Lumbar Puncture in Children from an Area of Malaria Endemicity Who Present with a Febrile Seizure

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Background. Although routine lumbar puncture (LP) is often recommended as part of the assessment of fever-associated seizures in children, accumulating evidence questions its value and reveals a decrease in its frequency. Our primary hypothesis was that children who present with a single seizure but with no clinical signs of meningism or coma do not require LP as part of initial diagnostic assessment.

Methods. We prospectively followed up 377 children aged 2 months through 10 years who presented with at least 1 fever-associated seizure to Modilon Hospital, Madang, Papua New Guinea, from November 2007 through July 2009. Clinical management was performed by hospital staff according to national pediatric guidelines.

Results. Of 188 children with a single seizure and 189 children with multiple seizures, 139 (73.9%) and 154 (81.5%), respectively, underwent a LP as part of their initial assessment. Of the 130 children with a single seizure but no evidence of meningism (ie, neck stiffness, positive Kernig's or Brudzinski's sign, and bulging fontanelle) or coma (Blantyre Coma Score ≤2), none (95% confidence interval, 0%–3.6%) had proven or probable acute bacterial meningitis, and only 1 patient had viral encephalitis (subacute sclerosing panencephalitis). Eighty-one of these children (62.3%) had a final diagnosis of a simple febrile seizure. Proven or probable acute bacterial meningitis was more common in children with a single seizure and meningism or coma (10; 17.2%) and in those with multiple seizures without or with meningism or coma (2 [2.0%] and 30 [33.7%], respectively).

Conclusions. Initial LP is unnecessary when careful clinical assessment indicates features of a simple febrile seizure.

Although a seizure is a common reason for a sick child to be hospitalized [1–3] and is considered a potential danger sign for sepsis [4], a frequent final diagnosis in such cases will be febrile seizure (FS). A FS is defined as a seizure occurring in a child 6 months through 5 years of age who has an acute febrile illness, who has not experienced a prior seizure without fever, and in whom intracranial infection or inflammation has been excluded [5]. A simple FS is brief, generalized, and nonrecurrent. A complex FS is uncommon and can be prolonged, focal, and/or multiple. FS is not associated with adverse outcome [6].

Seizures also occur in many infections. Human herpesvirus 6 infection and influenza infection are viral causes of seizure without a primary neurologic focus [6, 7]. Viral encephalitis and malaria can affect neurologic function, and associated seizures are common [8, 9]. Seizures complicate culture-positive acute bacterial meningitis (ABM) in some age groups [10–12]. Cerebrospinal fluid (CSF) examination can thus help to differentiate FS from other types of seizures and can facilitate the management of potentially serious infections, especially in young children with clinical signs that are nonspecific or difficult to elicit. US and UK practice guidelines during the past 20 years have recommended that a lumbar puncture (LP) be strongly considered in infants younger than 12 months of age.
with a fever-associated seizure, considered in those aged 12–18 months, and performed in older children as indicated clinically [13–15]. Nevertheless, accumulating clinical evidence and a decrease in the prevalence of LPs have called such guidelines into question [16–18].

In many developing countries, such as in Papua New Guinea, local guidelines strongly recommend that LP be performed in all febrile children after a seizure, regardless of age [19]. This recognizes the fact that severe malaria and ABM are common and may not be easy to differentiate clinically or with limited diagnostic laboratory tests and imaging. Nevertheless, because LP is an invasive procedure that can cause complications, including cerebral herniation [20] and meningitis [21], it is desirable to minimize the number of LPs without missing ABM, which is a treatable cause of death. There are limited data assessing the role of LP in children presenting with fever-associated seizures in the developing world. Some studies [22–25] but not others [26, 27] have shown significant rates of occult ABM. However, most have been retrospective with incomplete details of sample selection, clinical procedures, and laboratory methods.

As part of a prospective, observational study of severe childhood illness in Papua New Guinea, we aimed to establish the diagnostic utility of LP performed in febrile young children hospitalized with at least 1 seizure. We hypothesized that children who present with a single seizure but without clinical signs of meningism or coma do not require LP as part of their initial assessment.

PATIENTS AND METHODS

Study site and patients. This study was conducted from November 2007 through July 2009 at Modilon Hospital, which serves the predominantly rural population in Madang Province on the north coast of Papua New Guinea. There is local hyperendemic Plasmodium falciparum and Plasmodium vivax malaria [28], and Haemophilus influenzae type b (Hib) and Streptococcus pneumoniae infections are common. Hib vaccination began in 2007, but no pneumococcal vaccination program has been instituted, and less than one-half of children in the Madang Province receive both doses of measles vaccine before their first birthday [29]. All children between 2 months and 10 years of age who present with ≥1 fever-associated seizure within the previous 24 h were eligible. Written informed consent was obtained from parent(s) or guardian(s). Approval for the study was obtained from the Papua New Guinea Institute of Medical Research Institutional Review Board and the Medical Research Advisory Committee of the Papua New Guinea Health Department.

Clinical procedures. After recruitment, a standardized case report form was completed with assistance from the parent(s) or guardian(s). The form detailed demographic information, medical history, and features of the current illness, including the number and nature of prior seizures. A full clinical examination was performed by trained nurses or study clinicians. We defined a simple FS as a single generalized seizure lasting <15 min with full recovery within 30 min in a child with fever either reported by a parent or guardian or confirmed by an axillary temperature ≥37.5°C. Complex seizures were multiple (≥2) during the presenting illness, focal, or prolonged.

Level of consciousness was graded using the Blantyre Coma Score (BCS) [30], with deep coma and impaired consciousness scored as ≤2 and ≤4, respectively. The BCS was recorded at 30 min, 1 h, or 6 h after correction of hypoglycemia, a seizure, or administration of anticonvulsant therapy, respectively. Clinical signs of meningeal irritation were (1) neck stiffness (inability to flex the neck so that the chin touched the upper chest), (2) a positive Kernig’s sign (straightening of the knee joint eliciting discomfort with the hip and knee joints flexed to 90°), (3) a positive Brudzinski’s sign (involuntary hip flexion from 0° elicited on neck flexion), and (4) bulging fontanelle.

Clinical management, including the decision to perform LP, was coordinated by the attending ward clinician on the basis of presenting features, prognosis, and parental consent. Treatment was given according to Papua New Guinea national guidelines [31]. In all patients, blood was collected for culture, a full blood cell count, blood glucose and lactate measurement, and microscopy for malaria. Children were reviewed on the ward at least daily until hospital discharge.

Laboratory methods. Total and differential CSF white blood cell (WBC) counts were obtained using the Neubauer Improved chamber (Boe Co). When red blood cells (RBCs) were present, an adjusted WBC count (calculated as total WBCs – [RBCs/100]) [32] ≥20 cells/mm³ was considered to be evidence of meningeal inflammation. If the WBC count was ≥10 cells/mm³, the CSF was centrifuged, a Gram stain was prepared, and an aliquot of sediment was inoculated onto chocolate and blood agar plates, which were incubated in 5% carbon dioxide for up to 72 h. Indian ink staining was performed on CSF with a lymphocyte count >10 cells/mm³. Semiquantitative CSF glucose and protein levels were obtained by dipstick (Acon Laboratories). Blood (1–3 mL) in Bactec Peds Plus/F bottles (Becton Dickinson) was incubated using the Bactec system. Blood and CSF bacterial isolates were identified using standard procedures. CSF samples with ≥10 cells/mm³ and no cultured pathogen underwent latex agglutination testing (Wellcogen) for S. pneumoniae, Hib, and Neisseria meningitidis. Coagulase-negative staphylococci, Corynebacterium, and Bacillus species isolated from blood or CSF were considered to be contaminants. Blood glucose and lactate levels were measured using Hemocue Glucose 201+ (Hemocue) and Lactate Pro (Arkray) analyzers, respectively. Malaria was diagnosed by microscopy of Giemsa-stained thick blood smears.
Table 1. Admission Details and Outcome in Children Categorized by the Number of Seizures before Presentation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Single seizure (n = 188)</th>
<th>Multiple seizures (n = 189)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median months (interquartile range)</td>
<td>36 (12–48)</td>
<td>33 (14–51)</td>
<td>.97</td>
</tr>
<tr>
<td>Male sex</td>
<td>99 (52.7)</td>
<td>112 (59.3)</td>
<td>.20</td>
</tr>
<tr>
<td>Meningism</td>
<td>34 (18.1)</td>
<td>65 (34.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Coma (BCS &lt;=2)</td>
<td>31 (16.5)</td>
<td>49 (25.9)</td>
<td>.025</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>139 (73.9)</td>
<td>154 (81.5)</td>
<td>.08</td>
</tr>
<tr>
<td>Diagnostic category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proven bacterial or fungal meningitis</td>
<td>5 (2.6)</td>
<td>23 (12.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Probable meningitis</td>
<td>5 (2.6)</td>
<td>9 (4.8)</td>
<td>.28</td>
</tr>
<tr>
<td>Viral encephalitis</td>
<td>2 (1.1)</td>
<td>15 (7.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Malaria with cerebral involvement</td>
<td>46 (24.5)</td>
<td>90 (47.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Febrile seizure</td>
<td>94 (50.0)</td>
<td>0 (0.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other</td>
<td>36 (19.2)</td>
<td>52 (27.5)</td>
<td>.055</td>
</tr>
<tr>
<td>Discharged with disability</td>
<td>6 (3.1)</td>
<td>21 (11.1)</td>
<td>.003</td>
</tr>
<tr>
<td>Death</td>
<td>10 (5.3)</td>
<td>12 (6.4)</td>
<td>.67</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise indicated. BCS, Blantyre Coma Score.

a By the Mann-Whitney U test or χ² test.
filling the FS criteria in a child aged 2 months to 6 years who was not classified in any of the other groups. There were 94 children in this group.

The other illness group included 88 children (23%) who had other diagnoses, including non-MCI malarial infection, respiratory illness, and diarrhea in 23 (26%), 15 (17%), and 10 (11%), respectively. Five (6%) died and 1 had chronic disability. All children in this and the other groups with a positive blood smear for malaria were given antimalarial therapy regardless of primary diagnosis.

**Single seizures.** The patients were categorized according to the number of seizures and the presence or absence of clinical signs of ABM at the time of admission (meningism and/or coma [35], the latter defined as a BCS ≤2) and final diagnosis (Figure 1). Of the 188 patients presenting with a single seizure, nearly one-third had meningism or coma, but 10 (17%) of these did not undergo LP. Five of these patients had a positive blood smear for malaria (4 were comatose and 1 had neck stiffness), were treated with intramuscular artemether, and were discharged well. An additional child was diagnosed presumptively as having MCI based on a positive rapid diagnostic test result, negative blood smear, and preadmission intramuscular artemether therapy. Two children were diagnosed clinically as having FS despite neck stiffness and also recovered uneventfully. One child with neck stiffness and a non–central nervous system infection responded to antibiotic therapy. One child presented deeply comatose after a severe head injury and died within 12 h of admission.

Of the 130 without meningism or coma, 39 (30%) did not undergo LP. Most of these were diagnosed as having a FS and just more than one-quarter had MCI; all of these patients were discharged well. One child presented with a 1-month history of a clinical syndrome consistent with SSPE despite negative CSF measles serologic test results. He was discharged with a chronic disability. Another who presented with a blood smear positive for malaria, severe anemia, and hyperlactemia died before blood transfusion could be administered. The percentage of cases with a single seizure, no meningism or coma, but ABM was, therefore, 0.0%, with a 95% confidence interval (CI) of 0.0%–3.6%.

**Multiple seizures.** Thirty-five children with multiple seizures did not undergo LP. Most (28 [80%] of 35) had malaria parasites on blood smear and were diagnosed as having MCI. Two had a diagnosis of MCI based on a positive rapid diagnostic test result. Of the remaining 5, the final diagnoses comprised SSPE, appendicitis, severe pneumonia, otitis media, and upper respiratory tract infection. None of these children had meningism, and 1 had impaired consciousness (BCS of 4). This latter child was discharged from the hospital well after the completion of antibiotic therapy. Only 1 of the children in the group with multiple seizures who did not undergo LP died. This deeply comatose child had blood smear results that were positive for

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**Figure 1.** Consort diagram outlining categorization of children according to clinical features at presentation, whether or not a lumbar puncture (LP) was performed, and final diagnostic category (proven bacterial or fungal meningitis, probable meningitis, viral encephalitis, malaria with cerebral involvement, simple febrile seizure, or other illness). Data are no. (%) of children.
DISCUSSION

The present prospective observational study shows that Papua New Guinean children with clinical features of a simple FS have a low probability of ABM. Among 130 such children, an LP was of positive diagnostic utility in only 1 case, which involved a delayed diagnosis of SSPE. In the 100 children with multiple seizures but no meningism or coma, there were 2 cases of probable ABM and 5 cases of viral encephalitis, whereas definite or probable ABM was much more common among those with meningism or coma regardless of seizure number. These data suggest that LP is unnecessary when careful clinical assessment indicates a simple FS but that it should be performed promptly, when there are no contraindications, in all febrile children presenting with signs of meningism, coma, and/or multiple seizures.

Authoritative recommendations to perform routine LPs in patients with fever-associated seizure [13–15] have not been mirrored in clinical practice in developed countries. UK rates have decreased from 96% in the 1970s to 12% in 2000 [16]. Even among children 12–18 months of age and supposedly at high risk for occult ABM, LP rates in 2006 were only 5% in a North American study [17]. This trend may reflect increasing availability of alternative diagnostic modalities, shifts in likely pathogens (including a decrease in the prevalence of Hib and pneumococcal disease), and improved monitoring during the acute phase. In the developing world, there is a higher incidence of ABM, reflecting low rates of Hib and pneumococcal vaccination. In addition, there are other infections (including infections due to Plasmodium species) with potential neurologic effects and an often delayed presentation to facilities with limited ability to investigate and observe effectively. This may explain why most of our children underwent LP, including 70% of those with a single seizure and no meningism or coma.

There have been no definitive prospective studies showing that a simple FS can be the sole or major manifestation of ABM in children. In a review of largely retrospective, first-world studies up to 1999 [16], there were 7 cases of ABM without meningism among 4102 children with fever-associated seizures (0.2%; 95% CI, 0.1%–0.4%). However, the assessment of features of meningism was not recorded in 3 of these cases, whereas the CSF test results were initially normal in 2 other cases. More recent US studies found no cases of ABM in 160 (23%) of 704 children with simple fever-associated seizures and available CSF findings [17], whereas none of 503 consecutive patients with ABM presented with a simple seizure [36].

Data from the developing world show greater heterogeneity. In a Nepalese study involving 175 children 6 months to 5 years of age with a fever-associated seizure who underwent LP, 8 (5%) had culture-proven ABM without meningism; all 8 of these children were aged 6–12 months [23]. Details of how signs of meningitis were elicited, the number of seizures, and level of consciousness were, however, not provided, and clinical assessments were performed by postgraduate students. In an
African study involving 522 children 1 month to 6 years of age who underwent LP for febrile convulsion, 6 (1%) had ABM but no meningism [22]. These children were distributed across age groups. Although there was a significant association between ABM and seizure complexity, it was unclear whether the children with occult ABM had simple or complex seizures. In a small Saudi Arabian study, 3 (3%) of 95 children 6 months through 6 years of age had pyogenic meningitis without meningism [24]. One child had Hib diagnosed by latex agglutination (and had complex seizures), and 2 were partially treated on the basis of the CSF findings. Another small-scale African study found 3 children with meningitis among 45 children in whom >1 seizure was the only indication for LP [25]. Meningitis was, however, diagnosed when the CSF WBC count was >5 cells/mm³ or the CSF protein level was >4 g/L, regardless of Gram stain or bacterial culture results.

In other studies from Asia [26] and the Middle East [27], there were no cases of ABM in children presenting with a fever-associated seizure and no evidence of meningitis. In the former [26], there were 5 cases (2%) of ABM among 254 children aged 6 months to 5 years, all with evidence of meningitis. In the latter [27], 102 (51%) of 200 children 3 months to 5 years of age with a fever-associated seizure had an LP. Three children had ABM (2%), and all 3 of these children had complex seizure activity among other features of meningitis. In contrast to those studies that have shown significant rates of ABM among patients with febrile seizures [22–25], these 2 studies had adequate data on the nature and frequency of seizures.

The present study differs from most previous studies performed in developing countries in several respects. First, we used a standardized detailed clinical assessment performed by experienced staff so that we had adequate characterization of seizure activity and good evidence of the presence or absence of meningism and/or altered consciousness. Second, we applied strict definitions of proven or probable meningitis. Third, we followed up all children until hospital discharge or death to obtain a valid final diagnosis. As a result, and although ~25% of our children did not have an LP, the present study represents one of the largest and most rigorously conducted prospective studies to date.

LP remains an important diagnostic test in many clinical situations and may assist with disease surveillance. However, the present results suggest that current guidelines could be modified regardless of the clinical and epidemiologic situation (Figure 2). The main change is that children of any age with good evidence of a simple FS do not require an initial LP but should be observed and reviewed. If there is clinical concern at any stage, LP should performed promptly, whereas we have included impaired consciousness (BCS ≤4) rather than coma (BCS ≤2) as a further conservative measure. Nevertheless, if our data are pooled with those from the 1479 children in other studies from developing countries [22–25], the worst-case estimate for the percentage of children with a simple FS in whom ABM would be missed without LP is 1.4 (95% CI, 0.9–2.1%). This does not take into consideration empirical administration of broad-spectrum antibiotic therapy and should be addressed by regular reviews until the patient improves or a definitive diagnosis is made. Consistent with valid development of guidelines [37], our scheme respects recent evidence, justifiably simplifies management, and provides potential savings for health care systems that often struggle to cover essential services.

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