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Acute Bacterial Meningitis in an Adult Population Admitted in the ICU

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Abstract

Introduction: The Acute Bacterial Meningitis in Adults is an entity that keeps yet a high rate of mortality and neurological sequelae.

Patients: We present a series of 23 cases admitted in the ICU with Acute Bacterial Meningitis. Demographic, neurological and general severity characteristics are presented. They were divided in communitary (13) if presentation was with the patient at home and nosocomials (10) if presentation was around the hospital. Causes of admisión at the ICU, implicated bacteria and neurosurgical procedures, if necesary, were analyzed.

Results: the communitary and nosocomial meningitis have a different microbiological flora, inflammatory response and mortality rate. The low level of concious was related with mortality as well. Due to the small number of recruited cases the majority of analyzed variables didn´t reach statistical significance.

Conclusion: the demographic and bacteriological pattern of patients with Acute Bacterial Meningitis have changed in the last years; Still presents a high mortality rate, despite if appropriate antibiotic treatment is used when the patients are attended at the hospital.

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Introduction

The Acute Bacterial Meningitis (ABM) is a disorder which has been known for over two centuries. It has an incidence of about 2 cases per 100000 inhabitants/year [1,2]. It's a very serious process with a mortality rate which goes up to almost 100% when untreated [3]. The adherence to certain treatment protocols has been linked to a better prognosis [4]. However, its current mortality rate remains high (20-40%), making it one of the top ten infectious death causes. Any delay in the treatment is directly related to an increased motality rate as well as to long-term neurologic sequelae [5,6,7]. Factors such as advanced age, compromise of the level of conscience and the severity of the sepsis symptoms are usually linked to a worse prognosis and to a more difficult therapeutic assessment [8]. This usually leads to admission in intensive care units (ICUs), where the patients stay during the first days of the process. Patients with ABM which require admission in ICUs have a mortality rate of over 25% despite receiving an adequate, intensive and early treatment [9].

The ABM can be either nosocomial or community-acquired. The demographic patterns and the risk factors associated with each kind of ABM differ greatly. In community-acquired ABMs occurring in developed countries, the most frequently involved germs are, in decreasing order of prevalence, *S. pneumoniae, N. meningitidis, Group B Streptococcus, H. influenzae and L. Monocytogenes* [10]. In the case of nosocomial ABM, the most frequently involved germs are *S. epidermis and Gram-Negative Bacilli* [11].

The recent introduction of a compulsory vaccination against some serotypes of *S. pneumoniae, N. meningitidis* and *H. Influenzae* has reduced the incidence of community acquired ABM and it could be altering the patterns of the more frequently isolated germs [12]. Besides, the rise in the prevalence of immunocompromised patients and the increase in those with their craneal integrity affected by traumatic brain injury or recent neurosurgical procedures could be boosting the incidence of nosocomial ABM [12]. Consequently, we believe that the clinical characteristics, the microbiologic aspects and the therapeutic assessment of ABM needs to be permanently re-evaluated.

The targets of our study were: [1] to determine the demographic and microbiological patterns in patients with ABM who need to be admitted in ICUs of tertiary hospitals in developed countries, [2] to get to know the current death rate of ABM and the factors related to it.

Methodology and Material

Patients

We retrospectively collected a sample with all the patients diagnosed with ABM as the reason for admission in our hospital's ICU (patients over 14 years old, 28 beds) during the period between January the first, 2012 and the 28th of February, 2015. Our centre is a tertiary hospital with neurosurgery service. It takes care of all the brain traumas of a population of 1,500,000 inhabitants. The diagnosis of ABM was stablished when we faced a compatible clinical case (headache, fever, affected neurological function, stiff neck), confirmed with bacterial growth in samples or increase in cellularity in the cerebrospinal fluid, with a predominance of polymorphs or with positive blood cultures in cases where lumbar puncture was contraindicated. Cases with normal cerebrospinal fluid (CSF) or with CSF's cellularity suggesting viral causes were not included in the study. We considered the ABM to be community acquired when the symptoms started before the admission to the hospital in patients which hadn't required hospital admission during the previous 4 weeks. The criteria for ICU admission depended on the clinical judgement of the doctor who was treating the patient at the moment. Patients with open brain trauma were treated with amoxicylin + clavulanic acid every 8 hours as an antibiotic prophylaxis during a period stablished by the doctor treating the patient. Patients intervened in neurosurgery received cefazolin every 8 hours during 24 hours.

Analysed variables

We extracted some epidemiological data (including age, sex, immunity disorders and previous procedures which could alter the skull's anatomical integrity). We considered there to be an immune

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disorder whenever corticoids or cytostatic drugs had been recently administrated to the patients as well as whenever they suffered from any haematological maligne diseases. We considered an alteration of the skull's anatomical integrity any open head injury as well as any recent neurosurgical procedure.

Clinical and laboratory data

Cause of admission in ICU: reduced consciousness compromising the airways permeability, other neurological disturbances, septic shock according to stablished criteria (14), others

Patients course in the ICU: Apache II at the moment of admission, worse level of consciousness registered in the ICU admission using the Glasgow Scale Coma (GSC), need for mechanical ventilation (MV) through tracheal intubation, inotropic support during >24 hours using dopamine or noradrenaline or need for renal replacement therapy, length of ICU and hospital stay, ICU and global hospital mortality. All but two of the cases had head CT-scans done. All the cases which required any neurosurgical procedures during the stay at the ICU were registered. All but one of the patients had at least one CSF sample in order to carry out a leucocyte count as well as the protein level and to do cultures. The plasma C-reactive Protein levels were registered in 20/23 cases and blood cultures were done in 17/23 cases.

Microbiological data and antimicrobial therapy: results of the CSF and blood cultures, antibiotic treatment empirically prescribed was considered as correct if the germs later isolated were proved to be sensitive to it, adjunt iv steroids treatment. We registered if the patients had received any antibiotic therapy before their arrival to the hospital.

Statistic procedure

The quantitative variables were expressed as means +/- standard deviation. The qualitative variables were expressed as percentages. Cases of nosocomial and community acquired ABM were grouped and the demographic, microbiologic and severity patterns measured as hospital mortality, Apache II and plasma C-reactive Protein (CPR) on admission were compared using non parametric tests (U of Mann-Whitney) due to our sample size. Non-parametric tests for independent samples (U of Mann-Whitney) was used for comparing the age, Apache II and CPR on admission, MV, previous immunesupression, iv steroids for treatment of ABM between the group of survivors and non-survivors.

Results

23 cases were included (Table 1). They corresponded to 20 patients, one of them having been admitted to the ICU in four occasions, always coming from her place of residence, and therefore considered as 4 independent cases. 13 cases (56,5%) were community acquired and 10 of them (43,5%) were considered as nosocomial. The cause of admission in the ICU was deterioration of the level of consciousness compromising the patients'airway in 17 cases (74%), other neurological complications in 5 cases (21,7%) and septic shock in one case. 11 cases presented alteration of cranial integrity whose characteristics are shown on table 2. 10/11 cases (corresponding to nosocomial ABM vs 13 community ABM)) were inpatients or they had been recently admitted when they were diagnosed. Only one of the 11 cases hadnot been recently admitted to the hospital at the moment of diagnosis, but he had suffered from a severe head trauma with CSF fistula ten years before. In 21 out of 23 cases, a head CT-scan was performed, and in 8 cases (38%) this CT came out to be normal. In 8 cases (38%), hydrocephalus was discovered (7 nosocomial cases + 1 community acquired case). 10 patients (43,5%) required some sort of surgical intervention which was performed by members of the service of neurosurgery: 8 required the placement or substation of an external ventricular drainage, 1 required the puncture of the sphenoid sinus and another case required transcranial puncture in order to evacuate the pneumoencephaly.

Characteristics	n= 23
Age	51,6 (range 15-75)
Sex (%)	9 M (39,1%), 14 F (60,9%)
Comorbidity: DM (%) immunosuppression (%)	 2 (8,7%) 4 (19%)
Apache II on admission	17,14 (range 7-28)
CRP on admission (mgr/l)	141,7 (20 cases, 3 non-registered)
Positive CSF cultures	20 (87,47%)
Positive blood cultures	6 (28,57%)
Need of Mechanical Ventilation/ days of mechanical ventilation	10 (43,5%), average of 15 days.
Inotropic support	6 (28,57%)
Death rate in ICU, global death rate	4 (19%), 7 (30,4%)
iv steroids (%)	12 (57%)

Table 1: clinical features of patients with ABM admitted to the ICU.
M: male; F: female

Table 1 shows the main characteristics of the global population at the moment of admission, the characteristics of their stay in the ICU and the antimicrobial and iv-steroids treatment used.

Lumbar puncture or CSF extraction through the external device was performed in 22 cases. One of the cases didn't have a lumbar puncture done because the results of the CT-scan suggested a high risk of brain herniation. In all cases which had a CSF extraction performed, this came out positive, except for two in which it was negative and one which was positive for the Gram's stain but which had a negative culture. In one case mixed flora was found (*Enterococcus faecalis* + *Pseudomonas aeruginosa*). In the rest just one germ was found: *Streptococcus pneumoniae* in 6 cases, *Neisseria meningitidis* in 3 cases, *Staphylococcus epidermis* in 4 cases (corresponding to the same patient), gram-negative bacillus in 4 cases (3 *Serratia marescens* and 1 *Echerichia coli*), Listeria monocytogenes in one case, Streptococcus viridian in one case.

In 15 cases a blood sample for blood culture was taken before the beginning of the antibiotic treatment. 8 cases came out positive, always showing the same germ which grew in the CSF, except for one case where growth was only appreciated in the blood culture (Streptococcus pneumoniae) because a CSF extraction wasn't performed.

Table 3 presents the microbiological findings, referred as microbiological findings in CSF and blood, as well as the antibiotic treatment prescribed. 18 cases (85%) had a positive culture in CSF. One of them (case 18) had a negative culture but gram negative bacilli were observed in the CSF's Gram's stain. In 16 cases (69%) an initial empirical combined therapy consisting of a third generation cephalosporin and vancomycin or linezolid was used. In 5 cases ampicillin was associated. Cases where S. epidermidis was isolated received just linezolid. The rest were cases with a known allergy to betalactams. In all cases where we were able to isolate some microbe and to get to know its sensitivity, the empirical antibiotic therapy came out to be effective.

Gender Age	Related background/Time since it happened	CT-scan	Germ	Procedure
M70	Craniectomy after brain tumour / 11 days	Hydrocephalus	*A baumanii/S Marcences*	EVD
F64	SAH, EVD/1 month	Hidrocephalus	*S. epidermidis*	Replacement of VPS for EVD
F50	Craniectomy after brain tumour/ 16 days	Hidrocephalus	*E. coli*	EVD
F64	SAH, EVD/60d	No	*S epidermidis*	No
F64	SAH, EVD/45d	Hidrocephalus	*S epidermidis*	Replacement of EVD
M48	Brain trauma/10 años	Hidrocephalus	*S neumoniae*	No
F64	SAH, EVD/75d	Hidrocephalus	*S epidermidis*	No
F49	Neurosurgery in the posterior fossa/51d	Pneumoencephaly/ pneumoventricle	*S. millerii*	No
F38	Transphenoidal neurosurgery/10d	Pneumoencephaly	*S faecalis*	EVD replacement
F16	brain trauma /8 days	Hydrocephalus, pneumoencephaly, haemorragic foci	Gram-negative bacilli, negative culture	DVE placement
F32	Spinal anesthesia/1d	Hemoventricle	Negative	No

Table 2: characteristics of cases with ABM with altered cranial integrity.
M: male; F: female; SAH: subarachnoid hemorrhage; EVD: external ventricular device; VPS: ventriculoperitoneal shunt

Characteristics	n=23
Positive CSF cultures	18 (85,7%)
Positive blood cultures	8/15 (53,3%)
Cefriaxone/Vancomycin or Ceftriaxone/Linezolid	16 (69%)
Correct empirical treatment	100%

Table 3: Microbiologic findings and antibiotical therapy used.

Demographic patterns, severity on admission, microbiological findings and mortality rate were compared in both groups (community vs nosocomial). The mortality rate and plasma CRP were superior in nosocomial vs community ABM, but without statistical significance (Table 4).

A comparative study was done in order to analyse the variables (age, plasma CRP, Apache II, level of consciousness (GCS) on admission, and the most frequently isolated germs) related with the mortality rate, finding out statistical significance with the GCS on admission and the severity of the patients in Apache II (Table 5).

Discussion

The demographic patterns in patients with ABM has changed greatly since the universalisation of the use of certain vaccines against there germs which used to be more commonly involved: H. influenzae, S. pneumonia and N. meningitidis. H influenzae used to be the predominant germ in children. One serotype was responsible for over 90% of the cases of ABM in children and the vaccine against that serotype has practically eradicated ABM caused by H.influenzae and it has drastically decreased the incidence of childhood ABM in developed countries. The serogroups of S. pneumoniae and N. meningitidis which are responsible for ABM vary much more and can change over time, making vaccination less effective (the changes in the incidence of these germs hasn't been altered as significantly as the incidence of H. influenzae) [12]. The decline in the incidence of ABM caused by H. influenzae has lead to the rise in the average age of population which suffers from ABM. In our study there wasn't any case of H. influenzae for the reasons stated and because all the cases came from an adult ICU. However, the incidence of S. pneumoniae and N. meningitidis was still very relevant. The average age of our population (51.6) corresponds to the one which has been registered in recent studies, being much higher that the average age registered in historical series [13], when the infancy period corresponded to the peak of presentation.

	Nosocomial	Community acquired	p
Age	51,8 (+/-17,6)	51,5 (+/-17,9)	ns
Apache II (on admission)	16,8 (+/-5,8)	18,5 (+/-4,8)	ns
CRP (on admission)	98,0 (+/-99,5)	177,6 (+/-71,12)	0,05
In-hospital mortality rate	5/10 (50%)	2/13 (15,5%)	0,08
Microbiological findings in the CSF	*GNB 3/10* *S epidermidis 4/10* *Otros 2/10* *Negative 1/10*	*S pneumoniae 6/13* *N Meningitidis 3/13* *L monocytogenes 1/13* *GNB 1/13* *Negative 2/13*	

Table 4: comparative analysis of communityvs nosocomial acquired – ABM.

Nosocomial ABMs have also contributed in changing the demographic patterns of patients suffering from ABM. The development of craniectomy, the increase in the use of ventricular and lumbar catheters and open head injuries have contributed to an increase in

	Survivors	Non-survivors	P-value
Age	50,4 (+/-16,8)	54,6 (+/-19,8)	ns
Apache II	16,2 (+/-5,1)	21,0 (+/-4,2)	,04
GSC admission	10,44 (+/-3,7)	7,7 (+/-2,8)	,07 (ns)
CRP admission	145,0 (+/-86,8)	134,2 (+/-111,8)	ns
MV: Yes No	 54% 83%	 46% 17%	
Micro-organisms in CSF: S. pneumoniae GNB	 5 (6) 3 (5)	 1 (6) 2 (5)	
Inmunodepression	1	3	ns
Treatment with iv steroids	65%	66%	ns

Table 5: comparative analysis of survivors vs non-survivors ABM.

the number of patients with nosocomial ABM [14]. We consider ABM to be nosocomial when they appear in patients who had been admitted to the hospital more than one week before the development of meningitis. The characteristics of our patients are described in table 2. They were all admitted due to a severe head trauma, recent neurosurgical procedure or placement of an epidural catheter. Patient 6 had had a severe head trauma ten years before and he wasn't admitted when ABM was diagnosed. Therefore, it was considered a case of community-acquired ABM. The incidence of hospital-acquired ABM has increased due to the development of neurosurgical procedures. The incidence of nosocomial ABM following a craniectomy is approximately 1% [15]. In our study, 43% (10/23) of the ABM were nosocomial. We believe this proportion is related to the type of hospital where the study takes place (it has a neurosurgery department and it's a reference centre for severe head traumas of a population of 1,500,000 inhabitants). The microbiological pattern is very different to the one which appears in community-acquired ABM, showing a preponderance of gram-negative bacilli, Group B Streptococcus and S. epidermis (similar to the pattern described in other series [11]. The mortality rate was higher in patients with nosocomial ABM, however, the scarce number of cases made it impossible to reach statistical significance. The inflammatory response was measured using the level of CRP in plasma. It was higher in cases of community-acquired ABM, probably due to the germs involved.

Despite the improvements in antibiotic and support therapies, the death rate of ABM is still very high. In a retrospective analysis of 493 cases with ABM collected throughout 26 years, the death rate was stablished as 25% [16], with any significant changes throughout the period of 26 years. Advanced age, low level of consciousness, other neurological complications and lethargy have been classically linked with a worse prognosis regarding neurologic sequelae and mortality rate.

Some case series have showed a higher mortality rate when *S. pneumoniae* is involved [17]. The most frequent causes of admission in ICUs in patients with ABM are the need of monitoring the level of consciousness, keeping the airway permeable, and circulatory support (the need for any of this is related to a worse prognosis and a higher death rate) [18]. Our in-hospitalmortality rate was 30,4%, slightly higher than the majority of published series. The severity criteria which appeared in most of our patients; advanced age, low level of consciousness on admission (74%), other neurological complications on admission (21,8%) and a high incidence of Streptococcus pneumoniae, which was the most frequently involved germ (26%); could explain the fact that our mortality rate was slightly higher.

In the mortality analysis (Table 5) we only found statistic significance in the relation between the severity indexes on admission measured (Apache II), but there was a certain tendency to mortality in those patients with a low level of consciousness on admission and the need of mechanical ventilation. We believe that tendency could have reached statistical significance if the number of cases would have been higher. When analysing the mortality rate and its relation with the germ involved we didn't find any link in higher death rates and the presence of S.pneumoniae. The fact that, despite the adherence to good clinical practice [4] and the use of adequate antibiotic therapy, the mortality rate remains high is worrying. The use of ivsteroids, especially when used before or at the same time than the first antibiotic dose, has proved useful in reducing the neurological sequeleae and mortality rate in some series [19], but not in a systematic review which analysed the effect of early steroid treatment in all series published until that point [20]. The cause of this discrepancy in the results could be due to ABMs with different patterns of inflammatory response in the CSF, partly depending on the kind of involved germ. We didn't find any difference in the mortality rate when using iv steroids. In our series, iv steroids were used when was considered convenient by the responsable doctor. The period used was 5 days, according to the protocol of our Unit. Differences in mortality were not found. Probably the effects of steroids in mortality and neurological sequelae should be analyzed in the ABM caused by more inflammatory bacteria and be compared with a control group and finally comparing the effects of IV steroids in two groups of ABM with germs of different inflammatory degree.

Conclusion

The ABM at present is a process with a high mortality rate, even if a properly antibiotic treatment is proposed from the beginning. It would be advisable to search alternative therapies to diminish the brain injury secondary to infection. The use of vaccines against usually implicated bacteria and the spread of neurosurgical procedures can have contributed to the change of the demographic profile and the involved germs.

Competing Interests

The authors have declared that no competing interests exist.

Author Contributions

All the authors substantially contributed to the study conception and design as well as the acquisition and interpretation of the data and drafting the manuscript.

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