Intensive Care Med (2003) 29:1770–1773
DOI 10.1007/s00134-003-1948-z

Gender-based differences in children with sepsis and ARDS: The ESPNIC ARDS Database Group

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Received: 30 January 2003
Accepted: 16 July 2003
Published online: 15 August 2003

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Abstract Male gender predisposes to severe sepsis and septic shock. This effect has been ascribed to higher levels of testosterone. The ESPNIC ARDS database was searched, to determine if there was evidence of a similar male preponderance in severe sepsis in prepubertal patients in spite of low levels of male sex hormones at this age. A total of 72 patients beyond neonatal age up to 8 years of age with sepsis were identified. The male/female (M/F) ratio was 1.7 (1.0;2.7) and differed significantly from non-septic ARDS patients in this age group [n = 209; M/F = 1.0 (0.8;1.3)]. The highest M/F-ratio was observed in the first year of life. The gender-ratio was the same as reported in adult patients with sepsis. In infants between 1 month and 12 months of age, the ratio was 2.8 (1.2;6.1) (Chi^2= 5.6; P< 0.01), in children from 1 year to 8 years of age it was 1.2 (0.7;2.2) (n.s.). In a subgroup of patients with severe sepsis or septic shock, caused by other bacteria than

Neisseria meningitidis, the M/F-ratio was 2.1 (1.2;3.6) (Chi^2= 4.9; P<0.05), while in patients with meningococcal sepsis (n=20) the M/F-ratio was 1.0 (0.4;2.3). In prepubertal ARDS patients with sepsis an increased frequency of male patients is found, comparable to adults. No male preponderance exists in patients with ARDS due to meningococcal septic shock. Since levels of testosterone and other sex hormones are extremely low at this age, we conclude that factors others than testosterone are involved in the male preponderance in severe sepsis.

Background

A high proportion of male patients among surgical patients with sepsis was first reported by McGowan in 1975 [1]. Male gender as a risk factor for the development of severe sepsis and septic shock has been highlighted recently [2, 3, 4]. The interaction between gender and the occurrence of critical illness in children is not new. An excess morbidity of boys has been described in upper respiratory infection, bronchiolitis, pneumonia, and septicaemia [5]. The influence of sex hormones on the host immune response has been proposed as an explanation for this unequal gender distribution in sepsis [3, 6, 7, 8]. To investigate the influence of gender on the occurrence of severe sepsis and septic shock we analysed data of the ESPNIC ARDS database (www.meb.uni-bonn.de/ards). This database, originating from an informal German working group on paediatric Acute Respiratory Distress Syndrome (ARDS) and endorsed by the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) since 2000, has compiled clinical data on around 400 cases of paediatric ARDS since 1991. The data collection has been performed restrospectively and prospectively. All patients fulfil the definition criteria of ARDS according to the consensus conference [9]. Data have been made anonymous in accordance with European regulations [10].

To test the hypothesis that higher levels of testosterone or other sex hormones are responsible for male preponderance in severe sepsis and septic shock, the database was searched for patients without sepsis before puberty, in whom sex hormone levels are low.

Methods

The "ARDS Database" was searched for all prepubertal patients with a diagnosis of sepsis or septic shock, treated from 1 January 1991 through 31 December 2001. Precocious puberty is defined by the onset before the age of 8 years in females and 9 years in males. To avoid statistical bias, male patients between 8 years and 9 years of age were omitted. Patients with X-linked immunodeficiency (X-linked lymphoproliferative disease, Wiskott-Aldrich syndrome) were excluded. The database does not include any term neonates or ex-premature patients younger than 43 gestational weeks. Patient demographics and underlying diseases are given in Table 1. All patients fulfilled the criteria of severe sepsis or septic shock according to the ACCP/SCCM consensus conference, defining it as a systemic inflammatory syndrome (SIRS) in response to infection that is associated with acute organ dysfunction [11]. Descriptive statistics (frequency, 95% confidence interval) of the sex-ratio were applied to the group of patients with severe sepsis and/or septic shock as a whole, and to subgroups according to the causative agent, to chronic underlying diseases, and to age.

The frequency of male gender in the groups of patients with sepsis was compared to the frequency among ARDS patients of the same age group without sepsis, using the chi-square test where appropriate.

Table 1 Comparison of the gender-ratio (M/F-ratio) between prepubertal ARDS patients with and without sepsis

Acute causative disease	Male	Female	M/F-ratio	χ^2
Other than sepsis	105	104	1.0(0.8;1.3)	0.0; n.s.
Sepsis (total)	45	27	1.7(1.0;2.7)	3.2; P<0.05
Causative organism				
N. meningitidis	10	10	1.0(0.4;2.3)	0.00; n.s.
Other gram-negative	7	4	1.8(0.5;5.6)	n.a.
Gram-positive	7	2	3.5(0.8;15)	n.a.
Fungi, and not specified	21	11	1.9(0.9;3.9)	2.6; n.s
Organisms except *N. meningitidis* (total)	35	17	2.1(1.2;3.6)	4.9; P<0.05
Age	Male	Female	M/F-ratio	χ^2
1–12 months	22	8	2.8(1.2;6.1)	5.6; P<0.01
>12–96 months	23	19	1.2(0.7;2.2)	0.3; n.s.
Underlying chronic diseases	Male	Female	M/F-ratio	χ^2
None	22	15	1.5(0.8;2.8)	1.1; n.s.
Immunocompromising disease	15	9	1.7(0.7;3.7)	1.3; n.s.
Other chronic disease	8	3	2.7(0.8;9.3)	n.a.

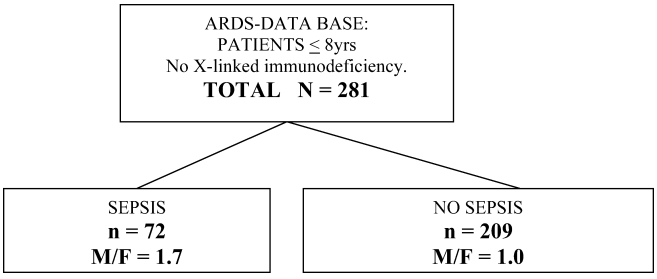

Fig. 1 Gender distribution (Male/Female ratio) in prepubertal patients with ARDS with and without sepsis

Results

Information on patient gender was available in 384/391 cases registered from January 1991 to December 2001. Five patients suffered from X-linked immunologic disorders (Wiskott-Aldrich Syndrome, septic granulomatosis, X-linked lymphoproliferative disease). Excluding patients older than 8 years and patients with X-linked chronic underlying disease, 281 cases were eligible for analysis (Fig. 1). Seventy-two patients had a diagnosis of sepsis with an overall mortality of 43.6%. The highest mortality (83.3%) was observed in immunocompromised patients, in immunocompetent patients it was 24%. Overall mortality declined from 58.3% before 1996 to 37.5% in later years. Mortality was 40% in boys and 53% in girls.

The descriptive statistics of the groups of patients are given in Table 1. Compared to patients without a diagnosis of sepsis, frequency of male gender was increased in the total group of patients with severe sepsis or septic shock (Table 1). Patients in various subgroups were not equally affected by an increased M/F-ratio. No male preponderance was found in a subgroup of meningococcal septic shock and it was not significant in children after infancy.

Discussion

Our data show that the increased prevalence of male gender in patients with severe sepsis and septic shock exists before the onset of puberty. There is no difference to the sex ratio observed in adults. Wichmann [3] reports a M/F-ratio of 1.86 in adult surgical ICU patients with an odds ratio for the development of septic shock of 1.5. The proportion of male patients in children with sepsis with ARDS is even higher than recently reported by Watson et al. [12], who found a M/F-ratio of 1.22 and 1.33 in infants and in children from 1 year to 9 years of age, respectively. This study analysed data of 9,675 patients from the USA, including neonates, who were treated in 1995 and had a diagnosis of sepsis with failure of one or more organ systems. A low case fatality rate of 10% shows that the average severity of disease in this analysis was lower than in patients of the ARDS database.

We found only a moderate increase in the M/F-ratio, comparable to the observation of Watson et al. [12] in children beyond infancy, while infants from 1 month to 12 months of age showed marked male preponderance. The difference between both age groups cannot be explained by the influence of sex hormones. No increased frequency of male gender was observed among patients with sepsis due to *N. meningitidis*. Seventy-five percent of these patients were older than 1 year. This may contribute to the unequal M/F-ratio in the two age groups. Unfortunately, the low number of patients and the lack of information about the causative organism in nearly half of the patients made multivariant statistical analysis impossible.

The only subgroup caused by a single organism, large enough to allow statistical testing, were patients with meningococcal sepsis. An equal gender distribution in meningococcal septic shock was also described in the patient characteristics of the rBPI21-study [13] and observed in the patients investigated for PAI-1-gene polymorphism (W. Zenz, personal communication). Patients with a severe course of meningococcal septic shock differ from others by the presence of purpura fulminans. Arterial thrombotic occlusion is pivotal for the clinical course in purpura fulminans and individual characteristics of the coagulation system predispose to a more severe course. Geishofer et al. [14] described an increased frequency of the 4G/4G polymorphism of the promoter region of the plasminogen activator inhibitor 1 (PAI-1) gene in patients with severe meningococcal sepsis, especially in patients with ARDS. This polymorphism correlates with a more severe course of the disease. PAI-1 is inherited autosomally. This may explain why no male preponderance was observed in patients with meningococcal septic shock.

Male preponderance was more pronounced in patients with sepsis-induced ARDS, due to other bacteria than *N. meningitidis*. The high proportion of male individuals is not explained by an elevated M/F-ratio in patients at risk. Severe sepsis and septic shock due to other organisms than *N. meningitidis* as the cause of paediatric ARDS mostly occurred in patients with immunocompromising disease, which in majority resulted from malignant diseases or in patients with other chronic underlying disease. It is a major disadvantage of this type of study that no exact denominator in terms of patients with chronic disease in the total population or total number of those patients treated at the participating institutions is available. It is known, however, that the M/F-ratio in paediatric patients with malignant disease is below 1.2/1 [15]. Patients with X-linked immuncompromising disease were excluded from our analysis. Selection bias could evolve from the fact that critical respiratory illness in children predominantly affects male patients [5]. However, the M/F-ratio was only 1.12 in patients in whom sepsis and ARDS were secondary to pneumonia, and no male preponderance was found in non-septic pae-

diatric ARDS cases. Selection bias might also result from male preponderance in immunocompetent patients with chronic disease. In these patients the need of invasive procedures or an impaired inability to clear secretions eventually increase the risk of sepsis. However, the M/F-ratio in infants with ARDS without sepsis was 1.35, while the M/F-ratio in patients with sepsis of the same age group was 2.7. From this we conclude that the observed gender difference is not explained by selection bias. Testosterone levels in prepubertal children are extremely low and are below the levels in adult women. Therefore, it is unlikely that the observation of a comparable sex-ratio in pre- and postpubertal patients with sepsis is due to the presence of high levels of testosterone or the absence of female sex. This is further supported by the observation that in adults the male preponderance of severe sepsis is lower in the age group with highest testosterone levels, in adolescents, and adult patients below 30 years of age [12, 16]. In contrast, a strong male preponderance is found in low birth-weight infants [12]. Neonates are not included in our study.

Since higher levels of male sex hormones are no explanation for the observed gender difference, it is likely that variations of X-chromosomal encoded regulatory factors of the immune system are contributing to a proinflammatory shift in immune response. These gender effects seemingly are not independent from the causative organism.

References

1. MacGowan JE, Barnes MW, Finland N (1975) Bacteremia at Boston City Hospital: occurrence and mortality during 12 selected years (1935–1972) with special reference to hospital-acquired cases. J Infect Dis 132:316–335
2. Schröder J, Kahlke V, Staubach KH, Zabel P, Stüber F (1998) Gender differences in human sepsis. Arch Surg 133:1200–1205
3. Wichmann MW, Inthorn D, Andress HJ, Schildberg FW (2000) Incidence and mortality of severe sepsis in surgical intensive care patients: the influence of patient gender on disease process and outcome. Intensive Care Med 26:167–172
4. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky R (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 29:1303–1310
5. Tasker RC (2000) Gender differences and critical medical illness. Acta Paed Scand 89:621–622
6. Angele MK, Schwacha MG, Ayala A, Chaudry IH (2000) Effect of gender and sex hormones on immune responses following shock. Shock 14:81–90
7. Losonczy G, Kriston T, Szabo A, Muller V, Harvey J, Hamar P, Heemann U, Baylis C (2000) Male gender predisposes to development of endotoxic shock in the rat. Cardiovasc Res 47:183–91
8. Ikejima K, Enomoto N, Iimuro Y, Ikejima A, Fang D, Xu J, Forman DT, Brenner DA, Thurman RG (1998) Estrogen increases sensitivity of hepatic Kupffer cells to endotoxin. Am J Physiol 274:G669–76
9. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, LeGall JR, Morris A, Spragg R, The Consensus Committee (1994) Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. Intensive Care Med 20:225–232
10. European Parliament (1995) Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data
11. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/ Society of Critical Care Medicine. Chest 101:1644–1655
12. Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC (2003). The epidemiology of severe sepsis in newborns, infants, and children in the U.S. AJRCCM167:695–701
13. Levine M, Quint PA, Goldstein B, Barton P, Bradley JS, Shemie SD, Yeh T, Kim SS, Cafaro DP, Scannon PJ, Giroir BP (2000) Recombinant bactericidal/permeability-increasing protein (rBPI21) as adjunctive treatment for children with severe meningococcal sepsis: a randomised trial. Lancet 356:961–967
14. Geishofer G, Mannhalter C, Häring D, Triebl K, Endler G, Panzer S, Zenz W (2002) Der 4G/4G-Polymorphismus der Promotorregion des Plasminogen Aktivator Inhibitor 1 Gens korreliert mit der Prognose der Meningokokkensepsis. Abstract presented at the "Jahrestagung Österreichische Gesellschaft für Kinder- und Jugendheilkunde, Wien"
15. German Childhood Cancer Registry (2000) Annual Report 2000. IMBEI, Mainz, p34
16. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 29:1303–1310