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Original Article

A Comparative Study between Children and Adults with Bacterial Neuroinfections

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Abstract

Introduction: Bacterial meningitis is an acute purulent infection of the meninges. There are significant differences in the etiological spectrum, clinical course and outcome of bacterial meningitis in the age groups, and their recognition is important for early diagnosis and adequate therapy.

Aim: The study aims to determine the differences in the etiology and clinical presentation of bacterial meningitis between children and adults.

Materials and methods: The study included 90 patients (25 children and 65 adults) with bacterial neuroinfection admitted to St George University Hospital, Plovdiv between January 1, 2016 and September 31, 2019. We applied epidemiological and clinical analysis, microbiological and statistical methods.

Results: In adults, the most common etiological agent was *Streptococcus pneumoniae* (20%), followed by *Staphylococcus spp*. (18.5%), *Listeria monocytogenes* (12.3%), *Streptococcus spp*. (3.1%), *Haemophilus influenzae* (3.1%), *Klebsiella pneumoniae* (1.5%), and *Mycobacterium tuberculosis* (1.5%). The etiological structure in children was different: *Neisseria meningitidis* (20%), *Streptococcus pneumoniae* (16%), *Klebsiella pneumoniae* (8%), *Enterococcus faecium* (8%), *Streptococcus salivarius* (4%), and *Mycobacterium tuberculosis* (4%). In 40% of the cases, both children and adults, the causative agent was not identified.

Conclusions: Regarding the clinical presentation, a statistical significance between the age groups was found with headache and alterations in consciousness, more commonly seen in adults, while vomiting, ear pain was more common in children ($p<0.05$). Concomitant otitis, sinusitis, pneumonia, and sepsis were often observed. The mortality rate was much higher in adults (43%) when compared with children (8%).

Keywords

age, etiology, meningitis, meningoencephalitis

INTRODUCTION

Bacterial meningitis is an acute purulent infection of the meninges and subarachnoid space. If the brain parenchyma is also involved in the inflammatory reaction, meningoencephalitis develops.[1] In adults, the majority of bacterial meningitis in Europe is caused by *S. pneumoniae* (53%), followed by *N. meningitidis* (27%). *L. monocytogenes* (4%) is the third most common cause in adults and is associated with old age and immunosuppression. *H. influenzae* (3%) in adults has been associated with concomitant conditions such as otitis and sinusitis. *Staphylococcus aureus* association with meningitis is rare (1-2%).[2] Bacterial meningitis in children in Europe is due to *N. meningitidis* (50%), *S. pneumoniae* (37%), and *H. influenzae* (5%). In China, the main etiological agent in this age group is *S. pneumoniae* (33.2%), followed by *Escherichia coli* (10.9%), *Enterococcus spp.* (10%), *Streptococcus group B* (8.2%), *S. aureus* (4.1%), *Pseudomonas aeruginosa* (4.1%), *Salmonella spp.* (3.6%).[3]

Bacterial meningitis in children usually begins with fever (93%). Headache is registered in 75% of children over 5 years; vomiting in 61%; rash - 60%; neck stiffness - 61%. Seizures occur in 33% of children, alteration in consciousness in 34.5%, and focal neurological deficit in 13.5%.[4] The most common symptoms associated with the disease in adults are headache, fever, neck stiffness, and changes in consciousness. Data from European studies (1996–2010) show that in adults fever occurs on average in 90% of cases; headache in 77%; vomiting - 60%; rash - 33%; seizures - 22.5%; neck stiffness - 75%, impaired consciousness - 57% (coma - 13%), and focal deficits in 23%.[5,6] Concomitant diseases occur in 48% of adults, with otitis or sinusitis (25%) and pneumonia (12%) being among the most common.[7,8]

There are significant differences in the etiological spectrum, clinical presentation and outcome of bacterial meningitis in the age groups, and their recognition is important for early diagnosis and adequate therapy.

AIM

The aim of the study was to establish the differences in the etiology and clinical course of bacterial neuroinfections between children and adults.

MATERIALS AND METHODS

The study included 90 patients with bacterial neuroinfection admitted to St George University Hospital in Plovdiv from January 1, 2016 to September 31, 2019. There were 25 children (up to 17 years of age) and 65 adults (range 18–87 years). The diagnosis was based on the clinical presentation, cerebrospinal fluid (CSF) examination, and microbiological testing.

Only patients with typical CSF abnormalities consistent with bacterial meningitis were included in the study (cell count >100×10^6/l, protein >1 g/l, CSF/serum glucose ratio ≤0.4) and/or identified etiology by the CSF microbiological analysis.

We used in the study:

1. Epidemiological data about age and sex;
2. Clinical analysis;
3. Microbiological testing included CSF Gram stain and culture. Multiplex PCR for viral and bacterial agents was performed in 28 of the patients with bacterial neuroinfection. It is based on the detection of specific target genes of the most common causative agents by Biofire FilmArray Multiplex PCR (bioMerieux, France). The panel simultaneously identifies the following bacterial pathogens: *S. pneumoniae, Streptococcus agalactiae, N. meningitis, L. monocytogenes, H. influenzae, Escherichia coli K1.*
4. Statistical analysis: descriptive methods; parametric and non-parametric methods: Fisher's exact test and χ^2; Kolmogorov-Smirnov test. The significance level of the null hypothesis is $p<0.05$. Statistical data analysis was performed using the software product SPSS v.17 (IBM, USA).

RESULTS

Distribution of patients according to age, gender, and etiology

Over the observation period, we found 25 children (27.8%) and 65 adults (72.2%) with bacterial meningitis/meningoencephalitis. Children were divided into the following age groups: <1 year (n=7); 1 to 4 years (n=10); 5 to 9 years (n=5), and 10 to 17 years (n=3).

The gender distribution showed that among adults males were 39 (60%) and females - 26 (40%). In the group of children, 16 were males (64%) and 9 females (36%).

In adults **(Fig. 1)** the most common etiological cause was *S. pneumoniae* (n=13), followed by *Staphylococcus spp.* (n=12), mainly *S. aureus* and two *Staphylococcus coagulase-negative (CoNS)*, *L. monocytogenes* (n=8). Less frequent agents were *Streptococcus spp.* (n=2), *H. influenzae* (n=2), *K. pneumoniae* (n=1), and *Mycobacterium tuberculosis* (n=1).

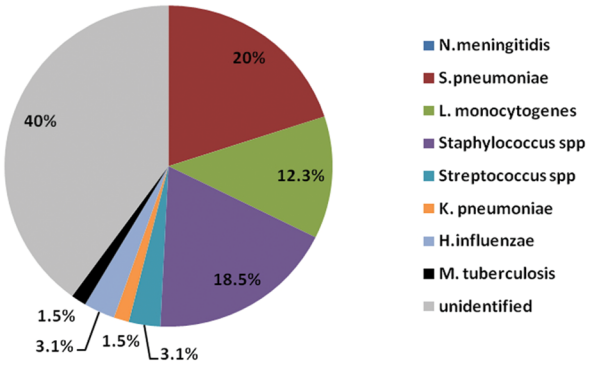

Figure 1. Etiology of bacterial neuroinfections in adults (n=65).

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The most common etiological cause in children **(Fig. 2)** was *N. meningitidis* (n=5), and *S. pneumoniae* came second (n=4). They were followed by *K. pneumoniae* (n=2), *Enterococcus faecium* (n=2), *Streptococcus salivarius* (n=1), and *Mycobacterium tuberculosis* (n=1). Forty percent of the cases remained unidentified in both age groups.

The etiological distribution in children and adults differed significantly (χ^2=23.799; p=0.0001) **(Table 1)**. Meningococcal meningitis affects only children, and listerial and staphylococcal meningitis - exclusively adults. Adults predominated (76.5%) in the group of pneumococcal meningitis. The ratio is similar for the etiologically unidentified cases of meningitis (72.2% were adults).

The period before hospitalization

Most of the children were admitted to the hospital within the first 3 days of the onset of the symptom (64%). Adult patients were hospitalized later (usually after 4-5 days), and in 21.5% we noticed hospitalisation to be delayed (>7 days from the onset of complaints). However, no significant difference was found between the age groups **(Table 2)**. Antibiotics were taken by 10 children (40%) and 28 adults (43.1%) prior to performing an initial lumbar puncture, without significant difference (p=0.817).

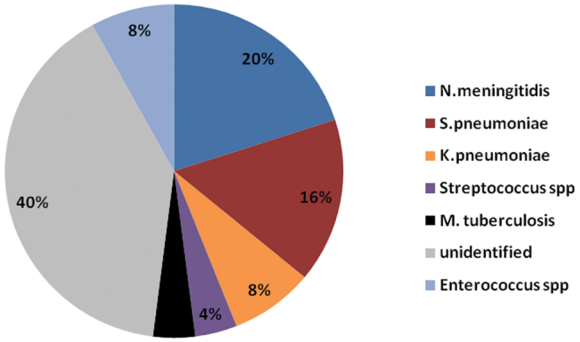

Figure 2. Etiology of bacterial neuroinfections in children (n=25).

Clinical features in children and adults

Significant differences between the age groups were found for some clinical symptoms **(Table 3)**. Headache was more frequent in adults, while vomiting was significantly more common in children, as well as otalgia and the presence of angina. Somnolence, sopor, coma, and especially qualitative alterations in consciousness (agitation, bradypsychia, hallucinations) were significantly more common in adults. Only 17.8% of patients had photophobia. The presence of rash (maculopapular, petechial, hemorrhagic), and seizures were more common in children, but without significant difference (p>0.05).

Neck stiffness, Kernig, Brudzinski's signs, and focal deficits (paresis, hemiparesis, aphasia) were more common in adults, even without a significant difference (p>0.05) **(Table 4)**.

Comparative assessment based on comorbidities and outcome

We found otitis media, mastoiditis, otomastoiditis, and sinusitis, pneumonia, and sepsis in patients with bacterial meningitis/meningoencephalitis. Sepsis was more com-

Table 1. Etiology of bacterial neuroinfections in children and adults

Etiology groups (EG)	Children n (% of EG)	Adults n (% of EG)	Total n (% of EG)
S. pneumoniae	4 (23.5%)	13 (76.5%)	17 (100%)
N. meningitidis	5 (100%)	0	5 (100%)
L. monocytogenes	0	8 (100%)	8 (100%)
Staphylococcus spp.	0	12 (100%)	12 (100%)
Other identified †	6 (50%)	6 (50%)	12 (100%)
Unidentified	10 (27.8%)	26 (72.2%)	36 (100%)
Total	25	65	90
	χ^2=23.799; p=0.0001		

† including *Streptococcus spp.*, *H. influenzae*, *K. pneumoniae*, *E. faecium*, *M. tuberculosis*

Table 2. Duration of the period before hospitalization

Period before hospitalization	Children (n=25)		Adults (n=65)		Total (n=90)		p-value
	n	%	n	%	n	%	
≤3 days	16	64%	28	43.1%	44	48.9%	χ^2=5.009 p=0.082
4-7 days	8	32%	23	35.4%	31	34.4%	
>7 days	1	4%	14	21.5%	15	16.7%	

Table 3. Clinical features in children and adults with bacterial neuroinfections

Symptoms	Children (n=25)		Adults (n=65)		Total (n=90)		*p* (Fisher)
	n	%	n	%	n	%	
Fever >37.5°C	24	96%	63	96.9%	87	96.7%	1.000
Headache †	10	40%	43	66.2%	53	58.9%	0.032
Vomiting †	20	80%	28	43.1%	48	53.3%	0.002
Photophobia	5	20%	11	16.9%	16	17.8%	0.763
Somnolence, sopor, coma †	11	44%	50	76.9%	61	67.8%	0.005
Agitation, hallucinations †	0	0	38	58.5%	38	42.2%	0.0001
Seizures	6	24%	12	18.5%	18	20%	0.566
Cough, sore throat	11	44%	15	23.1%	26	28.9%	0.69
Diarrhea	2	8%	7	10.8%	9	10%	1.000
Ear pain†	5	20%	3	4.6%	8	8.9%	0.035
Skin rash	6	24%	10	15.4%	10	16%	0.365
Angina †	15	60%	14	21.5%	29	32.2%	χ^2=12.233 p=0.002

† significant difference at $p<0.05$

Table 4. Neurological status in children and adults with bacterial neuroinfections

Signs	Children (n=25)		Adults (n=65)		Total (n=90)		*p* (Fisher)
	n	%	n	%	n	%	
Neck stiffness	21	84%	62	95.4%	83	92.2%	0.090
Kernig	13	52%	41	63.1%	54	60%	0.349
Upper Brudzinski	8	32%	23	35.4%	31	34.2%	0.810
Lower Brudzinski	3	12%	15	23.1%	18	20%	0.378
Focal deficits	2	8%	7	10.8%	9	10%	1.000
Cranial nerve palsy	2	8%	5	7.7%	7	7.8%	1.000
Babinski's signs (+)	9	36%	24	36.9%	33	36.7%	1.000

mon in adults, even without significant differences between children and adults **(Table 5)**.

The mortality rate was much higher in adults (43%) than in children (8%). Neurological sequelae (motor deficits and cognitive defects) in survivors were also more common in adults (13.8%) **(Table 6)**.

DISCUSSION

Streptococcus pneumoniae remains the most common etiologic agent of purulent meningitis in adults, although there has been a reduction in the incidence after the introduction of the pneumococcal vaccines. Unexpectedly high frequency was found for *Staphylococcus spp.* (18.5%), which according to other studies is quite a rare cause of neuroinfections.[9-11] This is probably due to a large number of patients with sepsis, in which staphylococcal meningitis followed. *Listeria monocytogenes*, which is the third leading cause of bacterial neuroinfections in our patients and according to numerous European studies, will be increasingly important in the near future, because of the growing number of people with concomitant oncological and autoimmune diseases and immunosuppression.

Similar to European data[2,12], the main causative agents of bacterial meningitis in children are *Neisseria meningitidis* and *Streptococcus pneumoniae*, but no case of *Haemophilus influenzae* was observed, in contrast to studies in Poland and Turkey, reporting an incidence of 18%.[13,14] There is still a high incidence of meningitis due to *Haemophilus influenzae* in countries with incomplete immunization programs such as Iran and Pakistan (12.4%).[15,16]

In our study, there is a high proportion of etiologically unidentified neuroinfections (40%). May be due to the fact that a significant proportion of patients were initiated on antibiotic therapy before undergoing a lumbar puncture, that makes it difficult to identify the cause by CSF culture

The distribution of patients by gender showed a male prevalence regardless of age. According to other authors, men and women suffer equally often, with insignificant differences.[5,17]

Table 5. Comorbidities in patients with bacterial neuroinfections

Comorbidities	Children (n=25)		Adults (n=65)		Total (n=90)		*p*-value
	n	%	n	%	n	%	
Otogenic †	7	28%	18	27.7%	25	27.8%	1.000
Pneumonia	3	12%	12	18.5%	15	16.7%	0.545
Sepsis	1	4%	10	15.4%	11	12.2%	0.279

† otogenic diseases in children - otitis (1), mastoiditis (1), otomastoiditis (3), sinusitis (3); in adults - otitis (4), mastoiditis (4), sinusitis (13)

Table 6. Outcome in patients with bacterial neuroinfections

Outcome	Children (n=25)		Adults (n=65)		Total (n=90)		*p*-value
	n	%	n	%	n	%	
Recovery	21	84%	28	43.1%	49	54.4%	χ^2=12.72
Neurological sequelae †	2	8%	9	13.8%	11	12.2%	p=0.002
Death	2	8%	28	43.1%	30	33.3%	

† motor deficits – facial nerve palsy (2), quadriparesis (2), hemiparesis (4), paraparesis (3); cognitive defects – cognitive slowness (3), neuropsychologic sequelae (2), and epilepsy (1)

The analysis of the clinical presentation showed that fever was the most common symptom (96.7%). While vomiting was more prevalent in children (80% vs. 43.1% in adults), the headache was more common in adults (66.2% vs. 40%). Similar data on the main clinical symptoms have been reported by a number of researchers in Europe.[8,13,18,19] Photophobia had an unexpectedly low frequency (17.8%). Our patients had a skin rash in 24% of children and 15.4% of adults. Many authors reported a significantly higher frequency of rash in both children (39-51%) and adults groups (20-26%).[17,20-22]

In the observed patients neck stiffness, Kernig and Brudzinski's signs are more widespread in adults. Seizures are more common in children (24%) than in adults (18.5%). These findings correlate with the data of many European authors.[6,23-25]

The frequency of cranial nerve palsy in the studied patients (7.8%) was several times lower compared to the data of Van de Beek et al. (28%).[8] The incidence of focal neurological deficit (10%) is also lower when compared to other European studies, reporting 15–34%.[17,20,26]

Comorbidities were more common in adults (53.8%) than in children (36%). Weisfelt et al. reported 32.5% for otitis or sinusitis, 15.2% pneumonia, and 13% sepsis, similar to our results.[6,7] The disease prognosis was more favourable for children. The mortality rate was much higher in adults, which is in accordance with the literature.[7,16,17]

CONCLUSIONS

The most common etiological agents of bacterial agents are *Streptococcus pneumoniae* in adults, and *Neisseria meningitidis* and *Streptococcus pneumoniae* in children. Headache and disturbances in consciousness are more common in adults, while vomiting and ear pain are more typical in children. Because of the high mortality and sequelae in patients with bacterial neuroinfections, rapid clinical recognition and laboratory diagnosis are needed in order to begin adequate treatment as soon as possible.

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Competing Interests

The authors have declared that no competing interests exist.

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Сравнительное исследование детей и взрослых с бактериальными нейроинфекциями

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Резюме

Введение: Бактериальный менингит — острая гнойная инфекция мозговых оболочек. Имеются существенные различия в этиологическом спектре, клиническом течении и исходе бактериального менингита в возрастных группах, и их выявление важно для ранней диагностики и адекватной терапии.

Цель: Исследование направлено на определение различий в этиологии и клинической картине бактериального менингита у детей и взрослых.

Материалы и методы: В исследование были включены 90 пациентов (25 детей и 65 взрослых) с бактериальной нейроинфекцией, поступивших в Университетскую больницу Св. Георгия, г. Пловдив, с 1 января 2016 г. по 31 сентября 2019 г. Мы применяли эпидемиологический и клинический анализ, микробиологические и статистические методы.

Результаты: У взрослых наиболее частым этиологическим агентом был *Streptococcus pneumoniae* (20%), за которым следовал *Staphylococcus spp.* (18.5%), *Listeria monocytogenes* (12.3%), *Streptococcus spp.* (3.1%), *Haemophilus influenzae* (3.1%), *Klebsiella pneumoniae* (1.5%) и *Mycobacterium tuberculosis* (1.5%). Этиологическая структура у детей была различной: *Neisseria meningitidis* (20%), *Streptococcus pneumoniae* (16%), *Klebsiella pneumoniae* (8%), *Enterococcus faecium* (8%), *Streptococcus salivarius* (4%), *Mycobacterium tuberculosis* (4%). В 40% случаев как у детей, так и у взрослых возбудитель не идентифицирован.

Заключение: Что касается клинической картины, то между возрастными группами выявлена статистическая значимость головной боли и нарушений сознания, чаще наблюдаемых у взрослых, тогда как рвота, боль в ушах чаще встречались у детей (p<0.05). Часто наблюдались сопутствующие отиты, синуситы, пневмонии, сепсис. Уровень смертности был намного выше у взрослых (43%) по сравнению с детьми (8%).

Ключевые слова

возраст, этиология, менингит, менингоэнцефалит