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Etiological Profile of Infectious Meningitis at "Dr. V. Babes" Clinical Hospital of Infectious and Tropical Diseases, Bucharest, Romania

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ABSTRACT

Infectious meningitis is a serious medical problem that can be fatal if treatment is delayed.
Objectives. There are presented clinical and laboratory aspects of patients with suspected meningitis, presented and hospitalized during 2014-2017 at Hospital for Infectious and Tropical Diseases Dr V. Babes **Bucharest.** Clinical and paraclinical variables that show statistically significant differences depending on the etiology of meningitis have been identified.
Methods. Patients who showed signs and symptoms according to the case definition would be included in the study. Clinical and laboratory values were recorded in a database which was then processed to identify statistically significant differences between the group of patients with suspicion only but subsequently not ill against the group of confirmed, and also among different subgroups within the confirmed.
Results. Of the **97** cases of infectious meningitis included within 3 years, **53** cases (55%) were viral, **31** (32%) bacterial, one case of fungal meningitis and 12 cases of tuberculous meningitis.

Keywords: meningitis, differential diagnosis, lumbar puncture

INTRODUCTION

Central nervous system infections, irrespective of their etiology (viral, bacterial or fungal), remain an important cause of morbidity and mortality. In an observational study performed in our hospital for a period of 2 years we recorded a mortality of 11.8% due to neurological infections (1). Sequelae of meningitis vary according to etiology and age, the most common being changes in the auditory sphere, especially after pneumococcal meningitis (up to 30% of patients remain with auditory sequelae after pneumococcal meningitis). Motor deficiencies, epilepsy or psychiatric retardation fortunately are rare, 3-4% of patients (2).

Infectious meningitis has bacterial, viral, fungal or parasitic etiology. In acute bacterial meningitis, early diagnosis and early treatment reduce the risk of death and subsequent complications. Viral meningitis benefits from etiological treatment only in the case of herpes virus infection, in all other etiologies, the treatment is only pathogenic and symptomatic (3).

The algorithm of suspicion of meningitis in children and adults consists of the following steps (4):

1. Clinical examination that identifies signs and symptoms of meningitis.
2. In the case of a suspicion of acute meningitis, the lumbar puncture of the cerebrospinal flu-

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id (CSF) is performed, which will be initially analyzed at the collection point (clear or cloudy) and subsequently in the laboratory to detect the presence of leukocytes, red blood cells, proteins, glucose and chlorine in cerebrospinal fluid. Gram staining exam can highlight the presence of bacteria.

3. Hemoculture and other blood tests (complete blood count, biochemistry and serology).

In some patients with tumors or cerebral abscesses, computer tomography should be performed prior to lumbar puncture (4). Molecular investigation techniques could be a real help: PCR multitarget for detecting all pathogenic bacteria in the CSF provides a rapid response in less than 3 hours (5) and for detecting enteroviruses and other tropic viruses for the nervous system can be accomplished in less than 2 hours (5).

MATERIALS AND METHODS

An observational study, approved by the Independent Ethics Commission, was conducted at the Clinical Hospital for Infectious and Tropical Diseases "Dr. V. Babes" Bucharest, as part of the research project No 35/2014_PN-II-PT-PCCA-2013-4-1836, financed by UEFISCDI, during 2014-2017. All patients with clinical suspicion of meningitis which gave their informed consent have been included (parents or family gave consent for children and comatose patients).

The inclusion criteria in the study were clinical (6,7,8), epidemiological and laboratory (8).

Clinical and paraclinical data were collected from the hospital information system and introduced in the research project database, from which they were subsequently extracted and processed statistically with IBM-SPSS statistics v. 20. The numerical variables were analyzed by *t-test* and the variable variables through the *chi-square* test. Numerical variables are expressed as mean plus 95% confidence interval. The threshold value for statistical significance is $p < 0.05$.

RESULTS AND DISCUSSIONS

175 patients were enrolled in the study, out of which 78 (44%) meningitis diagnosis was infirmed, and 97 patients (55%) were confirmed. 53 (55%) meningitis patients had viral meningitis, 31 (32%) bacterial meningitis, 12 (12%) tuberculous meningitis and one patient (1%) had cryptococcal meningitis.

In the comparative analysis between the group represented by unconfirmed meningitis and confirmed cases, statistically significant differences were identified both in signs and symptoms as well as in the paraclinical investigations of biological samples. Such signs and symptoms, statistically significant differences were recorded for:

- headache: 78% of those confirmed versus 60% of those clinically suspicioned and unconfirmed after the CSF ($p = 0.009$) and
- stiffness: 56% whitin confirmed versus 40% within unconfirmed suspicions ($p = 0.036$)

Other clinical signs, such as vomiting, photophobia and fever, were present in approximately similar proportions in the two groups (Table 1).

In the assays performed on the lumbar puncture of cerebrospinal fluid, there were found statistically significant differences in:

- albumin, with increased albuminorachia in the confirmed versus unconfirmed, 0.964 g/l versus 0.181g / l with $p < 0.001$,
- total protein, 1,569 g / l versus 0.313 g / l, with $p < 0.001$,
- nuclear elements 2.954.8 / ml vs. 35.99 / ml, $p = 0.007$,

TABLE 1. *Changes in CSF suggestive for the etiologic diagnosis of meningitis.*

Meningitis etiology	CSF aspect	No leukocytes (cells/mm^3/10 6 cells/l)	Predominant cell type	Glucose in CSF (Normal≥0.5)	Protein (g/L) (normal 0.2-0.4)
Viral	clear	50-1,000	mononuclear (may also be neutrophils in the early stage of the disease)	normal	0.4-0.8
Bacterial	cloudy or opalescent	100 -5,000 or over 5,000	neutrophils	<0.5	0.5-2
Tuberculosis	clear or serocytrin	50-300	(mononuclear can occur a er an bio c therapy or onset of onset)	<0.3	0.5-3
Cryptococcal	clear	20-500	mononuclear, monomorphic, small	<0.5	0.5-3

– Pandy 2.35 vs. 0.28, p < 0.001
– and the presence of polymorphonuclearles increased by 54.46% compared with only 4.00%, p = 0.007.

In the blood samples, different statistically significant values were found for:

– leukocytes: 12,209/µl in those confirmed versus 9,207/µl in unconfirmed, p = 0.001,
– neutrophil polymorphonuclear: 9,663/µl in those confirmed versus 6,888/µl in unconfirmed, p < 0.001
– glycaemia: 109.71 mg/dL in those confirmed versus 88.51 mg/dL in unconfirmed, p = 0.028.

The other investigated blood samples did not show statistically significant differences (Table 2).

In the comparative statistical analysis of the variables grouped according to the etiology of meningitis, bacterial meningitis or viral meningitis, statistically significant differences were found both in the demographic characteristics (age) and in the characteristics of the CSF and the blood analyzed. No symptoms and clinical signs were found that differ significantly between the two subgroups (Table 3).

Thus, among *demographic variables*, the **mean age** of patients with viral meningitis was 16.57 years old versus 36.61 years old in patients with bacterial meningitis, p <0.001.

In the *CSF analysis:* **albuminorrhia** was significantly increased among those with 1,705 g/L bacterial meningitis versus 0.541 g/L in those with viral meningitis (p < 0.001), **total protein** 2.854 g/l in patients with bacterial meningitis compared to 0.839 g/L in patients with viral meningitis (p < 0.001), **Pandy** 3.68 bacterial meningitis compared to 1.42 in patients with viral meningitis, respectively the **percentage of polymorphonuclears** among those with bacterial meningitis was 76.48% versus 33.12% in those with viral meningitis, the p value

***TABLE 2**. Demographic, clinical and paraclinical characteristics of patients suspected/ confirmed with meningitis.*

Variable N=175	Suspected/infirmed (n=78)	M (b,v,mTB*, mF**) (n=97)	*p* value
Age (95%CI)	19.04 (14.46-23.62)	25.44 (20.83-30.06)	0.055
Sex (M/F)	44/34	50/47	0.521
SIGNS AND SIMPTOMS			
Fever, n (%)	54 (81)	79 (69)	0.060
Cephalea, n (%)	47 (60)	76 (78)	*0.009*
Neck stiffness, n (%)	31 (40)	54 (56)	*0.036*
Vomiting, n (%)	35 (45)	43 (45)	0.943
Photophobia, n (%)	11 (14)	10 (10)	0.443
PARACLINIC INVESTIGATIONS			
Analysis of CSF			
Albumin (95%CI)	0.181 (0.132-0.231)	0.964 (0.693-1.236)	*<0.001*
Glucose (95%CI)	1.621 (-0.275-3.519)	0.811 (0.291-1.330)	0.374
Chlorine (95%CI)	7.291 (7.198-7.384)	7.203 (7.080-7327)	0.267
Protein (95%CI)	0.313 (0.233-0.394)	1.569 (1.125-2.013)	*<0.001*
Elements (95%CI)	35.99 (-1.73-73.70)	2,924.8 (1039.3-4819.3)	*0.007*
Pandy (95%CI)	0.28 (0.08-0.48)	2.35 (2.00-2.70)	*<0.001*
PMN procent (95%CI)	4.00 (-4.52-12.52)	54.46 (44.74 – 64.18)	*0.007*
Blood Parameters			
VSH (95%CI)	23.32 (16.94-29.70)	31.07 (25.38-36.76)	0.074
Leukocytes (95%CI)	9,207 (8,134-10,279)	12,209 (10,979-13,434)	*0.001*
Neutrophils (95%CI)	6,888 (5,970-7,806)	9,663 (8,541-10,784)	<0.001
Lymphocytes (95%CI)	1,612 (1,358-1,865)	1,653 (1,349-1,957)	0.840
Monocytes (95%CI)	655 (552-757)	663 (566-760)	0.901
Eosinophils (95%CI)	66 (32-99)	35 (19-51)	0.079
CRP (95%CI)	3.87 (2.39-5.34)	4.53 (2.9-6.1)	0.563
Creatinine (95%CI)	0.601 (0.539-0.663)	0.684 (0.607-0.762)	0.114
ALT/TGP (95%CI)	29.72 (23.35-36.08)	30.74 (25.21-36.27)	0.809
Glucose (95%CI)	88.51 (75.92101.11)	109.71 (96.02-123.40)	*0.028*

* mTB - tuberculous meningitis, ** mF fungal meningitis

being both < 0.001. **Glucose level** was higher in those with viral meningitis than those with bacterial meningitis (0.662 g/l versus 0.457 g/l, p <0.001).

Blood tests have shown a pattern of high levels (even over 9 times C-reactive protein, CRP) for patients with bacterial meningitis compared to patients with viral meningitis (Table 3).

Thus, the erythrocyte sedimentation rate (**ESR**) had a mean value of 46.04 mm/h in patients with bacterial meningitis compared to 19.33 mm/h in those with viral meningitis (p < 0.001), the **leukocyte count** was 16,654/µl in meningitis patients bacterial versus 9.984/µl in those with viral meningitis, p <0.001. Also, elevated values for **CRP**, **creatinine** and **neutrophils** are distinguished, with differences in statistical significance (p < 0.001). The increase in creatinine observed at the time of diagnosis can be explained by secondary dehydration associated with fever.

DISCUSSION

Based on the comparative analysis, there are statistically significant differences in clinical manifestations (signs and symptoms) and the values of laboratory investigations in the group of patients presenting at the hospital and were infirmed for meningitis compaired to those who were confirmed. Thus, 40% of the signs and symptoms differ, headache and neck stiffness remaining distinctive signs, consistent with literature (4). In confirmed cases of meningitis, in the subgroup analysis, bacterial meningitis versus viral meningitis, signs and symptoms no longer have a distinctive pattern for one group or another.

In the CSF analysis, 5 out of 7 parameters (71%) are influenced in the meningitis group, indicating and confirming once again (9) that the CSF is the primary biological product that helps establish the meningitis diagnosis.

TABLE 3. *Demographic, Clinical, and Paraclinic Characteristics of Patients Depending on Etiology: Bacterial Meningitis (BM) or Viral Meningitis (VM), (Tuberculous Meningitis and fungal Meningitis were excluded from the comparison)*

Variable N=84	BM (n=31)	VM (n=53)	P value
Age (95%CI)	36.61 (28.23-45.00)	16.57 (11.28-21.85)	*<0.001*
Sex (M/F)	17/14	29/24	0.991
Inpatient duration (95%CI)	15.58 (12.57-18.59)	11.72 (10.75-12.68)	*0.004*
SIGNS AND SIMPTOMS			
Fever, n (%)	29 (93)	41 (77)	0.055
Cephalea, n (%)	22 (71)	45 (85)	0.125
Neck stiffness, n (%)	23 (74)	28 (53)	0.053
Vomiting, n (%)	10 (32)	27 (51)	0.096
Photophobia, n (%)	3 (10)	6 (11)	0.814
PARACLINIC INVESTIGATIONS			
Analysis of CSF			
Albumin (95%CI)	1.705 (1.091-2.319)	0.541 (0.251-0.831)	*<0.001*
Glucose (95%CI)	0.457 (0.347-0.567)	0.662 (0.604-0.719)	*<0.001*
Chlorine (95%CI)	7.27 (7.07-7.48)	7.16 (6.99-7.33)	0.492
Protein (95%CI)	2.854 (1.789-3.918)	0.839 (0.426-1.251)	*<0.001*
Elements (95%CI)	5,951 (2,594-9,308)	1,725 (-1,058-4,508)	0.058
Pandy (95%CI)	3.68 (3.29-4.06)	1.42 (0.99-1.84)	*<0.001*
PMN procent (95%CI)	76.48 (65.50-87.46)	33.12 (21.08-45.15)	*<0.001*
Blood Parameters			
VSH (95%CI)	46.04 (33.98-58.10)	19.33 (15.37-23.29)	*<0.001*
Leukocytes (95%CI)	16,654 (14,267-19,040)	9,984 (8,992-10,976)	*<0.001*
Neutrophils (95%CI)	14,131 (11,838-16,423)	7,486 (6,592-8,379)	*<0.001*
Lymphocytes (95%CI)	1,674 (1,065-2,284)	1,643 (1,297-1,991)	0.925
Monocytes (95%CI)	765 (598-931)	564 (445-682)	*0.046*
Eosinophils (95%CI)	20 (0.32-39.61)	38 (13.11-62.33)	0.308
CRP (95%CI)	11.49 (7.51-15.47)	1.23 (0.58-1.87)	*<0.001*
Creatinine (95%CI)	0.960 (0.80-1.11)	0.527 (0.45-0.60)	*<0.001*
ALT/TGP (95%CI)	34.97 (26.24-43.69)	23.78 (19.91-26.09)	*0.002*
Glucose (95%CI)	141.02 (108.75-173.29)	96.49 (81.50-111.49)	*0.005*

Also, the CSF parameters are fast and reliable indicators of discrimination (or differentiation) between a bacterial meningitis and a viral meningitis, as, according to our study, there are statistically significant differences in 5 out of 7 parameters analyzed.

The analysis of blood values did not indicate relevant differences between control and confirmed meningitis patients, only 3 out of 10 (30%) of the parameters presenting elevated values in the confirmed group, concordant values with the literature (10).

Blood counts differ in 8 out of 10 (80%) of the investigated parameters when comparing subgroups of bacterial meningitis with viral meningitis, the values being greatly increased in bacterial meningitis.

We mention that within the framework of the UEFISCDI-financed research project, besides the study of meningitis cases for a 3 yesrs period, we also sought identification of the most predictive laboratory parameters for device design that will guide the appropriate attitude towards meningitis suspicion, in the shortest possible time; this is important especially in non-infectious diseases clinical departments and units, without permanently functioning laboratory facility.

CONCLUSIONS

- The CSF exam is a key element in diagnosing meningitis and differentiating the viral or bacterial etiology of meningitis;
- In bacterial meningitis, the blood parameters of inflammation have elevated net values from those in viral meningitis.

LIMITATIONS

The results of the study can not be extrapolated to larger samples or to the general population of meningitis patients because they are based on a small number of cases presented in a single clinical center.

PERSPECTIVES

Introduction of an algorithm/medical device that guides with high and rapid accuracy, the diagnosis of acute meningitis and differential diagnosis between bacterial and viral meningitis, avoiding the negative effects of delayed diagnosis and unnecessary antibiotic treatment in viral meningitis cases.

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