

This study describes the characteristics and predisposing factors for recurrent pneumococcal meningitis in adults from a large tertiary referral center in Bucharest, Romania and compares them to those of patients without recurrent meningitis.

In this study, recurrent meningitis represented 20% of community-acquired pneumococcal meningitis cases. Other authors reported that between 2.3% and 12.8% of cases of community-acquired meningitis in adults are recurrent, *S. pneumoniae* being the most frequent etiology.[1-3,5] The high proportion of recurrent meningitis in this study might be due to the fact that the hospital where the study was conducted is a referral center where complex cases are being treated, while many patients with non-recurrent meningitis are admitted to smaller centers.

Table 2: Risk factors associated with in-hospital mortality in patients with pneumococcal meningitis

	Deceased N=43	Discharged alive N=151	p-value
Age, median (IQR)	59 (47-66)	49 (28-62)	0.02
Hematogenous spread, n (%)	3 (7)	11 (7.2)	0.9
Impaired immune response[a], n (%)	24 (56)	52 (34.5)	0.01
Neurological symptoms[b], n (%)	19 (44)	60 (40)	0.5
Recurrent meningitis, n (%)	1 (3)	37 (97)	< 0.001

[a]Impaired immune response: diabetes mellitus, alcohol abuse, end-stage liver disease, malignancy, malnutrition, splenectomy, immunosuppressive therapy, pregnancy, autoimmunedisorders, advancedchronickidneydisease.
[b]Neurologic symptoms: impaired consciousness on admission, cranial nerve palsies, seizures and/or focal neurologic deficits).

Most studies on recurrent meningitis describe cases with two episodes.[3,5-7] In one study, up to 84% of patients with recurrent bacterial meningitis experienced only two episodes.[3] However, one of the patients included in this study had experienced no less than 40 previous episodes[8] and other authors report a case with 12 recurrent episodes in a patient with a minor head injury and a skull base defect.[9] The case of the patient who experienced 40 recurrent pneumococcal meningitis episodes had been published elsewhere.[8] The recurrences of bacterial meningitis were due to CSF leakage and the presence of chronic sinusitis. In this patient the recurrences were not influenced by the surgical repair of a fistula and repeated surgical draining interventions on suppurating chronic sinusitis. Long-term prophylaxis with phenoxymethylpenicillin reduced the number of recurrences and there were no further episodes following anti-pneumococcal vaccination for a 5-year period.

In this study, recurrent meningitis was not more common in men, in contrast to previous reports.[1,3,5,7] More frequent recurrent meningitis in men might be related to a higher frequency of head trauma.[3]

We found a significant age difference between patients with recurrent meningitis, who were younger as compared with the patients from the non-recurrent group. This is consistent with data reported by others.[1,3,10,11]

In this study, anatomical defects associated with CSF leakage were a major predisposing factor for developing recurrent pneumococcal meningitis. Cranial skull defects are a well-recognized risk factor for *S. pneumoniae*-recurrent meningitis in adults, especially following head trauma.[1-3,5,12,13] In a review of 363 cases of recurrent bacterial meningitis, 214 episodes (59%) were related to anatomical defects, in which the abnormality was located in the majority of cases in the cranial or cervical region. Traumatic head injury with secondary CSF fistulae, accounted for almost half of all cases in this group (47%).[1] In another study, the most common predisposing conditions for recurrent bacterial meningitis were prior head injury in 53% of 32 episodes and CSF leakage in 32% of 28 episodes.[3]

Predisposing conditions for non-recurrent pneumococcal meningitis, especially in patients with an impaired immune response led to dissemination of infection from a contiguous site (especially otitis and mastoiditis) and hematogenous spread. This is consistent with data reported by one review of 493 episodes of acute bacterial meningitis in adults which included 404 single episodes.[2] In our study, a small number of cases in the recurrent group were related to an immunosuppressive condition. This was also found by other authors, where only 9% of 34 patients were immunosuppressed.[3]

In-hospital mortality due to pneumococcal meningitis was associated with immunosuppression and impaired consciousness on admission. There was only one death in the recurrent meningitis group which prevented us to analyze the risk factors associated with mortality. In our study, there was a significant difference in mortality between recurrent and non-recurrent meningitis, with 3% versus 27%, respectively, which is similar with other reports. In a cohort from the Netherlands the mortality in patients with non-recurrent meningitis was more than double compared with patients with recurrent meningitis (34 vs. 15%).[3,11] In another study of patients from the US which included 38 episodes of recurrent community-acquired meningitis and 253 community acquired single episodes over a 27-year period, the overall mortality rates (*per* patient) were 6% for recurrent community-acquired meningitis and 25% in patients admitted for their first episode.[2] The difference in mortality between the groups, beyond their age and underlying conditions, might be due to the fact that patients who had experienced previous episodes of meningitis are likely to recognize the symptoms early and seek medical attention sooner, being referred from the onset of symptoms to a specialized tertiary health-care hospital, thereby improving their prognosis. This could be an explanation also reported by another study.[3]

The limitations of our study are related to its retrospective nature, to the fact that only in-hospital mortality could be evaluated, while long-term morbidity (including neurological sequelae) and mortality were not assessed. Additionally, serotyping for *S. pneumoniae* and information on antipneumococcal vaccination were not available. However, we present data from a relatively large cohort of 182 patients with pneumococcal meningitis.

In conclusion, this study showed that patients with recurrent pneumococcal meningitis were younger, had less co-morbidities and a better outcome compared with patients with non-recurrent meningitis. Overall, an unfavorable course was more likely to occur in patients with advanced age and an impaired immune status. It is important to diagnose underlying predisposing conditions in patients with recurrent meningitis in order to prevent further episodes.

DISCLOSURE

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