Factors associated with the risk of recurrent pneumococcal meningitis in children

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Introduction

Pneumococcal meningitis (PM) is a serious disease that can exceptionally recur at a distance from the initial episode.

Methods

Design

- Retrospective, national, case-control study in October 2015
 - Data of the National Observatory of bacterial meningitis in children (250 pediatric unit and 168 microbiology laboratories) were collected from January 2001 to September 2015

Definitions

- **PM** was defined by the presence of clinical and CSF signs of meningitis and either the culture of *Streptococcus pneumoniae* in CSF or blood, and/or positive pneumococcal antigens or PCR in the CSF.
 - **Cases** were all children less than 18 years of age, with recurrent PM (RPM) defined as the presence of at least two episodes of PM with an interval between episodes of at least 28 days during the study period.
 - **Controls**: Each case was matched to two randomized controls with a single episode of PM (SPM) in the year of the 1st episode of PM in the case and born the same year.
 - **Risk factors for PM** identified in the literature were: CSF leaks, presence of a ventricular shunt, congenital or acquired immune deficiency, any sort of asplenia and presence of a cochlear implant (1, 2).
 - **Risk factors for CSF leak**: trauma (surgical or not), inflammatory, congenital, neoplasm(3)

Process of data collection

- Cases and controls were identified from the ACTIV National database.
 - Standardized additional data useful for this research were collected from each pediatric unit where a case or a control was admitted.
 - Data collected:
Anamnestic: sex, age, season at admission, siblings, risk factors for IPD, PCV7, PCV13;
Clinical: ENT infection, seizure, coma, septic shock, purpura, assisted ventilation;
Biological: WBC count, CRP, procalcitonin, CSF data, search for immune deficiency;
Microbiological: pneumococcal identification, serotype if available, antimicrobial susceptibility;
Therapeutic: antimicrobial and steroid treatment;
Outcome: complications, CSF leaks search & treatment, ICU admission, sequels, death.

Statistical analyses

- Frequency of RPM cases in the national database.
 - Comparison between the 1st episode of PM in cases and PM of controls of anamnestic, vaccine and clinical data.
 - Comparison of all PM episodes in the cases with PM episode in the controls.
 - Comparison of outcomes and risk factors for PM between cases and controls. - Quantitative data were analyzed using a student t-test or non-parametric Mann-Whitney test where applicable. Qualitative values were analyzed in comparison with the explanatory variable, by a Chi-2 or Fisher Exact test.

Objectives

The main purpose of this study was to assess risk factors for RPM in children in using the national ACTIV database. Secondary objectives were to estimate the frequency of these RPM cases and the outcome of these patients.

Results

Identified **risk factors for PM** were not different between cases and controls after the first PM.

ID search: more frequently in cases (58%) than in controls (29%), $p=0.01$. No ID was identified among cases vs. seven (15%) among controls, $p=0.09$. The IDs were: 4 congenital (1 Down syndrome and 3 functional asplenia) and 3 acquired IDs, including 1 HIV infection, 1 dysmyelodysplastic disease and 1 chemotherapy for brain tumor.

CSF leak search: Brain imaging: 86% of all PM episodes without differences between cases and controls. **CSF leak identification**: After the 1st episode: 25% in cases vs. 11% in controls ($p=0.12$). At the end of all episodes: 20 in cases vs. 5 in controls (83% vs. 10%, $p<10^{-7}$)

Table 2. Number of PM-related deaths and short and long-term outcome of patients alive after a single and multiple episodes of PM

Outcome	Cases (n=24)		Controls (n = 48)		p*	p**
	After first PM n/N (%)	After last PM n/N (%)	After first PM n/N (%)	After last PM n/N (%)		
Death	-	4/24 (17)	7/48 (15)	-	1.00	
Deafness	7/20 (35)	5/20* (25)	10/31 (32)	0.84	0.58	
Neurological sequelae	10/23 (44)	11/20 (55)	12/36 (33)	0.43	0.11	
Epilepsia	2/23 (9)	4/20 (20)	3/36 (8)	1.00	0.67	
SM deficiency	6/23 (26)	5/20 (25)	11/36 (31)	0.71	0.12	
Mental deficiency	6/23 (26)	5/20 (25)	2/36 (6)	0.05	0.17	

SM = Sensory-Motor; # Two patients with deafness after the first PM died;
 * First cases vs. controls; **Last cases vs. controls

The median time between the first and the second episode was 21 months (IQR: 6–37). Characteristics of cases and controls are presented Table 1 and outcome in table 2. Identified vaccination serotypes were more frequent in cases than in controls (18% vs. 0%, $p=0.02$).

Table 1. Description of the population with recurrent Pneumococcal meningitis (PM) (cases) compared to 48 children with single PM episodes (controls)

Variables	Cases (recurrent PM)		Controls (single PM)	p*	p**
	First episode (n = 24)	All episodes (n = 62)	(n = 48)		
Male/Female ratio	1.40	-	1.86	0.74	-
Premature birth, n/N (%)	6/21 (29)	-	3/32 (9)	0.13	-
Median age, years (IQR)	3.8 (2.6–7.2)	6.1 (3.0–10)	4.0 (2.5–8.0)	0.82	0.08
Median weight, SD (IQR)	-0.25 (-1.0–1.0)	0.5 (-1.0–1.0)	0.0 (-1.0–1.0)	0.34	0.70
Pre PM abnormal psychomotor dvlpmnt, n/N(%)	8/21 (38)	30/57 (53)	8/37 (22)	0.18	0.01
Community childcare, n/N (%)	19/23 (83)	54/60 (90)	31/39 (79)	1.00	0.14
≥1 Sibling, n/N (%)	9/20 (45)	25/54 (47)	15/28 (54)	0.56	0.53
PCV status ^a					
- No PCV, n (%)	11 (46)	24 (39)	24 (50)	0.70	0.20
- PCV 7, n (%)	9 (37)	25 (40)	17 (35)	0.90	0.60
- PCV 13, n (%)	4 (17)	13 (21)	7 (15)	1.00	0.54
Wintertime, n ^a (%)	6 (25)	17 (27)	23 (48)	0.06	0.03
Clinical presentation					
- Associated ENT infection, n/N (%)	7/23(30)	16/58(28)	27/48(56)	0.04	<0.01
Acute otitis media, n/N (%)	6/23(26)	10/58(17)	15/48(31)	0.66	0.09
Other ENT infection, n/N (%)	3/24(13)	9/61 (15)	16/47(34)	0.05	0.02
- Seizures***, n/N (%)	3/24(13)	7/61(11)	14/48(29)	0.12	0.02
- Shock, n/N (%)	7/24(29)	12/61(20)	12/48(25)	0.71	0.50
- Purpura, n/N (%)	3/21(14)	6/56 (11)	6/41 (15)	0.64	0.56
- Purpura fulminans, n/N (%)	0/23 (0)	2/60 (3)	1/48 (2)	0.68	1.00
- Assisted Ventilation, n/N (%)	7/23(30)	14/61(23)	19/48(40)	0.45	0.06
- Coma, n/N (%)	10/23(44)	21/61(34)	21/48(44)	0.99	0.32

PM, Pneumococcal Meningitis; IQR, Inter-quartile range; SD, Standard Deviation; CSF, Cerebrospinal fluid; PCV, Pneumococcal Conjugate Vaccine; ENT, Ears Nose and Throat. *No missing data.
 * First cases vs. controls; **All cases vs. controls; *** Seizures before or during antimicrobial treatment;

Conclusion

An anatomical abnormality (CSF leak) may be the main and only factor in the development of RPM. It would then appear that an ENT gateway (otitis or other local infection) or the occurrence of a predisposing winter viral infection is not entirely necessary. The lower level of positive blood cultures in RPM could mean that the CSF leak would be enough to promote PM by loco-regional diffusion with less bacteremia. We emphasize here the importance of looking for a predisposing factor in any episode of PM (i.e., ID or CSF leak). CSF leaks should be searched especially when the PM occurs outside the winter period, and/or without any concomitant ENT infection and in case of RPM.

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