Predictors of Acute Bacterial Meningitis in Children from a Malaria-Endemic Area of Papua New Guinea

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Abstract. Predictors of acute bacterial meningitis (ABM) were assessed in 554 children in Papua New Guinea 0.2–10 years of age who were hospitalized with culture-proven meningitis, probable meningitis, or non-meningitic illness investigated by lumbar puncture. Forty-seven (8.5%) had proven meningitis and 36 (6.5%) had probable meningitis. Neck stiffness, Kernig's and Brudzinski's signs and, in children < 18 months of age, a bulging fontanel had positive likelihood ratios (LRs) ≥ 4.3 for proven/probable ABM. Multiple seizures and deep coma were less predictive (LR = 1.5–2.1). Single seizures and malaria parasitemia had low LRs (≤ 0.5). In logistic regression including clinical variables, Kernig's sign and deep coma were positively associated with ABM, and a single seizure was negatively associated ($P \leq 0.01$). In models including microscopy, neck stiffness and deep coma were positively associated with ABM and parasitemia was negatively associated with ABM ($P \leq 0.04$). In young children, a bulging fontanel added to the model ($P < 0.001$). Simple clinical features predict ABM in children in Papua New Guinea but malaria microscopy augments diagnostic precision.

INTRODUCTION

Although meningitis is an important contributor to childhood disability and mortality in developing countries,^{1–4} appropriate vaccinations and antibiotic therapy are often unavailable and laboratory facilities may be limited.^{5–8} Diagnosis and management can therefore be challenging,⁹ especially when young children with ABM present with non-specific features, including lethargy or irritability rather than the classic clinical signs of meningeal irritation.¹⁰ In malaria-endemic areas, the symptoms and signs of severe malarial illness can overlap with those of ABM, further complicating assessment.^{11,12} Lumbar puncture is commonly recommended as a routine part of the investigation of febrile illness of uncertain etiology in this setting,^{13,14} even though reliable biochemical and microbiologic testing of cerebrospinal fluid (CSF) may not be available.

Ideally, the clinical features of a febrile child should inform diagnosis and facilitate rational initial treatment where there is no laboratory support. In studies from the highlands of Papua New Guinea, where there is no malaria transmission⁸ and from countries in Africa with holo-endemic *Plasmodium falciparum* malaria,^{9,15} neck stiffness and a bulging fontanel were independently associated with ABM. Other features such as refusal to eat, staring eyes, and convulsions were inconsistent associates. Microscopy is often available in facilities treating febrile children in malaria-endemic areas, but the presence of malaria parasites on a blood film did not add significantly to clinical variables in studies of predictors of ABM in children in Africa with severe febrile illness.^{9,15}

A recent systematic review of the clinical features of pediatric ABM in which 8 of 10 included studies were from tropical countries¹⁶ concluded that many individual predictive

variables and especially their combinations warranted further evaluation. In addition, available data from malaria-endemic versus non-malaria-endemic areas^{8,9,15} emphasize that clinical prediction algorithms for ABM will depend on local epidemiology. Because low-lying areas of Papua New Guinea and other countries in the Oceania region are epidemiologically distinct from the highlands of Papua New Guinea and sub-Saharan Africa in that there is transmission of *P. vivax* as well as *P. falciparum*, the aim of the present study was to prospectively identify clinical and basic laboratory predictors of ABM in well-characterized severely ill children who came to the provincial referral hospital in Madang Province on the northern coast of mainland Papua New Guinea.

MATERIALS AND METHODS

Patients. From November 2007 through May 2010, children 2 months to 10 years of age admitted to Modilon Hospital in Madang, Papua New Guinea were screened for eligibility for enrolment into a longitudinal observational study of severe childhood illness. The estimated age-specific populations of children in Madang Province who are < 1 year of age, 1–4 years of age, and 5–9 years of age are 12,000, 60,000 and 45,000, respectively.¹⁷ These children are exposed to hyperendemic transmission of *P. falciparum* and *P. vivax*,¹⁸ with approximately 50 infective bites/child/year.¹⁹ The *Haemophilus influenzae* type b (Hib) vaccine was added to the national vaccine schedule in 2007 but was not implemented at a local level until 2008. Pneumococcal vaccination is not yet part of the vaccine schedule.

Children were eligible for recruitment if a lumbar puncture had been performed for suspected ABM. The decision to proceed to lumbar puncture was made by attending ward doctor after initial clinical and laboratory assessment in accordance with local protocols.^{13,14} The study was approved by the Papua New Guinea Institute of Medical Research Institutional Review Board and the Medical Research Advisory Committee

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of the Papua New Guinea Health Department. Written informed consent for participation was obtained from parents or guardians of children.

Initial assessment. A standardized case report form was completed by research nurses. This form included demographic details, history of current/past illness, examination findings, and results of investigations. Clinical signs of meningeal irritation were neck stiffness (inability to flex the neck so that the chin touched the upper chest), a positive Kernig's sign (straightening of the knee joint eliciting discomfort with the hip and knee joints flexed to 90°), a positive Brudzinski's sign (involuntary hip flexion from 0° elicited on neck flexion), or a bulging fontanel in children < 18 months old.²⁰ Deep coma and impaired consciousness were defined as a Blantyre coma score (BCS)²¹ ≤ 2 and ≤ 4 , respectively.

Cerebrospinal fluid was examined by using standard methods.²⁰ An adjusted leukocyte count ≥ 20 cells/mm³ was considered evidence of meningeal inflammation. If a leukocyte count ≥ 10 cells/mm³ was present, CSF was centrifuged and the sediment was used to prepare a slide for Gram staining. An aliquot of sediment was inoculated on to chocolate and blood agar plates that were incubated in an atmosphere of 5% CO₂ for up to 72 hours. An Indian ink stain was performed on all samples with > 10 leukocytes/mm³. The CSF samples with ≥ 10 leukocytes/mm³ and no cultured pathogen underwent latex agglutination testing (Wellcogen™; Remel Europe Limited, Dartford, United Kingdom) for *Streptococcus pneumoniae*, Hib, and *Neisseria meningitidis*.

When available, venous blood (1–3 mL) was placed in BACTEC™ PEDS PLUS/F bottles (Becton Dickinson, Sparks, MD) for culture by using the BACTEC™ system. Preliminary identification of *S. pneumoniae* was based on the presence of Gram-positive cocci that formed flat α -hemolytic colonies with inhibition zone > 14 mm around an optochin disc. Small gram-negative coccobacilli growing preferentially on chocolate agar were assumed to be *H. influenzae*. Coagulase-negative staphylococci, *Corynebacterium*, and *Bacillus* spp. isolated from blood or CSF were considered contaminants. Invasive isolates were stored frozen in skim-milk broth until confirmatory identification, serotyping, and susceptibility testing was performed. The presence of malaria parasites was determined by examination of Giemsa-stained thick blood smears by at least two trained microscopists.²²

Patients were categorized as proven bacterial/fungal meningitis (CSF leukocyte count ≥ 20 cells/mm³ plus a positive culture from CSF or blood, a positive latex antigen test result, or *Cryptococcus gattii* identified by Indian ink CSF staining); probable meningitis (CSF leukocyte count ≥ 20 cells/mm³ and with negative CSF culture, negative latex antigen test result, and no *C. gattii* identified by Indian ink staining; or neither proven nor probable meningitis).

Inpatient management. Children were reviewed at least daily until discharge or death. Treatment was according to current Papua New Guinea national recommendations^{13,14} that include empiric antimalarial and antibiotic therapy for all severely ill children. Initially, ceftriaxone was given to children < 12 months of age with proven ABM. Older children received chloramphenicol, 25 mg/kg every 6 hours with ceftriaxone substituted at 48 hours if there was no clinical improvement. From late in 2008 when all Hib isolates were found to be chloramphenicol resistant, parenteral ceftriaxone, 50 mg/kg twice a day, was administered as initial

therapy for all children if CSF features suggested ABM, with reversion to chloramphenicol if cultures were negative. Although not specified in national recommendations, a similar strategy has been successfully applied in Papua New Guinea research settings.²³ Dexamethasone was not routinely given in conjunction with the first dose of antibiotics. Children without proven meningitis who did not respond to two weeks of antibiotic therapy were given empiric anti-tuberculosis treatment.

Data analysis. Data are presented as median and interquartile range. Between-group comparisons were performed by using non-parametric methods. Odds ratio, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are presented with 95% confidence intervals (CIs). Positive (LR+) and negative (LR-) likelihood ratios were also calculated. Independent predictors of ABM were identified by using backward stepwise logistic regression. Candidate variables other than age were included on the basis of biological plausibility and $P < 0.10$ by bivariate regression analysis. The most parsimonious model was chosen by using the minimum Aikake's information criterion after the removal of each variable.

RESULTS

Diagnostic categorization. During the 30-month study period, 2,725 children were admitted (Figure 1). Of these children, 554 (20.3%) were 2 months to 10 years of age and underwent lumbar puncture. Reported indications for lumbar puncture were seizure(s) (38.5%), signs of meningeal irritation (21.4%), impaired consciousness (12.5%), other neurologic signs (8.7%), and irritability (5.6%). The median age of the children was 24 (8–56) months and 57.3% were boys. Ninety-five (18%) were deeply comatose (BCS ≤ 2) and 170 (33.1%) had multiple convulsions.

Forty-seven (8.5%) and 36 (6.5%) children who underwent lumbar puncture were given a diagnosis of proven or probable meningitis, respectively. Based on above numbers and local population data,¹⁷ the annual incidence rate (95% CI) for proven ABM was 100 (64–136), 7 (3.5–10.5), and 5 (0–10) cases per 100,000 per year for children 2–11 months, 1–4 years, and 5–9 years of age, respectively. The remaining 471 children had malaria with cerebral involvement (21.8%), simple febrile seizure (15.7%), febrile encephalopathy (7.6%), or other

FIGURE 1. Consort diagram of screened pediatric admissions to Modilon Hospital, Madang Province, Papua New Guinea.

diagnoses (54.7%). The latter group comprised those with respiratory infections (27.9%), malaria without cerebral involvement (19.0%), diarrheal illness (11.6%), other unspecified infections (31%), or non-infective illnesses with non-specific signs requiring lumbar puncture to exclude ABM (10.5%).

Features of acute bacterial meningitis. The clinical signs, laboratory features and outcome of children with proven or probable ABM and those with non-meningitic illness are summarized in Table 1. The children with proven ABM were more likely to have multiple convulsions and a positive Brudzinski's sign than those with probable ABM, and they also had higher CSF leukocyte counts and semi-quantitative protein concentrations. However, there was no significant difference in either permanent disability or mortality between the children with proven or probable ABM. Overall, 46 (8.3%) died in hospital, including 21 (25.3%) with proven or probable ABM. Only one child 4 months of age with probable ABM also had evidence of malaria infection. He had no signs of meningism, a low *P. falciparum* density (240 asexual forms/ μ L of whole blood), and a CSF leukocyte count of 35 cells/mm³ (71% neutrophils). He responded to parenteral antibiotics and artemether and was discharged well.

Given that treatment of ABM should be based, at least in part, on initial CSF microscopy²⁴ and the overall clinical similarity (including outcome) between children with proven and probable ABM, we combined the 83 children in these two groups in subsequent analyses. The odds ratio, sensitivity, specificity, PPV, NPV, LR+, and LR- for clinical signs in proven/probable ABM are shown in Table 2. Specific signs of meningeal involvement (neck stiffness, Kernig's and Brudzinski's signs and, in younger children, bulging fontanel) had LR+s that were high (≥ 4.3), but neck stiffness had the best sensitivity. The non-specific neurologic features of multiple seizures and coma were less predictive (LR+ = 1.5–2.1), and single seizures and especially a malaria-positive blood slide were associated with low LR+s for proven/probable ABM.

To examine the relative importance of predictors of proven/probable ABM, we included neck stiffness, Kernig's sign, Brudzinski's sign, deep coma, multiple seizures, and a history of single seizure in a logistic regression model (Table 3). Neck stiffness, Kernig's sign, and deep coma were independently and positively associated and a single fit was negatively associated. When a positive blood film for malaria was added to the model, neck stiffness and deep coma remained positively associated, and the presence of malaria parasites (*P. falciparum* and/or *P. vivax*) was significantly negatively associated with proven/probable ABM. A single seizure and Kernig's sign were no longer independent associates.

A separate logistic regression analysis in children < 18 months of age was performed to determine whether the presence of a bulging fontanel was a predictor of ABM. This sign was recorded in 91% of 238 eligible children. In a model including other clinical features, a bulging fontanel was a significant determinant of proven/probable ABM together with neck stiffness, Kernig's sign, and a history of multiple convulsions (Table 3).

Bacteriologic findings in proven ABM. A causative organism was identified from CSF culture or India ink staining in 45 children, 21 with Hib, 22 with *S. pneumoniae*, and 2 with *C. gatti*. Of this subgroup, blood cultures were also positive in 5 children (3 with Hib and 2 with *S. pneumoniae*). Latex agglutination testing identified one additional child with Hib meningitis. *Staphylococcus aureus* was identified as the causative organism in one child who had clinical features of ABM with > 1,000 leukocytes/mm³ in CSF, but the organism was isolated only from blood cultures.

We included the 2 cases of cryptococcal meningitis in the analyses because the leukocyte predominance in CSF seen in these children can occur in some cases of ABM, especially in patients that are partially treated. Appropriate initial antibiotic therapy should be administered in this situation. When we repeated the analyses summarized in Tables 2 and 3 and

TABLE 1

Clinical and laboratory features, and outcome of proven and probable bacterial meningitis, and non-meningitic illness requiring lumbar puncture in children in Papua New Guinea*

Characteristic	Proven (n = 47)	Probable (n = 36)	Other (n = 471)	Total (n = 554)	P†
Age (months)	8 (4–44)	25 (10–42)	27 (24–34)	25 (7–53)	0.001
Blantyre coma score					
≤ 2	36.2	25.0	12.7	15.5	< 0.0001
3 or 4	23.4	19.4	17.6	18.2	
5	40.4	55.6	69.7	66.2	
No. seizures					
0	31.9	61.1	41.6	42.1	< 0.0001
1	12.8	13.9	29.7	27.3	
≥ 2	55.3‡	25.0	28.7	30.1	
Signs of meningism					
Neck stiffness	89.4	66.7	18.5	28.0	< 0.0001
Kernig's sign	46.8	27.8	5.1	10.1	< 0.0001
Brudzinski's sign	27.7§	19.4	2.8	6.0	< 0.0001
Opisthotonus	14.9	5.6	1.9	3.2	< 0.0001
Cerebrospinal fluid					
Leukocyte count/mm ³	635 (252–1,097)‡	113 (52–450)	0 (0–0)	0 (0–10)	< 0.0001
Protein (g/L)	3 (1–3)¶	1 (1–1.8)	0.3 (0.3–0.3)	0.3 (0.3–0.3)	< 0.0001
Outcome					
Permanent disability	23.4	22.2	9.8	11.7	< 0.0001
Mortality	27.7	22.2	5.3	8.3	

* Values are medians (interquartile ranges) or percentages.

† Kruskal-Wallis and chi-square tests were used to compare continuous and categorical variables, respectively, across diagnostic groups.

‡ $P < 0.01$ vs. probable acute bacterial meningitis.

§ $P < 0.05$ vs. probable acute bacterial meningitis.

¶ $P < 0.001$ vs. probable acute bacterial meningitis.

TABLE 2

Utility of clinical signs and blood film microscopy in predicting proven or probable acute bacterial meningitis in children in Papua New Guinea*

Clinical sign (no./total)	Odds ratio	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	Positive likelihood ratio	Negative likelihood ratio
Neck stiffness (155/554)	17 (10–31)	80 (69–88)	82 (78–85)	43 (35–51)	96 (93–98)	4.3	0.3
Kernig's sign (56/548)	8.1 (4.6–14)	39 (28–50)	93 (90–95)	48 (36–61)	90 (86–92)	5.3	0.7
Brudzinski's sign (33/547)	9.6 (4.6–20)	23 (14–33)	97 (95–98)	58 (39–75)	88 (85–90)	7.7	0.8
Single seizure (151/548)	0.4 (0.2–0.7)	13 (7–23)	70 (66–74)	7.3 (3.7–13)	82 (78–86)	0.5	1.2
Multiple seizures (170/548)	1.8 (1.1–2.9)	42 (31–53)	71 (67–75)	21 (15–27)	88 (84–91)	1.5	0.8
Deep coma (86/530)	2.7 (1.6–4.5)	31 (22–42)	85 (82–88)	27 (19–37)	88 (84–90)	2.1	0.8
Malaria parasites (155/408)	0.02 (0–0.15)	2 (0–9)	56 (50–61)	0.7 (0–3.9)	74 (68–80)	0.04	1.8
Bulging fontanel† (23/217)	11.1 (4.3–28)	35 (21–51)	95 (91–98)	65 (43–84)	85 (80–90)	7.6	0.7

* Values in parentheses are 95% confidence intervals.

† Children less than 18 months old.

excluded the two cases of cryptococcal meningitis, the nature and strength of the derived parameters and associations did not change significantly.

DISCUSSION

In resource-poor healthcare settings in many tropical countries, important initial management decisions may have to be made on clinical grounds alone. In the case of a child with possible ABM in this situation, a variety of specific signs of meningism and non-specific neurological features can be used in diagnostic assessment. Our data suggest that neck stiffness, deep coma, and a bulging fontanel in a child < 18 months of age are the most important clinical predictors of ABM when a blood smear is negative in a malaria-endemic area. When a blood film result is not available, a positive Kernig's sign is also independently predictive and, while a single convulsion is a negative associate in this situation, the magnitude of LR+ (0.5) and LR– (1.2) are not low enough to suggest that a single seizure alone excludes ABM. In contrast, multiple convulsions appear to be an additional positive predictive feature in young children. Regardless of age and availability of malaria microscopy, Brudzinski's sign and opisthotonus are of limited diagnostic value in pediatric ABM.

In the recent systematic review,¹⁶ neck stiffness, bulging fontanel, and Kernig's sign were also among the clinical features with the highest LR+s (3.5–4.5) for pediatric ABM. Brudzinski's sign had a lower LR+ (2.5) but was still significantly predictive, albeit available for only 172 children compared with 3,118 in the case of neck stiffness. Deep coma was a relatively weak predictor (LR+ = 1.8). Our data from a sample that is larger than many of those incorporated in the systematic review¹⁶ are broadly consistent with these findings, both in the individual clinical features identified as predictive and

in the strength of their association with ABM. However, and in contrast with studies in Africa,^{9,15} the availability of a blood film microscopy had a significant impact on independent predictors of ABM.

In a study in The Gambia, 10% of children with definite ABM had malaria parasites on blood film microscopy, a percentage that was not significantly different from that in non-meningitic children.⁹ Although, by contrast, a positive blood film in children in Kenya was independently associated with the absence of ABM, a negative malaria slide added little to a predictive model of ABM.¹⁵ In the present study, no child with proven ABM and only one with probable ABM had malaria identified by microscopy. Malarial parasitemia, regardless of the infecting species, was independently associated with the absence of ABM and, more importantly, the addition of presence of malaria parasites to the logistic regression model influenced the utility of clinical signs. Neck stiffness and deep coma were of particular diagnostic importance in this situation.

The lack of overlap between malaria and invasive bacterial disease in children in Papua New Guinea contrasts with studies from Africa where 5–8% of children with well-defined severe malaria had co-existing invasive bacterial infections.^{25,26} This finding indicates the need for ABM predictive models specific to local epidemiology, a situation further emphasized by the finding that the sign with the highest LR (37.0) in the systematic review was petechiae.¹⁶ The relevant data were from 4 of 341 patients with ABM from Nigeria²⁷ where *N. meningitidis* is a major pathogen. Petechiae were not observed in any of our patients, reflecting the fact that *N. meningitidis* was not isolated from any blood or CSF cultures. Meningococcal infection was common in Papua New Guinea in the 1960s but its prevalence has been low in recent years.^{8,28,29}

The magnitude of the LR+s for individual clinical signs in our patients indicated that their presence increased the

TABLE 3

Independent predictors of acute bacterial meningitis identified by multiple logistic regression analysis in children in Papua New Guinea*

Characteristic	All children				Children < 18 months of age	
	Clinical features only		Clinical features and blood film		Clinical features only	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age (months)					0.86 (0.76–0.97)	0.02
Neck stiffness	10.2 (5.3–20)	< 0.0001	9.7 (4.5–22.0)	< 0.0001	4.6 (1.7–12.9)	0.003
Kernig's sign	2.8 (1.4–5.8)	0.005			6.1 (1.6–26.5)	0.01
Deep coma	2.4 (1.2–4.6)	0.01	2.3 (1.05–5.1)	0.04	4.6 (1.7–12.9)	0.01
Single convulsion	0.4 (0.2–0.8)	0.01				
Multiple convulsions					5.7 (2.2–16.5)	0.0004
Bulging fontanel					10.1 (3.1–35.1)	0.0002
Malaria slide positive			0.03 (0–0.13)	0.0004		

* CI = confidence interval.

pre-test probability of ABM by, at most, 30%.³⁰ Our study and others¹⁶ recruited children with clinical suspicion of ABM. These children have a pre-test probability or prevalence of ABM higher than that expected in unselected children who come to a health care facility with any illness. Differences in prevalence or pre-test probability will influence the PPV and NPV of individual signs in the diagnosis of ABM but LRs, being derived from sensitivity and specificity, are not affected. The use of logistic regression models identifying combinations of independent predictors in a study of children in Africa has shown that a history of seizures, lethargy/unconsciousness, and a stiff neck have 98% sensitivity and 70% specificity.⁹ Our data do not contradict this finding but highlight the importance of a bulging fontanel in younger children and the importance of blood film microscopy in malaria-endemic areas.

The present LP rate of 20.3% of total admissions was similar to that in non-malarious highland areas of Papua New Guinea and Africa (11–22%),^{9,15,31} as was the percentage of cases with proven ABM (1.7% versus 2.0–2.7%). Our overall annual ABM incidence was lower than that reported from the Papua New Guinea highlands (100 versus 600 per 100,000 children < 1 year of age per year),⁸ possibly reflecting relatively poor infrastructure and more limited access to tertiary level care. Although we may have underestimated ABM incidence in Madang Province, it was still similar to that reported for indigenous populations in Alaska and The Gambia.^{5–7}

The present findings have important clinical implications for Papua New Guinea and other countries in Oceania and beyond that have similar epidemiology. The presence of neck stiffness, deep coma (BCS ≤ 2) and, in a young child, a bulging fontanel and multiple convulsions, are strong evidence of ABM. A positive Kernig's sign also indicates that ABM is likely. In children without these features (including those with a single febrile seizure²⁰) and who have a positive blood film for malaria, lumbar puncture and empiric antibiotic therapy with a third-generation cephalosporin could be deferred pending further investigation and monitoring after administration of antimalarial therapy. However, physical examination findings are subject to technical competence, individual interpretation, and inter-observer variability. This issue could explain why some signs are clearly predictive of ABM in clinical research studies with clear definitions implemented by experienced clinicians¹⁶ but not when usual clinical practice has been evaluated.^{32,33} Similarly, blood film microscopy for malaria depends on the experience of the microscopist. Therefore, the validity of a simple predictive algorithm incorporating important clinical and, where available, laboratory features of ABM in a particular epidemiologic situation should be assessed in a field situation before it is formally adopted.

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