Hearing impairment after childhood bacterial meningitis dependent on etiology in Luanda, Angola

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ABSTRACT

Objective: Childhood bacterial meningitis (BM) damages hearing, but the potential of different agents to cause impairment in developing countries is poorly understood. We compared the extent of hearing impairment in BM caused by Haemophilus influenzae type b (Hib), Streptococcus pneumoniae or Neisseria meningitidis among children aged 2 months to 13 years in Luanda, Angola.
Methods: Hearing of 685 ears of 351 (78%) survivors among 723 enrolled patients was tested by brainstem-evoked response audiometry on day 7 of hospitalization. The causative agent was sought by cerebrospinal fluid culture, PCR or the latex-agglutination test.
Results: Altogether, 45 (12%) of the survivors were deaf (threshold >80 dB), and 20 (6%) had a threshold of 80 dB. The incidence of any kind of hearing loss, with ≥60 dB, was 34% with Hib, 30% with S. pneumoniae, 19% with N. meningitidis and 33% with other bacteria. Examining all ears combined and using the ≥60 dB threshold, the agents showed dissimilar harm ($P = 0.005$), Hib being the most frequent and N. meningitidis the most infrequent cause. Compared to other agents, S. pneumoniae more often caused deafness ($P = 0.025$) and hearing impairment at ≥60 dB ($P = 0.017$) in infants, whereas this level of hearing loss in older survivors was most commonly caused by Hib ($P = 0.031$).
Conclusions: BM among children in Angola is often followed by hearing impairment, but the risk depends on the agent. S. pneumoniae is a major problem among infants, whereas Hib is mainly a risk beyond 12 months. N. meningitidis impairs hearing less frequently.

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1. Introduction

Childhood bacterial meningitis (BM) remains a global problem, especially in developing countries where the incidence is higher, and mortality and complications more common than in the industrialized world [1–3].

Hearing loss is the most common complication [2,4,5], its severity ranging from mild hearing impairment to total deafness. Globally, BM is the most important cause of acquired hearing loss among children [6], as 10–34% of survivors develop it to some extent [2]. Hearing impairment can be unilateral or bilateral. The exact mechanisms remain unclear.

Children with pneumococcal meningitis are especially prone to adverse outcomes [2,4]. Although the association between pathogens and hearing impairment depends on circumstances, Streptococcus pneumoniae (S. pneumoniae) has shown the highest risk in many retrospective [5–7] and a few small prospective studies [8–10] conducted in western countries. Few data are available from the developing world.

Against this background we set up the present study to explore the frequency of hearing impairment in childhood BM, with special attention to the causative agents in resource-poor settings. Because hearing impairment may be unilateral, we analyzed the children's hearing and the ears separately.

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2. Methods

2.1. General

The present study forms part of our large [N 723] prospective, randomized treatment trial (ISRCTN62824827) in Hospital Pediátrico David Bernardino, Luanda, Angola [11]. The ethics committee of the hospital approved the study, and a legal guardian's consent was obtained prior to enrolment. If the guardian was illiterate, he or she expressed agreement with a fingerprint once the study had been explained by the attending physician.

The set-up details have been published earlier [11]. In short, lumbar puncture and Gram staining were performed on all patients attending with symptoms and signs suggestive of BM. Cerebrospinal fluid (CSF) samples were cultured routinely, and the latex agglutination test for *Haemophilus influenzae* type b (Hib), *S. pneumoniae* (*S. pneumoniae*), and *Neisseria meningitidis* (*N. meningitidis*) was carried out in cases where Gram staining and culture remained negative. The remaining CSF sample was frozen and transported to Lisbon (National Health Institute) for PCR testing. BM was considered confirmed with a positive CSF culture or PCR. A child with symptoms and signs of BM with positive blood culture, or with at least two of the following: leucocyte concentration in CSF exceeding 100×10^6/L (predominantly polymorphs), positive Gram-staining, positive latex-agglutination test, or serum C-reactive protein concentration higher than 381 mmol/L (40 mg/L), was considered confirmed with BM. Basic blood tests, malaria thick and thin films, and HIV screening were also performed routinely.

2.2. Auditory testing and patient categorization

On day 7 (±1) in hospital, trained study nurses measured hearing with a brainstem-evoked response audiometry (BERA) device (MADSEN Octavus Otometrics, Taastrup, Denmark), using auditory click stimuli of 40 dB, 60 dB, and 80 dB. These hearing thresholds served to indicate normal hearing, moderate to severe hearing impairment, and severe hearing loss, respectively; a hearing threshold >80 dB indicated deafness. The BERA results were uploaded to the Audiology Center of Helsinki University Hospital, where all readings were performed by an expert who remained blinded to study details.

Cases were categorized into six etiological groups by causative agent: Hib, *S. pneumoniae*, *N. meningitidis*, other identified bacteria, confirmed BM with unknown etiology, or BM not confirmed.

Data were analyzed with StatView software (version 5.1.). The chi-square test served to test the association between different pathogens and hearing levels. All hearing thresholds were analyzed separately.

2.3. Literature search

A literature search using the Ovid Medline database and combining the keywords "bacterial meningitis" (limited to humans) and "child" with "developing country", "hearing loss", or "prospective study", yielded 84, 240 and 30 trials, respectively. Combining more than three keywords at a time yielded no significant results. We also scanned references from existing meta-analyses [2,4], reviews [12] and previously included articles. In many trials the abstract mentioned no exclusion criteria, so we revised the full text. In total, 53 trials from developing countries were revised in this way. The 13 meeting the inclusion criteria appear in Table 2.

3. Results

Of the 723 patients enrolled in the study, 451 (63%) children survived. On day 7, hearing testing was successfully completed on 351 (78%) children and 685 (76%) ears. The characteristics of the patients are summarized in Table 1. Among children who

Table 1
Characteristics of survivors from bacterial meningitis from Luanda, Angola.

	Streptococcus pneumoniae	*Haemophilus influenzae*	*Neisseria meningitidis*	Other bacteria*	Other confirmed bacterial meningitis**	Not confirmed bacterial meningitis	All	*P*-value
	n = 102 N (%) Median (IQR)	n = 126 N (%) Median (IQR)	n = 42 N (%) Median (IQR)	n = 13 N (%) Median (IQR)	n = 65 N (%) Median (IQR)	n = 103 N (%) Median (IQR)	n = 451 N (%) Median (IQR)	
Age in months	13.5 (33)	7 (6)	32 (56)	7 (30)	17 (35)	25 (54)	12 (33)	<0.0001
Male sex	55 (54)	57 (45)	24 (57)	4 (30.7)	39 (60)	58 (56)	237 (53)	0.1773
Glasgow coma score	12 (7)	13 (6.25)	15 (3)	15 (5)	14 (3)	14 (6)	14 (6)	0.0085
Previous antimicrobials	26 (25)	58 (46)	10 (24)	7 (54)	29 (45)	30 (30)	160 (35)	0.0035
Seizures at home	64 (63)	81 (64)	14 (33)	7 (54)	41 (63)	75 (73)	282 (63)	0.001
Seizures at hospitalization	46 (45)	60 (48)	7 (17)	6 (46)	26 (40)	45 (44)	190 (42)	0.0194
Seizures at ward	59 (58)	76 (60)	7 (17)	7 (54)	30 (46)	43 (42)	222 (49)	<0.0001
Sick for how many days	4 (3)	5 (4)	3 (2)	5 (3)	3 (3)	4 (4)	4 (4)	0.0003
CSF glucose concentrations (mmol/L)	10 (13)	14 (19)	10 (13)	9 (18)	13 (18)	38 (24)	16 (28)	<0.0001
CSF leucocyte count (×10E6/L)	1250 (2430)	1065 (1970)	2450 (4789)	3200 (2819)	880 (2796)	133 (292)	862 (2165)	<0.0001
Haemoglobin at hospitalization (g/L)	7.1 (2.2)	7.0 (2.2)	8.7 (2.0)	8.0 (1.5)	8.0 (2.4)	8.0 (2.0)	7.8 (2.3)	<0.0001
Leucocytes during hospitalization	13 (12)	18 (14)	13 (8)	12 (5)	12 (5)	12 (7)	14 (10)	0.0006
Fever at hospitalization	37.6 (1.2)	38 (1.6)	37.4 (1.5)	37.7 (2)	37.2 (1)	37.5 (1)	37.5 (1)	0.0764
Highest sedimentation rate	86 (55)	100 (59)	78 (55)	61 (50)	88 (60)	61 (69)	83 (59)	0.0005
CRP at hospitalization (mg/L) (day 1–2)	161 (18)	156 (82)	138 (92)	90 (122)	144 (85)	34 (92)	140 (104)	<0.0001
HIV positive	11 (11)	7 (6)	2 (5)	1 (8)	3 (5)	6 (6)	30 (7)	0.6374
Malaria parasites	38 (37)	35 (28)	9 (21)	3 (23)	10 (15)	43 (14)	138 (31)	0.036
Tuberculin test >10 mm	6 (6)	8 (6)	4 (10)	4 (31)	4 (6)	19 (18)	45 (10)	0.0042
Ataxia (day 7)	77 (75)	84 (67)	16 (38)	8 (62)	42 (65)	47 (46)	274 (61)	<0.0001

* *Proteus mirabilis* (3), *Salmonella* spp (3), other streptococcal species (3), *Staphylococcus aureus* (2), *Klebsiella* (1) and unidentified bacteria (1).
** Symptoms and signs of BM with positive blood culture, leucocyte concentrations in CSF exceeding 100×10^6/L, CRP concentration higher than 381 mmol/L (40 mg/L) or positive gram staining.