Meningococcal Disease Admissions in a Paediatric Intensive Care Unit

Doença Invasiva Meningocócica em Cuidados Intensivos Pediátricos

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ABSTRACT

Introduction: Meningococcal infection has a high mortality and morbidity in children. Aggressive initial shock approach, early referral, secondary transport and vaccination are potential factors with impact in reducing its mortality. Objectives were to characterize children admitted to intensive care due to invasive meningococcal disease, to evaluate their prognostic scores and mortality.

Material and Methods: Observational study, with retrospective data collection. Two periods were created according to the year of admission (A: 2000-2005 and B: 2006-2011). Prognostic parameters, organ failure and mortality rates were compared in these groups.

Results: 70 children were admitted with invasive meningococcal disease. When compared with other causes of admission, a decrease in the number of admissions due to invasive meningococcal disease was observed (period A: 3.4%; period B: 1.5%; $p = 0.001$). The presence of meningitis was 41% in period A and 29% in period B ($p = 0.461$). Rapidly progressive purpura occurred in 78% in period A and 50% in period B ($p = 0.032$). Children from period A had multi-organ failure (80%), disseminated intravascular coagulation (76%) and coma (22%) more frequently than children from period B (29%, 29%, 0%; $p < 0.05$). Mortality was 26% in period A and 0% in period B ($p = 0.006$) and standardized mortality by PRISM was 1.3 and 0 in period A and B respectively.

Discussion: The decrease in the number of admissions due to invasive meningococcal disease can be explained by the introduction of anti-meningococcal C vaccine in 2006. Mortality decline can be possibly explained by an improvement in the initial patient stabilization and to secondary transport.

Conclusion: A decrease in the number of admissions due to invasive meningococcal disease and in mortality was observed.

Keywords: Child; Infant; Intensive Care Units, Pediatric; Meningococcal Infections; Multiple Organ Failure; Mortality; Portugal; Sepsis.

RESUMO

Introdução: A infecção meningocócica tem uma elevada mortalidade e morbilidade em crianças. O tratamento agressivo do choque, a referenciação precoce, o transporte secundário especializado e a vacinação são factores com impacto potencial na redução da mortalidade. Foram objectivos caracterizar as crianças com doença invasiva meningocócica admitidas em cuidados intensivos, avaliar parâmetros de gravidade e mortalidade.

Material e Métodos: Estudo observacional, cujo método de colheita de dados foi retrospectivo. Foram constituídos dois períodos, de seis anos cada, de acordo com o ano de admissão (A: 2000-2005 e B: 2006-2011) e nestes compararam-se índices de gravidade, disfunção orgânica e mortalidade.

Resultados: Foram admitidas 70 crianças com doença invasiva meningocócica. Quando comparadas com as outras causas verificou-se uma redução nas admissões por doença invasiva meningocócica (período A: 3,4%; período B: 1,5%; $p = 0,001$). A ocorrência de meningite foi de 41% no período A e de 29% no período B ($p = 0,461$). Tiveram púrpura rapidamente progressiva 78% no período A e 50% no período B ($p = 0,0032$). As crianças do período A tiveram disfunção multi-órgão (80%), coagulação intravascular disseminada (76%) e coma (22%) mais frequentemente que as crianças do período B (29%, 29%, 0%; $p < 0,05$). A mortalidade foi 26% no período A e 0% no período B ($p = 0,006$) e a mortalidade estandardizada pelo PRISM foi 1,3 e 0 no período A e B respectivamente.

Discussão: A redução do número de admissões por doença menigocócica invasiva pode ser explicada pela introdução da vacina anti-meningocócica C em 2006. Pensa-se que a redução da mortalidade observada, possa ser atribuível à melhoria da estabilização inicial e ao transporte secundário.

Conclusão: Nos últimos anos houve uma redução significativa no número de admissões e na mortalidade por doença invasiva meningocócica.

Palavras-chave: Infecções Meningocócicas; Cuidados Intensivos Pediátricos; Mortalidade; Insuficiência de Múltiplos Órgãos; Portugal; Sepsis.

INTRODUCTION

The incidence of meningococcal disease has decreased over the last few years although still related to a high mortality and morbidity.[1,2] Recent data show an incidence rate in Portugal below 1 per 100.000 in 2010, similar to what has been described in other European countries.[3,4]

In Portugal, B and C are the predominant serogroups. The number of patients related to serogroup B has remained stable, unlike the number of patients affected by serogroup C, which has declined since 2002.[2]

One of the most important and well-studied factors related to the reduction of invasive meningococcal disease has been the national anti-meningococcal C vaccination program.[5] This vaccine has been marketed in Portugal since 2001 and was universally included in the Portuguese National Vaccination Program (*Programa Nacional de Vacinação (PNV)*) in 2006. Since it was first introduced, its coverage rate ranged between 39-69%, a rate which has constantly increased over the years, reaching a national

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vaccination coverage rate above 80% by the end of 2006. A 90-95% coverage rate is currently estimated in Portuguese children below five, in line with what has been described in the UK and in other European countries.[2]

Despite a small number of patients, severity remains high, with 5-10% mortality rate.[4] Permanent impairments, amputations, hearing loss, developmental disorders and epilepsy occur in approximately 25% of survivors.[1,6]

The severity of meningococcal disease depends on several factors, namely host characteristics, the microorganism itself and the quality of healthcare.[7]

Over the last years, international guidelines on sepsis and septic shock management, namely those published in 2005 and 2009, have been recognized as very important in the improvement of the outcome of children affected by invasive meningococcal disease.[8,9] Several studies show this positive impact, namely related to an earlier awareness and more aggressive treatment of septic shock and also to an earlier referral of patients to central and more experienced paediatric ICUs.[7,10,11] The presence of a specialized paediatric inter-hospital transport has also been referred as a factor with potential impact on reducing mortality, an infrastructure which has been in place in the Central Region of Portugal since 2005 (STEP-INEM).[10,12]

Our study aimed to characterize children admitted to ICU with meningococcal invasive disease, to determine severity parameters and mortality.

MATERIAL AND METHODS

An observational study has been carried out through retrospective data collection. The study was carried out in the ICU (CIPE) of a tertiary paediatric reference hospital for the Central Region of Portugal.

Every child admitted between January 2000 and December 2011 (12 years) with a definite or probable diagnosis of invasive meningococcal disease was included.

Invasive meningococcal disease was defined according to the 2010 Centres for Disease Control and Prevention criteria. A definite diagnosis was considered upon the isolation of *Neisseria meningitidis* in a sterile fluid culture (blood, cerebrospinal fluid) and a probable diagnosis when clinical manifestations were compatible, in the absence of micro-organism isolation.[13] Sepsis, organ dysfunction and multi-organic failure have been defined according to the International Paediatric Sepsis Consensus Conference criteria.[8]

The following variables were collected through analysis of clinical records and database: year of admission, age, gender, time lapse between the start of disease and ICU admission, use of secondary inter-hospital transport (STEP-INEM), Meningococcus isolation and serotype, severity index (paediatric risk of mortality - PRISM score), organ dysfunction type, administered therapy, mortality and PRISM standardized mortality ratio.[14]

Two periods of time were considered, according to the year of hospital admission: period A from 2000 up to 2005 and period B from 2006 up to 2011 and the above mentioned variables were compared within these timeframes.

Data statistical analysis was carried out using Statistical Package for the Social Science® software, version 19. Our group of patients was characterised through assessment of central tendency and dispersion measures for quantitative variables and by determination of absolute and relative frequencies for qualitative variables. Normality testing (Kolmogorov-Smirnov) was used and as the quantitative variables did not present a normal distribution, they were therefore characterised by median and interquartile ranges (IQR). When comparing nominal and ordinal or quantitative variables without a normal distribution, the Mann-Whitney test was used. Chi-square or Fisher exact test were used to compare nominal variables, according to Cochran rules.

A 5% significance level was considered.

RESULTS

Seventy children with a diagnosis of meningococcal invasive disease were admitted over the study period, accounting for 2.4% of all ICU admissions. The distribution over the years was variable, with a minimum number of 0 patients in 2011 and a maximum number of 12 patients in 2002 (median of 5.5 patients/year) - see Fig. 1. Median age was 2.2 (IQR: 0.8-4.5). A male predominance was observed (41/70, 58.6%). Median time between disease onset and hospital admission to the CIPE was 15.6 hours (IQR: 10.8-20). The specialized paediatric inter-hospital transport system (STEP-INEM) was activated for ten patients.

Meningococcus was isolated in biological fluids in 60% of the patients (42/70), namely in blood cultures (29/42, 69.0%), cerebrospinal fluid cultures (5/42, 11.9%) or in both (8/42, 19.0%). The serogroup of *N. meningitidis* was identified for 19 patients (45.2%) and serogroup B was the most common (n=10), followed by C (n=8) and Y (n=1). Clinically, most patients (48/70, 68.6%) presented with rapidly progressing purpura and meningitis was diagnosed in a smaller group of patients (26/70, 37.1%). Organ dysfunction was a frequent event (66/70, 94.3%). As infection progressed, 44 (62.9%) patients developed multi-organic failure criteria. The most frequent complications were cardiovascular (64/70, 91.4%), followed by haematological (42/70, 60.0%) and respiratory (19/70, 27.1%). Most patients required cardiovascular support (65/70, 92.9%) and some needed invasive ventilation (19/70, 27.1%) and/or haemodiafiltration (3/70, 4.3%). Median PRISM score was 3% (IQR: 1-19%). During the study period 12 deaths occurred, corresponding to 17.1% of the patients.

Forty-six patients were included in period A and 24 in period B. When compared to other admission causes, we found a significant reduction in admissions related to meningococcal invasive disease from period A (3.4%) to period B (1.5%; p = 0.001; Chi-square). Median age was 2.4 in period A (IQR: 1.3-5.6) and 1.5 in period B (IQR: 0.6-4.2) (p = 0.160; Mann-Whitney). In period A, 45.7% (21/46) of the patients and 83.3% (20/24) in period B (p = 0.002; Chi-square) were male. Median time between disease onset and hospital admission to the CIPE was 14 hours

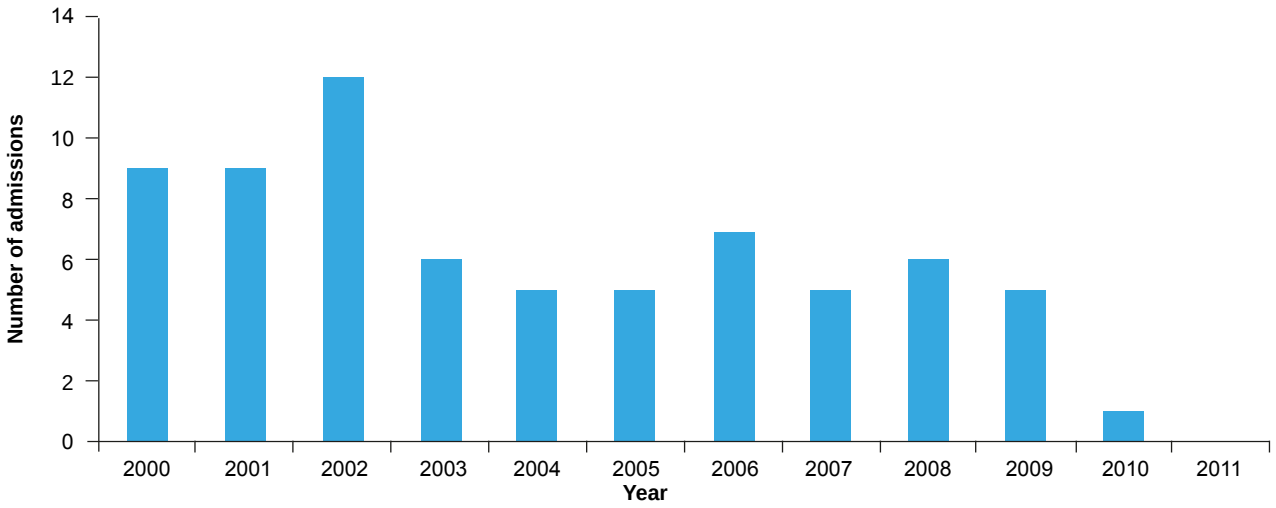

Figure 1 - Annual distribution of hospital admissions related to meningococcal disease (*n* = 70)

(IQR: 10.8-20.3) during period A and 13 hours (IQR: 9-18.8) during period B (p = 0,498; Mann-Whitney). Transport by the STEP-INEM system involved 6.5% and 29.2% of the patients during periods A and B, respectively (p = 0.026; Fisher exact test).

Meningococcus was identified in 54% (25/46) and 71% (17/24) of the patients, respectively during periods A and B (p = 0.181; Chi-square). Serogroup C was identified in 73% (8/11) of the patients over period A and in none (0/8) over period B (p = 0.003) - see Table 1. No significant difference in both periods regarding the presence of meningitis (A: 41% *vs.* B: 29%; p = 0.318; Chi-square) was found. Rapidly progressing purpura occurred in 78% of the patients over period A and in 50% over period B (p = 0.016; Chi-square). When organ dysfunction was compared, the patients in period A presented multi-organic failure (80%), disseminated intravascular coagulation (76%) and coma (22%) more frequently than patients in period B (29%, 29%, 0%; $p < 0.05$). Median PRISM score was 9.1% (IQR: 1.1-28.5) in period A and 2.3% (IQR: 1-5.7) in period B (p = 0.057). Mortality was 26% over period A and 0% over period B (p = 0.006) and PRISM standardized mortality ratio was 1.3 and 0 over period A and B, respectively (Table 2).

Table 1 - Temporal distribution of the number of patients per Meningococcus serogroup

Serogroup	Period A (*n* = 11)	Period B (*n* = 8)
C	8	0
B	3	7
Y	0	1

Comparison between serogroup C and other serogroups; p = 0.003; Fisher exact test.

Table 2 - Characterisation of time periods A and B regarding types of organ dysfunction and mortality

Organ dysfunction	Period A (*n* = 46)	Period B (*n* = 24)	*p* value
MOF	37	7	$p < 0,001$ (Chi-square)
Shock	43	21	$p = 0,406$ (Fisher exact test)
DIC	35	7	$p < 0,001$ (Chi-square)
Respiratory	17	2	$p = 0,011$ (Chi-square)
Renal	10	1	$P = 0,083$ (Fisher exact test)
Coma	10	0	$p = 0,012$ (Fisher exact test)
PRISM *score* (median)	9,1%	2,3%	$p = 0,057$ (Mann-Whitney)
Mortality	12	0	$p = 0,006$ (Fisher exact test)

MOF – multi-organic failure, DIC – disseminated intravascular coagulation

DISCUSSION

Over the last few years, a significant reduction in the number of admissions due to meningococcal disease in intensive care has been found, according to other descriptions[7,15] This change is in line with the decrease in the incidence of meningococcal invasive disease described in European epidemiological studies and it seems to be directly related to the introduction of anti-meningococcal C vaccination, that systematically occurred in several countries.[4]

In Portugal, upon the introduction of meningococcal C vaccination, vaccination coverage rates above 90% have been achieved and the incidence of this infection almost halved over the last years, currently estimated in approximately 0.61 cases/100,000 population.[4] This decrease in incidence was mainly related to the absence of new identified cases of serogroup C invasive meningococcal disease, in line with what has been described by other authors.[7,16]

In our study, in addition to the decrease of the number of

hospital admissions, a significant reduction in mortality has also been observed over the last years, with no reported deaths by meningococcal disease since 2005. This decrease in mortality, also described in other studies, does not seem to be explained by a lower severity of the cases, as we were not able to find any significant differences regarding severity scores, namely the PRISM score, over the two considered time periods.

Although the severity score used in our study did not show any differences in both periods, the patients in period A presented with more severe multi-organic failure, disseminated intravascular coagulation and coma. We attribute this difference to an improvement in the initial stabilization, obtained both from the presence of a specialized inter-hospital transportation system - carried out by experienced teams since 2005 - and from an earlier referral of patients to tertiary specialized medical units.[10,11,17] Despite a similar time between disease onset and ICU admission in both groups, patients in period B underwent an earlier and more effective clinical stabilization related to inter-hospital transportation. Over the last decade, different studies showed the impact of this transportation system and other measures in the better outcome of patients with sepsis, namely guideline implementation[10,11] and an earlier and more aggressive treatment of shock.[10,11,18-20] It would have been important, in order to demonstrate this impact, to have documented "early" shock recognition, as well as therapeutic management on both periods. This was not possible due to the retrospective nature of the study.

CONCLUSION

In conclusion, over the last years, there has been a significant decrease in the number of hospital admissions and in mortality related to meningococcal invasive disease. These results are probably explained by the introduction of anti-meningococcal C vaccination, improved initial clinical stabilization, earlier referral of patients to specialized medical units as well as increased availability of a secondary inter-hospital transport system since 2005.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest in the writing of this manuscript.

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