SEX-BASED DIFFERENCES IN PATIENTS WITH COMMUNITY-ACQUIRED BACTERIAL MENINGITIS: A PROSPECTIVE NATIONWIDE COHORT STUDY

Sara Dias[1,2], Matthijs C. Brouwer[2], Merijn W. Bijlsma[2], Arie van der Ende[3], Diederik van de Beek[2]

1- Department of Neurology, Centro Hospitalar de Lisboa Central (Portugal) 2- Department of Neurology, Center of Infection and Immunity Amsterdam (CINIMA), Academic Medical Center (The Netherlands)
3- Department of Medical Microbiology, The Netherlands Reference Laboratory for Bacterial Meningitis, Center of Infection and Immunity Amsterdam (CINIMA), Academic Medical Center (The Netherlands)

Introduction and aims

Sex-based issues have been increasingly recognised in infectious diseases, influencing susceptibility, immune reaction, disease course and response to treatment;[1,2] females are thought to have more robust immune responses to infection than males.[3]
Our aim was to investigate sex-based differences in clinical features, management and outcome in adults with community-acquired bacterial meningitis.

Methods

From 2006-14, adults (>16 years) with community-acquired bacterial meningitis were prospectively evaluated in an ongoing genetic association study in the Netherlands (the MeninGene study).[4] We used parametric and nonparametric tests to compare features between men and women, and logistic regression to examine the association between sex and unfavourable outcome, along with previously known predictors,[5] using IBM SPSS (v22.0).

Results

Table 1 | Characteristics of the study population.

Characteristic *	Men (n=720)	Women (n=720)	p-value
Age (years)	60 (45-68)	62 (49-71)	0.002
History of otitis/sinusitis	219/718 (30)	270/712 (38)	0.003
Remote head injury	42/679 (6)	14/673 (2)	<0.001
Immunocompromise	214/720 (30)	159/720 (22)	0.001
Alcoholism	63/662 (10)	24/675 (4)	<0.001
HIV-positive	10/691 (1)	2/698 (0.3)	0.02
Seizures	60/689 (9)	39/691 (6)	0.03
Symptoms and signs on presentation			
Headache	515/623 (83)	519/623 (83)	0.76
Neck stiffness	461/662 (70)	533/685 (78)	<0.001
Fever (≥ 38 ºC)	528/706 (75)	522/711 (73)	0.56
GCS score	11 (9-14)	11 (9-14)	0.07
Focal neurologic deficits	208/715 (29)	174/716 (24)	0.04
Laboratory findings			
Serum ESR (mm/h)	33 (17-66)	48 (28-75)	<0.001
Serum CRP (mg/l)	170 (78-288)	211 (97-328)	<0.001
CSF white cells (/uL)	2528 (570-7540)	2236 (507-6229)	0.07
CSF protein (g/L)	3.8 (2.2-6)	4 (2.3-6.2)	0.63
CSF:blood glucose ratio	0.06 (0-0.27)	0.03 (0-0.25)	0.08
Dutch meningitis risk score †	26±12	28±12	0.01
Clinical course			
Neurological complications	412/515 (80)	383/482 (80)	0.83
Systemic complications	302/706 (43)	238/702 (34)	0.001
Respiratory failure	192/696 (28)	172/690 (25)	0.26
ICU admission	455/720 (63)	400/720 (56)	0.003
Mechanical ventilation	264/693 (38)	203/689 (29)	0.001
Death	133/720 (18)	113/720 (16)	0.16
Unfavourable outcome	282/720 (39)	257/720 (36)	0.17
Dexamethasone	190/537 (35)	175/556 (32)	0.17
No dexamethasone	85/170 (50)	75/147 (51)	0.86

* Values are n/N (%), median (IQR) or mean±SD. † Validated bedside risk score ranging from 0-65.

We identified 1440 cases (**Table 1**). Women were older than men, and more frequently presented with otitis/sinusitis and neck stiffness and less frequently with focal neurological deficits and seizures. Males more frequently had a history of head injury and immunocompromise. CSF profile was similar in both sexes, but women had higher levels of serum acute phase reactants. Pathogen distribution differed due to a higher rate of listeria meningitis in men (**Fig. 1**).

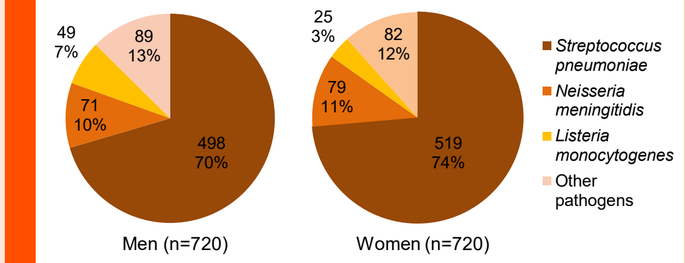

Fig. 1 | Causative pathogens.

Table 2 | Predictors of unfavourable outcome (Glasgow Outcome Scale<4).

Characteristic *	Favourable (n=901)	Unfavourable (n=539)	Multivariate OR (95% CI) †	p-value
Male sex	438/901 (49)	282/539 (52)	1.56 (1.13-2.16)	0.007
Age >70 years	148/901 (16)	194/539 (36)	2.22 (1.54-3.22)	<0.001
Otitis or sinusitis	345/895 (39)	144/535 (27)	0.77 (0.55-1.07)	0.12
Immunocompromise	198/901 (22)	175/539 (32)	1.38 (0.97-1.96)	0.08
Headache	731/838 (87)	303/408 (74)	0.67 (0.45-1.00)	0.05
Heart rate (bpm)	98 (82-110)	102 (89-120)	1.06 (0.99-1.14)	0.11
GCS score	12 (9-14)	10 (8-13)	0.91 (0.86-0.96)	0.001
Cranial nerve palsy	49/812 (6)	62/457 (14)	2.82 (1.66-4.78)	<0.001
CSF white cells <1000/uL	222/864 (26)	250/514 (49)	1.86 (1.33-2.59)	<0.001
Positive blood culture	560/796 (70)	383/477 (80)	1.72 (1.17-2.52)	0.006
CRP (mg/l)	161 (71-272)	248 (134-370)	1.03 (1.02-1.04)	<0.001

* Values are n/N (%) or median (IQR) . † OR for GCS score is per 1 point increase; OR for heart rate and CRP per 10 unit increase.

During clinical course, systemic complications were more frequent in men. Despite greater illness severity (based on the Dutch meningitis risk score), women were less likely to be admitted to an ICU (adjusted OR 0.66, 95% CI 0.52-0.85; p=0.001) or receive mechanical ventilation (adjusted OR 0.52, 95% CI 0.36-0.74; p<0.001) than men.

Rates of unfavourable outcome were high, and in a multivariate analysis, male sex was an independent predictor of adverse outcome (**Table 2**).

Dexamethasone improved prognosis in both sexes, and this effect was more prominent in women (RR 0.62, 95% CI 0.50-0.75; ARR 20%) than in men (RR 0.71, 95% CI 0.59-0.86; ARR 15%), although we did not find a significant interaction between sex and dexamethasone (p=0.40).

Conclusions

- There are sex-based differences in patients with community-acquired bacterial meningitis.
- Male sex is an independent risk factor for adverse outcome, and a stronger pro-inflammatory response may render women more responsive to treatment with dexamethasone.

Sources: [1] Klein SL. The effects of hormones on sex differences in infection: from genes to behavior. Neurosci Biobehav Rev 2000;24:627-38. [2] Klein SL, Jedlicka A, Pekosz A. The Xs and Y of immune responses to viral vaccines. Lancet Infect Dis 2010;10:338-49. [3] Fish EN. The X-files in immunity: sex-based differences predispose immune responses. Nat Rev Immunol 2008;8:737-44. [4] van de Beek D. Progress and challenges in bacterial meningitis. Lancet 2012;380:1623-4. [5] Bijlsma MW, Brouwer MC, Kasanmoentalib ES, et al. Community-acquired bacterial meningitis in adults in the Netherlands, 2006-14: a prospective cohort study. Lancet Infect Dis 2015;16:339-47.

Contact: s.dias@amc.nl

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