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RISK FACTORS AND COMORBIDITY IN PATIENTS WITH BACTERIAL MENINGITIS

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Abstract. Introduction. *Bacterial meningitis is a severe disease with high mortality and frequent residual neurological sequelae. It is associated with multiple risk factors. The aim of the study was to establish the main risk factors associated with bacterial meningitis and to outline the incidence of chronic diseases in patients with bacterial meningitis and their relationship to the patients' age and etiology of meningitis, if any.* ***Materials and methods.*** *The study included 90 patients with bacterial meningitis admitted to the Clinic of Infectious Diseases, University Hospital "Sv. Georgi" – Plovdiv during the period January 1, 2016 – September 30, 2019. Epidemiological analyses, clinical examinations, laboratory and microbiological tests, and statistical methods were used.* ***Results.*** *A total of 76.8% of patients had concomitant conditions: cardiovascular diseases (38.9%), diabetes mellitus (16.7%), immunosuppression (16.7%), liver diseases (11.1%), pulmonary diseases (10%), neoplasms (7.8%), chronic kidney diseases (7.8%). The incidence of immunosuppression (p = 0.009), cardiovascular disease (p = 0.0001), and diabetes (p = 0.009) were significantly higher in adults compared to children. Risk factors were present in 37.8% of patients (44% in children and 35.4% in adults, p > 0.05), especially in patients with pneumococcal meningitis (47.1%). The main risk factor was otitis or sinusitis in the last 3 months before meningitis (17.8%), followed by head trauma (6.7%), alcoholism (6.2%), recurrent episode of meningitis (4.4%), nasal leakage of cerebrospinal fluid (3.3%), general surgery (3.3%), and splenectomy (2.2%).* ***Conclusion.*** *Elderly patients with meningitis had more frequent comorbidities than children, mostly cardiovascular diseases, diabetes, and immunosuppression. The highest incidence of chronic diseases was found in patients with listerial meningitis. Risk factors were found in both age groups.*

Key words: *bacterial meningitis, etiology, risk factors, comorbidity*

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INTRODUCTION

Acute bacterial meningitis is a severe disease, still with high mortality and residual sequelae in survivors. Many distinct risk factors have been described to be associated with a higher frequency of bacterial meningitis – age, immune deficiency, genetic variations, and anatomical defects [1].

According to many studies, the terminal age groups – infants and elderly – are the most frequently affected by bacterial neuroinfections. Newborns and infants have an immature immune system and higher permeability of the blood-brain barrier [2]. The function of the immune system weakens in people over 65 (immune senescence), which leads to increased susceptibility of the host to infections and also a decreased efficacy of vaccines.

The number of *immunocompromised* people has increased in recent decades due to demographic tendencies, increased prevalence of oncological diseases and increasing number of transplant recipients.

Diabetes mellitus is a risk factor for bacterial infections. Approximately 7-10% of patients with community-acquired bacterial meningitis have diabetes, and *S. pneumoniae* and *L. monocytogenes* are the most common etiological agents [3].

Alcoholism is a risk factor due to the increased risk for head injury and chronic liver disease [4]. Common etiologic agents are *S. pneumoniae* (70%) and *L. monocytogenes* (19%). Patients with alcohol dependence who have meningitis are more likely to develop complications than non-alcoholic patients, most notably cardiorespiratory failure due to underlying pneumonia or endocarditis (81% vs. 62%) and an unfavorable prognosis (67% vs. 33%). Also, recurrent meningitis is more common in people with excessive alcohol use [5, 6].

Malignant diseases predispose to systemic infections. Immunosuppressive therapy, malnutrition, and permanent venous catheters are important factors. The risk of meningitis is particularly high in patients with leukemia, lymphoma, and following neurosurgical interventions for brain tumor. The most common pathogens in this population group are *S. pneumoniae*, *L. monocytogenes*, and *C. neoformans*. Sometimes the correct diagnosis and adequate therapy may be delayed because of atypical clinical presentation and/or postponed lumbar puncture due to thrombocytopenia or an intracranial space-occupying process [7].

Transplant organ recipients are at increased risk of invasive pneumococcal infections (meningitis, sepsis). Pneumococcal vaccination before transplantation reduces the risk. Other causative agents of meningitis in this group are *L. monocytogenes* and *Nocardia spp*., especially when multiple brain abscesses are present [8].

Hypo/asplenia – dysfunction or absence of spleen predispose to invasive infections with encapsulated bacteria such as *S. pneumoniae* and *H. influenzae*. Hyposplenism can be congenital or acquired (splenectomy). It can be also functional due to allogenic bone marrow transplantation, graft-versus-host disease, sickle cell anemia, celiac disease, and HIV infection [9]. Asplenia is found in only 2.5% of community-acquired meningitis and is associated with high mortality (25%) and residual neurologic sequelae (58%) [10].

HIV-infected people have mainly cell-mediated immune deficiency but also inadequate humoral response because of impaired B-cell activation. Most often meningitis occurs in HIV-positive individuals with advanced immunodeficiency (CD4+ T-Ly < 200/mm^3) [11]. The majority of these patients are not on antiretroviral treatment and have a very advanced immune deficiency (CD4+ T-Ly < 50/mm^3). The most common etiological agents in HIV-positive patients are *S. pneumoniae*, as well as *Salmonella spp*. Furthermore, tuberculous, cryptococcal, and toxoplasmic meningoencephalitis should also be considered in this population group [12, 13]. Nearly 90% of HIV-infected patients worldwide live in underdeveloped countries, where the incidence of bacterial meningitis is particularly high [14]. According to an analysis of 715 cases of bacterial meningitis from Malawi, sub-Saharan Africa, 87% of patients with meningitis were HIV-positive and the most common pathogens were *S. pneumoniae* (84% of cerebrospinal fluid isolates) and *N. meningitidis* (4%) [15].

The *genetic characteristics* of the host are also important. An increased incidence of meningococcal meningitis has been found in patients with a deficiency of properdin and the late complement factors (C5-C9) [13].

Anatomical defects of cranial bones. The blood-brain barrier (BBB) maintains stable homeostasis in the nervous system. Head trauma, surgical procedure, birth defect, and ear or sinus infection can damage the barrier, providing a passage for bacteria [16, 17]. Impaired BBB integrity should be suspected in a patient with recurrent meningitis especially when *S. pneumoniae*, *N. meningitidis*, *S. aureus*, and *H. influenzae* are isolated or cerebrospinal fluid leakage is presented. Thin-section computer tomography (CT) of the skull in combination with magnetic resonance 3D reconstruction is the optimal imaging method for visualizing an anatomical defect. Examination by CT alone may miss small bony defects. When an anatomical defect is established, an ear-nose-throat specialist or neurosurgeon should assess the need for surgical correction [18].

Recurrent meningitis is rare (5% of bacterial meningitis cases) [16]. The majority of patients are men

(75%), with predisposing disease (77%), including head injury (53%), CSF leak (32%), and less often immunosuppression (9%) [18]. Risk factors for recurrence in children are congenital anatomical defects and primary immunodeficiencies [13].

MATERIALS AND METHODS

The study included 90 patients with bacterial meningitis admitted to the Clinic of Infectious Diseases, University Hospital "Sv. Georgi" – Plovdiv during the period January 1, 2016 – September 30, 2019. The following methods were used:

1. Epidemiological and clinical analysis.
2. Laboratory tests of cerebrospinal fluid: leukocytes count, protein and glucose levels, meningogram.
3. Microbiological (direct microscopy and culture) and molecular methods (multiplex PCR was performed in 28 patients). The method was based on the identification of specific target genes of the most common pathogens by BioFire FilmArray Multiplex PCR (bioMerieux, France). The panel identifies the following bacterial pathogens: *S. pneumoniae*, *S. agalactiae*, *N. meningitis*, *L. monocytogenes*, *H. influenzae*, *E. coli K1*.
4. Statistical analysis: descriptive methods, parametric and non-parametric methods, Fisher's exact test, and χ^2. The level of significance of the null hypothesis was $p < 0.05$. SPSS v.17 software product was used.

Only patients with an identified etiologic agent or a typical CSF constellation for bacterial meningitis (leukocytes > 100.10^6/l, protein > 1g/l, CSF/serum glucose ratio ≤ 0.4) were included in the study.

RESULTS

A total of 90 patients with bacterial meningitis were treated at the Clinic of Infectious Diseases from January 1, 2016, to September 30, 2019. Of them, 65 patients were adults (over 18 years old) and 25 were children (under 18 years old). Etiological agents were identified in 54 patients (60%) and included: *S. pneumoniae* in 18.9% (n = 17), *Staphylococcus spp.* (*S. aureus* n = 10; *coagulase-negative staphylococci* n = 2) – 13.3% (n = 12), *L. monocytogenes* – 8.9% (n = 8), *N. meningitidis* – 5.6% (n = 5), *Streptococcus spp.* (*S. equi subsp. zooepidemicus*, *S. salivarius*, and *α-hemolytic Streptococcus spp.*) – 3.3% (n = 3), *K. pneumoniae* – 3.3% (n = 3), *H. influenzae* – 2.2% (n = 2), *E. faecium* – 2.2% (n = 2), and *M. tuberculosis* – 2.2% (n = 2). Meningitis was etiologically unidentified in 36 patients (40%).

Analysis of comorbidity and risk factors by etiologic groups

A significant proportion of patients had accompanying chronic diseases (76.8%), with 40% having two or more. Cardiovascular diseases (CVD) were the most common (38.9%) (Table 1): arterial hypertension – 33.3%, ischemic heart disease – 16.7%, cerebrovascular disease – 13.3%, chronic heart failure – 3.3% and arrhythmias – 1.1%. The frequency of CVD was highest in patients with listerial meningitis (87.5%), followed by staphylococcal (75%). Diabetes mellitus (16.7%) was also the most common in these two groups.

Pulmonary diseases included chronic obstructive pulmonary disease (7.8%), tuberculosis (2.2%); liver diseases – chronic hepatitis B or C (7.8%), cirrho-

Table 1. Chronic diseases in patients with bacterial neuroinfections of different etiology

Chronic diseases	*S. pneumoniae* (n = 17)		*N. meningitidis* (n = 5)		*L. monocytogenes* (n = 8)		*Staphylococcus* spp. (n = 12)		Unidentified (n = 36)		Total (n = 90)	
	N	%	N	%	N	%	N	%	N	%	N	%
Cardiovascular	8	47.1%	0		7	87.5%	9	75%	9	25%	35	38.9%
Pulmonary	1	5.9%	0		1	12.5%	1	8.3%	5	13.9%	9	10%
Diabetes mellitus	3	17.6%	0		2	25%	3	25%	5	13.9%	15	16.7%
Immunosuppression	0		0		2	25%	1	8.3%	10	17.8%	15	16.7%
Cancer/oncohaematological disorders	0		0		2	25%	0		5	13.9%	7	7.8%
Renal	1	5.9%	0		2	25%	0		3	8.3%	7	7.8%
Liver	0		0		1	12.5%	1	8.3%	6	16.7%	10	11.1%
Others*	3	17.%	1	20%	2	25%	5	41.7%	14	38.9%	32	35.6%

* "Others" included: anemia (6.7%); hypothyroidism (3.3%); mental disorders (schizophrenia, bipolar affective disorder) (3.3%); congenital hydrocephalus (3.3%); secondary epilepsy (2.2%); Down syndrome, pontocerebellar hypoplasia, renal agenesis, chronic pharyngitis, Crohn's disease, rheumatoid arthritis, hiatal hernia, gastric ulcer, chronic pancreatitis, lower back pain, gout (1.1% each)

sis (4.4%); renal diseases – nephritis (5.6%), chronic renal failure and patients on hemodialysis (2.2%); oncologic and haematologic diseases – breast carcinoma (2.2%), cervical carcinoma, acute lymphoblastic leukemia, Hodgkin's lymphoma, Non-Hodgkin's MALT-lymphoma, and myelodysplasia (1.1% each). The highest incidence of chronic diseases was found in patients with listerial meningitis.

The „immunosuppression" group included patients with HIV/AIDS (6.7%) and patients taking immunosuppressive medications (glucocorticosteroids, post-transplant immunosuppressants, chemotherapy) (10%). Again, immunosuppression was most common in listerial neuroinfections (25%).

Patients with meningitis caused by some rare pathogens also had comorbidities. Among three patients with streptococcal meningitis, two had AIDS and one had congenital hydrocephalus. One patient with *H. influenzae* had CVD and diabetes. One of the patients with tuberculous meningoencephalitis also had pulmonary tuberculosis. One infant with enterococcal meningitis had congenital hydrocephalus. All patients with meningitis caused by *K. pneumoniae* also had comorbidities: an infant with congenital hydrocephalus, a child with renal agenesis and scoliosis, and an adult with CVD, diabetes, and pyelonephritis.

The risk factors (RF) in patients from different etiologic groups were presented in Table 2. No RF were found in meningococcal meningitis patients. RF were the most frequent in the pneumococcal meningitis group (47.1%) and the main factors were otitis or sinusitis in the last 3 months before meningitis occurrence. Recent surgical intervention (16.7%) was the most common risk factor in staphylococcal meningitis patients.

Analysis of comorbidity and risk factors by age groups

A total of 86.2% of adults and 32% of children with bacterial meningitis had chronic comorbidities. Significant differences between children and adults were found for immunosuppression (p = 0.009), CVD (p = 0.0001), and diabetes mellitus (p = 0.009). The presence of risk factors was found in both age groups with a slight prevalence in children (44% vs. 35.4%) (Table 3).

Among adult patients 46.2% were smokers, 7.8% were intravenous drug users, and 6.2% were alcohol addicts.

DISCUSSION

Our data showed significantly more concomitant chronic diseases in adults (86.2%) compared to children (32%). Diabetes, CVD, pulmonary, oncologic, haematologic, renal and liver diseases, HIV infection, and immunosuppressive therapy were established only in adults. Congenital diseases were observed in children (hydrocephalus, Down syndrome, pontocerebellar hypoplasia, renal agenesis) as well as some cases of epilepsy and anemia.

The incidence of CVD in our study (53.8%) differs from the data of other authors, who report a significantly lower incidence (27%) [19]. A higher frequency of diabetes in our patients (16.7%) compared to other authors (13%) was also registered [20]. Diabetes mellitus was associated with a 2-fold higher risk of developing bacterial meningitis. According to most of the studies, the highest frequency of diabetes was established in patients with listerial and pneumococcal meningitis [3, 20], while in ours it was found mostly in listerial and staphylococcal meningitis.

Table 2. Risk factors in patients with bacterial neuroinfections of different etiology

	S. pneumoniae (n = 17)		*N. meningitis* (n = 5)	*L. monocytogenes* (n = 8)		*Staphylococcus* spp. (n = 12)		Unidentified (n = 36)		Total (n = 90)	
	N	%		N	%	N	%	N	%	N	%
Risk factors (total)	8	47.1%	0	2	25%	4	33.3%	15	41.7%	34	37.8%
Otitis/sinusitis*	7	41.2%		0		0		9	25%	16	17.8%
Head trauma	1	5.9%		0		1	8.3%	3	8.3%	6	6.7%
Recurrent**	0			0		0		3	8.3%	4	4.4%
CSF leak	1	5.9%		0		0		1	2.8%	3	3.3%
Surgery ***	0			1	12.5%	2	16.7%	0		3	3.3%
Splenectomy	1	5.9%		1	12.5%	0		0		2	2.2%
Alcoholism	1	5.9%		0		1	8.3%	2	5.6%	4	-

*medical history for otitis and/or sinusitis in the last 3 months; **previous episode of bacterial meningitis; *** general surgical procedure (not neurosurgical) in the last 2 weeks

Table 3. Comorbidity and risk factors in children and adults with bacterial meningitis

Comorbidity	Children (n = 25)		Adults (n = 65)		p-value
	N	%	N	%	
Cardiovascular	0	0	35	53.8%	**0.0001**
Pulmonary	0	0	9	13.8%	0.058
Diabetes mellitus	0	0	15	23.1%	**0.009**
Immunosuppression	0	0	15	23.1%	**0.009**
Cancer/oncohaematological disorders	0	0	7	10.8%	0.184
Renal	0	0	7	10.9%	0.184
Liver	0	0	10	15.4%	0.056
Other	8	32%	24	36.9%	0.807
Risk factors	11	44%	23	35.4%	0.475
Otitis or sinusitis*	7	28%	9	13.8%	-
Head trauma	2	8%	4	6.2%	-
Recurrent**	2	8%	2	3.1%	-
SCF leak	1	4%	2	3.1%	-
Surgery***	0	0	3	4.6%	-
Splenectomy	0	0	2	3.1%	-

*medical history for otitis and/or sinusitis in the last 3 months; **previous episode of bacterial meningitis; ***general surgical procedure (not neurosurgical) in the last 2 weeks

The incidence of cancer and oncohaematological diseases in our patients (7.8%) is close to the incidence reported in the literature (6%) and supported that *L. monocytogenes* is a major causative agent [7, 21].

HIV infection rate of 6.7% differs significantly from data reported among African countries, where 87-90% of patients with bacterial meningitis are co-infected with HIV [23, 24], but is close to data reported in Western Europe and the USA – 1-5.8% [22].

In the pediatric population group, we often observed congenital diseases (20%), mainly hydrocephalus. All three children with hydrocephalus developed meningitis within 2 months after ventriculoperitoneal shunt implantation.

A slight prevalence of risk factors was found in children (44%) compared to adults (35.4%). In our study 28% of children and 13.8% of adults had a history of otitis and/or sinusitis in the last 3 months before bacterial meningitis dignosis. These data are similar to data reported by other authors [13, 25]. The majority of patients with this risk factor had pneumococcal and less often etiologically unspecified meningitis. It is possible that in some of them, the causative agent was still *S. pneumoniae* and microbiological identification was unsuccessful because of prior antibiotic use.

Bacterial neuroinfections associated with head trauma were 6.7%, with similar frequency reported by other authors [12, 16]. The trauma is probably the cause of an available anatomical defect to the cranial bones, predisposing to bacterial meningitis and even a recurrent course. A nasal CSF leak (3.3%) as a risk factor is usually associated with head trauma, a cranial defect, and the possibility of a recurrent episode.

The frequency of splenectomy in our study (2.2%) is identical to other authors' data. Adriani K. et al., 2013 reported that 2.5% of patients with meningitis had anatomic or functional asplenia. According to these results, *S. pneumoniae* was the only etiologic agent whereas in our study meningitis was caused by *S. pneumoniae* and *L. monocytogenes* [10].

Previous general surgery (excluding ventriculoperitoneal shunt in children with congenital hydrocephalus) was performed in 3.3%. These were patients mainly with staphylococcal meningitis, which probably developed as a late complication due to haematogenous dissemination. Similar cases were described by Pintado V. et al., 2002 [26]. We found no other publications describing general surgical interventions as a risk factor for the development of bacterial meningitis.

The frequency of alcohol abuse (6.2%) correlates with that reported in the literature (4–6%). Alcoholism is considered to be an immunosuppressive factor and is often associated with the risk of traumatic brain injury and chronic liver disease [27]. Among our alcoholic patients, there were some with head trauma and liver cirrhosis.

CONCLUSION

According to our findings comorbidity in patients with meningitis was more common in adults (86.2%) compared to children (32%). CVD, diabetes, and im-

munosuppressive conditions were observed only in the elderly. Congenital diseases were established in children, especially hydrocephalus.

The concomitant chronic diseases were most often in the patients with listerial neuroinfections followed by staphylococcal ones.

Risk factors existed in 37.8% of patients with bacterial neuroinfections, with a slight prevalence in children (44% vs. 35.4%). Major risk factors for bacterial meningitis are recent otitis or sinusitis, with the highest incidence of *S. pneumoniae* meningitis.

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