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PARTIALLY TREATED BACTERIAL MENINGITIS; THE DILEMMA CONTINUES

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ABSTRACT

Objective: This study aimed to determine the effect of pretreatment with antibiotics before lumbar puncture on cerebrospinal fluid profile(CSF) compared with the CSF results' of patients who were not pretreated with antibiotics. **Methods:** This is a retrospective study composed of all children (newborns until 12 years old); who reviewed the Children University Hospital Between 1/1/2015 and 20/11/2017 and were diagnosed with acute bacterial meningitis. **Results:** A total of 55 children were diagnosed with acute bacterial meningitis and were included in this study. However only 23.6% (13 cases) of all patients received antibiotics before cerebrospinal fluid analysis (CSF) and those were studied to determine the changes due to the pretreatment. Those patients (13 patients) CSF results' revealed decreased WBC (white blood cell count) in 38.4% of them, lymphocyte dominance in 61.5% of them, 62% of their culture results were sterile, high glucose levels in 38.4% cases and low protein levels in (23% of them). Ceftriaxone was the most common antibiotic given in this study and it caused significant differences in the CSF profile. **Conclusion:** We cannot dogmatize that prior treatment may cause a complete change in the CSF analysis results, and suggest a diagnosis of another form of meningitis based on the CSF profile, but we are confident that the inappropriate pre-treatment will blur the diagnosis of bacterial meningitis and make it harder to establish.

KEYWORDS: Acute bacterial meningitis; antibiotic pretreatment; CSF analysis.

INTRODUCTION

Meningitis is an inflammation of the three anatomical layers (meninges) that covers the brain and spinal cord. It is a medical emergency and if left untreated, its morbidity and mortality

rate might reach 100%. It should be noticed that even with advanced medications and intensive care units (ICU) worldwide, the morbidity rate of meningitis is about 10%.[1-2] This could even be higher in developing countries, in wars and in immunocompromised patients (tuberculosis and HIVs).[1-2] Acute bacterial meningitis (ABM) is a very common form of meningitis, and even children who recover from it might complain of long-term complications.[3] There is no single clinical feature that is sufficiently distinctive to make a firm diagnosis of meningitis; but a history of fever, seizures and altered consciousness with the presence of meningeal signs are indicative features of ABM.[4] The gold standard diagnosis of meningitis is the cerebrospinal fluid (CSF) pathogen culture; however, in countries with limited resources, alternatives could be used such as CSF cytology and biochemistry. Although, the effect of prior antibiotic therapy on CSF cellular and chemical profiles were studied in previous studies, it has remained a matter of controversy. Some studies showed concerns about possible changes in the cytology and Gram-staining of CSF.[5] This study aimed to evaluate the effect of antibiotics pretreatment on CSF profile and to determine any clinical differences that could have resulted from the prior treatment.

Up to our knowledge, this is the first study of its kind in Syria.

MATERIALS AND METHODS

This is a retrospective study composed of all children (newborns until 12 years old) who were admitted to the children's university hospital between 1/1/2015 and 20/11/2017, and were diagnosed with acute bacterial meningitis (ABM). It should be noted that the children's university hospital, Damascus, Syria has become the main pediatric hospital in Syria during the crisis and receives patients from all over the country.

This study included all the patients (55 patients) diagnosed with acute bacterial meningitis between 1/1/2015 and 20/11/2017. We excluded meningitis caused by viral, tuberculous and parasitic meningitis. We also excluded immunocompromised children and those with CSF shunts due to differences in inflammatory response and pathological agents in both groups, respectively.

The criteria used to establish ABM diagnosis included one or both of the following: 1-presence of bacteria in CSF culture. 2-CSF analysis revealed high predominance polymorph nuclear cell count (WBC more than 100 cell/mm3), protein level more than 50mg/100ml, and low sugar level less than 40mg/100ml. Statistical analysis was done using SPSS 23.0.

RESULTS

The total number of untreated cases was 42(76.4% of all cases) and the partially treated cases were 13(23.6%). Table 1 shows the changes in the CSF analysis in both the untreated meningitis and partially treated meningitis along the type of antibiotics that caused these abnormal changes. All units for the lab tests (WBC, Glucose, and Protein) in the tables are stated in the Methods and Discussion. All values in our tables are from 55 total cases. All missing or less than total data are due to missing data from the records.

Table 1: CSF analysis in our study.

		Untreated group		Partially treated (treated group)		
	Total cases=55 (42 untreated, 13 partially treated	**N**	**%**	**N**	**%**	**Antibiotic Type**
		42	76.4%	13	23.6%	
CSF analysis	WBC less than 100	34	81%	5	38.4%	1,2,3,4,11
	WBC more than100	5	12%	8	61.5%	1,2,5,6,7,8
	Lymphocytes ↑	34	81%	8	61.5%	1,2,4,5,6,7,11
	Neutrophils ↑	8	19%	2	15.4%	1,8
	Glucose < 40	16	38.1%	5	38.4%	1,4,7
	Glucose > 40	18	43%	5	38.4%	1,2,5,6,8,11
	Protein ↑	33	78.6%	8	61.5%	1,2,5,6,7,11
	Protein ↓	9	21.4%	2	15.4%	

Abbreviations for table 6: 1= ceftriaxone 2= vancomycin, 3= cefotaxime, 4= beta-lactamase, 5=aminoglycosides, 6=meropenem, 7= Cefepime, 8= third generation cephalosporin, 11= unknown antibiotics.

Table 2 and 3 shows the difference between partially treated cases for 4 days and those treated for more than 4 days.

Table 2: CSF analysis ad symptoms in patients partially treated with antibiotics within 4 days of treatment administration.

PRIOR TREATMENT WITHIN 4 DAYS					
Clinical symptoms	**WBC**	**Cell types**	**Glucose**	**Protein**	**Antibiotic**
Fever-vomiting-headache	More than 100	lymphocyte	Less	high	Cefepime
Fever-vomiting	More than 100	lymphocyte	High	high	Not known
Fever-vomiting	Less than 100	lymphocyte	Less	Low	Ceftriaxone+ beta-lactamase
Fever-vomiting	More than 100	lymphocyte	High	low	Ceftriaxone
Fever-vomiting	More than 100	neutrophils	High	high	Third generation cephalosporin
Fever-vomiting	Less than100	lymphocyte	High	high	Not known

Table 3: CSF analysis and symptoms in partially treated patients with antibiotics for more than 4 days.

Prior treatment more than 4 days:					
Clinical symptoms	**WBC**	**Cell types**	**Glucose**	**Protein**	**Antibiotic**
Fever- poor feed -convulsion	More than 100	lymphocyte	Low	High	Not known
Fever+ convulsion	More than 100	lymphocyte	Low	high	Not known
Fever-vomiting	Less than 100	lymphocyte	Low	high	Ceftriaxone
Fever-convulsion	More than 100	lymphocyte	High	high	Ceftriaxone+ vancomycin+ aminoglycoside
Fever-convulsion	Less than 100	neutrophils	Missing	Low	cefotaxime+ vancomycin
Fever- convulsion	More than 100	lymphocyte	Missing	High	Ceftriaxone+ vancomycin
Fever	Less than 100	missing	Missing	Missing	Ceftriaxone

Table 4 shows all the partially treated cases with antibiotics and the results of CSF analysis in these patients.

Table 4: CSF analysis in all cases (13) partially treated with antibiotics.

CSF analysis							
WBC <100	**WBC >100**	**Lymphocytes↑**	**Neutrophils↑**	**Glucose<40**	**Glucose≥40**	**Protein**	**Antibiotics**
	Yes	Yes			Yes	↑	Not known
	Yes	Yes		-	-	↑	Ceftriaxone+ vancomycin
Yes				-	-	↓	Ceftriaxone
Yes				-	-	↓	Cefotaxime +vancomycin
	Yes				Yes	↓	Ceftriaxone
Yes		Yes			Yes	↑	unknown
Yes		Yes		Yes			B-lactamase+ Ceftriaxone
	Yes		Yes	Yes		↑	Uncompleted meningitis treatment
	Yes	Yes			Yes	↑	Ceftriaxone +vancomycin+ aminoglycoside+ meropenem
	Yes	Yes		Yes			Uncompleted meningitis treatment
Yes		Yes		Yes		↑	Ceftriaxone
	Yes	Yes		Yes		↑	Cefepime
	Yes		Yes		Yes	↑	third generation cephalosporin

Table 5: Pathogens causing bacterial meningitis in our study.

	Untreated patients		Partially treated (pretreated) patients	
Variable	**frequency**	**percent**	**frequency**	**percent**
Sterile	16	38.1%	8	61.5%
Staphylococcus	1	2.4%	1	7.7%
Streptococcus pneumoniae	13	30.2%	0	0.00%
Streptococcus type b	1	2.4%	0	0.00%
Haemophilus influenza type b	2	5.5%	1	7.7%
Multiple organisms	0	0%	1	7.7%
Not available	8	19%	0	0.00%
Pseudomonas	1	2.4%	2	15.4%
Total	42	100%	13	100%

DISCUSSION

Acute bacterial meningitis (ABM) is a concerning diagnosis among both parents and practitioners, therefore a fast diagnosis is needed in order to prevent serious outcomes, which could reach death especially when left untreated.

The CSF profile of bacterial meningitis differs between different studies; our criteria for diagnosis ABM based on CSF analysis was as followed.

1- WBC count (more than 100 cell/mm3) with dominance of polymorph nuclear neutrophils (PMN). 2-Glucose level: Low (<40% of serum glucose). 3-Protein level: Elevated (>50 mg/dl).[6]

Since decades, several studies have discussed the possibility that prior antibiotic treatment of bacterial meningitis may alter CSF findings and make it like aseptic meningitis findings, which could cause confusion to the clinician. Heycock had anticipated the importance of describing not only the typical clinical picture of an infective disease such as ABM but also its pattern when modified by incomplete treatment. In fact, studies in the late of the previous century had different results and statements about certain different partial treatment.[7-8]

The fear of mistakenly diagnosing different forms of meningitis is rarely justified[9], even though certain studies reported notable differences regarding diagnosis in the pretreated cases, and some studies even reported a minority of cases that could have aseptic results in the CSF culture.

However, in the last decade, studies showed more solid evidence about the effect of partial treatment and the difficulties it represents on making the proper diagnosis.

In our study (23.6%) of the cases were partially treated (referred to as treated) while the rest were not treated (referred to as untreated). It is possible that misdiagnosing meningitis as otitis media or other infectious diseases caused this high percent (23.6%).

In our study, the patients symptoms were similar (fever- poor feeding -headache -...), with fever being the most common symptom. Many papers studied the relation between prior treatment and clinical presentation of the children, and some suggested that the partial treatment had no significant effect on the symptoms nor on the signs in children.[10] Unfortunately, we were not able to determine if the therapy had any effects on the fever degree or duration due to uncompleted charts. Heycock stated that a short course of antibiotic can change the clinical picture of the disease and the child might enter a chronic phase in which irritably and anorexia are the prominent features.[8] In our study, 5 out of 7 children of who had clinical symptoms and were treated for more than 4 days developed convulsions, while none of the 6 cases who were treated for less than 4 days developed convulsions. (Table 2, 3).

It is of clinical importance to consider the effects of prior therapy on CSF profile when examining partially treated meningitis. Furthermore, it was theorized that the diagnosis of ABM for example would be difficult and puzzled, and may lead into a complete viral form. Early studies could not find any effect of the prior treatment effect on CSF profile.[9,10,11] This is probably because many of these studies examined penicillin which has little effect on Haemophilus Influenzae[12] and it could also be due to the differences in both the standards of diagnosis and the patients among the studies.[13] While recent studies are showing alteration to the cultures and specific differences in the CSF profile that may lead to mistakenly diagnosing ABM as another form of meningitis (e.g. Viral).

Our study documented 13 cases of partially treated meningitis, although the given antibiotics were known, their doses were missing from the records. Differences were noted among these cases. Table (4). The given antibiotics included (ceftriaxone – vancomycin – cefepime – cefotaxime – beta-lactamase – aminoglycoside – third generation cephalosporin – meropenem).

Many studies stated that previous treatment with antibiotics has certain impact on the CSF profile (described above). This effect differs according to medication used. Although some of

these drugs are already included in the treatment plan of ABM, but in our study, none of them was given in the proper doses or duration.

Numerous studies suggest that antibiotic pretreatment does not affect CSF white blood cell count (WBC) nor does the duration of the treatment.[5, 12, 13] We found (38.4%) cases with decreased WBC count (under 100 cell/mm3) in CSF analysis. Furthermore, 3 out 7 patients who were treated with antibiotics for more than 4 days showed decreased WBC.

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Moreover, a study done in Nepal[5,14] concluded that antibiotic treatment is associated with decreased neutrophils and increased lymphocyte counts. This is compatible with our study that showed a lymphocyte dominance in (61.5%), and high cerebrospinal glucose levels in (38.4%). However, Nepal study did not report any changes in the cerebrospinal fluid protein levels unlike another study (Nigrovic et al) which reported low protein level just like our study (23% of treated cases).

Our study has some advantages over other similar studies, because we have the type of antibiotics used and even without their doses, we can still define the impact they had on the CSF profile (Table 4).

The most common results of CSF culture in our study in both groups (untreated and treated) were sterile (16 and 8 cases, respectively). In addition, the most common pathogen in the untreated group was Streptococcus pneumoniae (30.2% of untreated group culture results) while pseudomonas was the most common in the treated group (15.4% of pretreated group culture results).(Table 5)

It was shown in previous studies that prior antibiotic therapy decreases the concentration of some organisms in the CSF hence decrease the effectiveness of CSF gram stain, which means that partial therapy might sterilize the CSF in some cases.[15] In our study, out of the 13 partially treated cases (the “treated” group), we found 8 cases (61.5%) with sterile CSF culture results.(Table 5)

Ceftriaxone was the most common antibiotic given in our study (6 patients out of 13 patients) and was prescribed alone in 3 patients, and was a part of the uncompleted treatment of AMB of 2 patients.

Ceftriaxone effect was not the same in all patients (pretreated or partially treated); it was associated with decreased WBC count in (37.5% of the patients who took ceftriaxone), lymphocytes dominance in (62.5% of the patients who took ceftriaxone) and only one case with neutrophils dominance (12.5% of the patients who took ceftriaxone). Sugar ratio was an elevated in (37.5% of the patients who took ceftriaxone) and the protein ratio was decreased in (25%). It is very interesting to note the effect of these medications (antibiotics) on the CSF profile and culture in our study. In addition, even though we cannot confirm a possible shifting into a total aseptic form, it is clear that antibiotic pretreatment for doubted meningitis can cause a distortion in CSF profile, longer duration of illness and major difficulties in diagnosis. Moreover, the increased usage of random antibiotics has a bad influence on economy due to the increased need of multiple medications to treat various illness (antibiotic resistance).

Many argue about the usefulness of the CSF results after prior treatment, but the Lumbar puncture is still helpful for diagnosing meningitis especially when accompanied by clinical examination.

Our limitation in this study is similar to any other retrospective study, which is the missing data, limited resources and laboratory mistakes.

CONCLUSION

Our study showed in evidence that children who have acute bacterial meningitis and are pretreated (partially treated) with antibiotics will have changes in the CSF profile and culture tests, such as a distorted profile (Specifically, it caused lymphocytes dominance and high sugar with low protein) and a sterile result in the CSF culture.

We cannot dogmatize that prior treatment may cause a complete change in the CSF analysis results, and suggest a diagnosis of another form of meningitis based on the CSF profile (e.g. viral), but we are confident that the inappropriate pre-treatment will blur the diagnosis of bacterial meningitis and make it harder to establish.

Compliance with Ethical Standards

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