Pediatric Acute Severe Neurologic Illness and Injury in an Urban and a Rural Hospital in the Democratic Republic of the Congo

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Abstract. Empirical knowledge suggests that acute neurologic disorders are common in sub-Saharan Africa, but studies examining the true burden of these diseases in children are scarce. We performed this prospective, observational study to evaluate the prevalence, clinical characteristics, treatment approaches, and outcomes of children suffering acute neurologic illness or injury (ANI) in an urban and rural site in the Democratic Republic of the Congo. Over 12 months, 471 out of 6,563 children admitted met diagnostic criteria for ANI, giving a hospital-based prevalence of 72/1,000 admissions. Two hundred and seventy-two children had clinical findings consistent with central nervous system infection but lacked complete diagnostic evaluation for definitive classification. Another 151 children were confirmed to have cerebral malaria ($N = 109$, 23% of admissions), bacterial meningitis ($N = 38$, 8% of admissions), tuberculous meningitis ($N = 3$, 0.6% of admissions), or herpes encephalitis ($N = 1$, 0.21% of admissions). Febrile convulsions, traumatic brain injury, and epilepsy contributed less significantly to overall hospital prevalence of ANI (3.19/1,000, 1.37/1,000, and 1.06/1,000, respectively). Overall mortality for the cohort was 21% (97/471). Neurologic sequelae were seen in another 31% of participants, with only 45% completing the study with a normal neurologic examination. This type of data is imperative to help plan effective strategies for illness and injury prevention and control, and to allow optimal use of limited resources in terms of provision of acute care and rehabilitation for these children.

INTRODUCTION

Sub-Saharan Africa has the highest childhood mortality rate in the world. Globally, half of the deaths in children occur in this region. Empirical knowledge suggests that acute neurologic disorders are common contributors to morbidity and mortality. However, little is known about the true incidence, clinical characteristics, treatment approaches, or outcomes of children suffering from these diseases in sub-Saharan Africa. One study, in primarily adult patients in Tanzania, reported that 8.5% of admissions were diagnosed with a neurologic condition, with seizures (26.6%) and infectious diseases (18.1%) as the two most common entities described.¹ Overall mortality for patients meeting criteria for neurologic disease in their study was 21%. The limited pediatric data that is available on this topic was retrospectively collected by chart abstraction in two studies in Nigeria.^{2,3} In those studies, acute neurologic illness or injury (ANI) accounted for 11–16% of all pediatric admissions. Febrile convulsions were the most common cause of admission in 28–35% of children. This was followed closely by cerebral malaria in 21–28% and bacterial meningitis in 18–27%. Afebrile seizures were seen in 5–15% and traumatic brain injury in 2–6%. Overall mortality for these patients was as high as 15%. Most of these children died within 24 hours of admission to the hospital. These findings suggest that ANI significantly contributes to poor child health in sub-Saharan Africa. One of the most challenging public health problems in Africa is data collection. Data that are available are often fragmented or partial. As such, the prevalence reported in these retrospective studies likely underestimates the true prevalence and impact of these diseases in children.

Observational epidemiologic data are imperative to help plan effective strategies for illness and injury prevention and control. Improved understanding of the epidemiologic characteristics of ANI is necessary to allow optimal use of limited resources in terms of provision of acute care and rehabilitation for these children. The purpose of this study was to prospectively generate data on the causes, severity, treatment, and outcomes of children suffering acute neurologic diseases in both an urban and a rural setting in the Democratic Republic of the Congo (DRC).

MATERIALS AND METHODS

Ethics and protocol. Before participant recruitment, the study protocol was approved by the Institutional Review Board at both Nationwide Children's Hospital/The Ohio State University and the University of Kinshasa, School of Public Health. All participating subject's guardians provided verbal informed consent before enrollment in the study.

Study site and setting. The study was conducted from September 2015 to August 2016 in the city of Kinshasa (Kinshasa province in northwest DRC, Central Africa) and the village of Lodja (Kasai province in central DRC, Central Africa). The participating hospital in Kinshasa was Kalembe Lembe Children's Hospital, a 122-bed teaching and referral hospital in urban Kinshasa. It is the only free-standing children's hospital in Central Africa. In this hospital, children are first seen in the emergency department. Patients are then triaged into the intensive care unit (nine beds, double or triple occupancy per bed), surgical, or medical units. In Lodja, the participating hospital was L'Hopital General de Reference de Lodja, a 50-bed district hospital in rural DRC. Children are first seen in the outpatient department and are then admitted to the inpatient unit. Study sites were selected because of the presence of local collaborators experienced in the conduction of operational research. At both sites, basic laboratory examinations,

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microbiology, cerebrospinal fluid (CSF) analysis, and conventional X-rays are available. Neither site has access to sophisticated neuroimaging such as computed tomography or magnetic resonance imaging. Neither site has access to electrophysiologic testing or to electroencephalogram.

Study. The primary objective of this project was to gather quantitative data on acute severe neurologic illness and injury in children in both an urban tertiary care referral center and a rural district hospital in the DRC. Acute neurologic illness and injury were defined as the acute onset (< 1 month) of abnormal function of the central or peripheral nervous system as evidenced by impaired consciousness, encephalitis/encephalopathy, convulsions, or neuromuscular weakness. A one-page data registry form was designed and included four main areas: demographics (age and gender), neurologic illness or injury event information (date and time of illness onset/injury occurrence, cause), severity of event (physiologic variables, Blantyre Coma scoring) and treatment information (confirmatory testing, medications/treatments administered), and neurological outcomes data (2 weeks from the time of admission). One nursing supervisor and one physician at each location underwent training in the following areas: the purpose of research, the purpose of disease registries, and the purpose of the proposed study. The data collection form was reviewed with research team members. Each item on the form was discussed to the satisfaction of both the trainer and the trainees to ensure an appropriate level of understanding of the form itself was achieved.

A second stage of training then occurred with research staff that imparted the skills needed for the actual use of the registry form. Children with ANI were assessed and registry forms were filled out concurrently by both the nursing supervisor and physician in each location under the supervision of the research lead and discussed immediately to ensure clarity and consistency. This practice was continued until forms on 10 consecutive patients were filled out identically by all research personnel. The study then started enrollment of patients when any acute neurologic condition was identified.

All participants, following physical examination and laboratory evaluations were categorized into clearly defined diagnostic groups. Performance of confirmatory diagnostic testing and medications used for treatment of the presenting clinical condition were left to discretion of the admitting physician. Group 1 included disorders without diagnostic uncertainty based on medical history and clinical examination alone (febrile seizures, tetanus, and epilepsy with status epilepticus). Group 2 was divided into two sections. Group 2a included disorders identified based on medical history and clinical examination together with basic confirmatory tests, including cerebrospinal analysis (cerebral malaria and meningitis). Cerebral malaria was diagnosed according to the World Health Organization (WHO) definition as a clinical syndrome characterized by an inability to localize to painful stimulus at least 1 hour after termination of a seizure and correction of hypoglycemia, detection of asexual forms of *Plasmodium falciparum* malaria parasites on peripheral blood smears (which was determined after the rapid malaria test returned positive), and exclusion of other causes of encephalopathy (negative results for bacterial or fungal elements on CSF analysis).⁴⁻⁸ Bacterial meningitis was diagnosed when CSF Gram stain or culture was positive for a bacterial organism.⁹ Group 2b included disorders identified based on medical

history and clinical examination but for which basic laboratory elements that were available were not performed (presumed central nervous infection based on clinical presentation without CSF examination). Group 3 included disorders that are known in which a presumptive diagnosis can be reached based on medical history and clinical examination, but in which there remains some diagnostic uncertainty, given lack of confirmatory testing (hydrocephalus, botulism, and Guillain-Barré syndrome). Group 4 included syndromes that were unknown with major diagnostic uncertainties. Cases within this group were identified to have a combination of neurologic signs and symptoms but without clear causative mechanism based on history, physical examination, or available laboratory data (impaired consciousness and encephalopathy). Two weeks from the time of admission, neurologic outcomes of participants were placed into one of five categories by research study physicians: 1) Normal for age, 2) Alert and appropriate for age but with some neurologic changes (e.g., ataxia, agitation, disinhibition, deafness, and epilepsy), 3) Unresponsive, 4) Dead, and 5) Unknown. Neurologic outcomes of participants were classified as unknown if the participant, at 2 weeks from admission, was discharged, did not return to the clinic for follow-up, and were not known to have died.

Children were identified prospectively by study team members on daily ward rounds at both hospitals. Following completion of the data record sheet for each patient, paper records were stored in a secure location and converted to PDF for electronic review (Genius Scan for iOS). The research lead evaluated registry forms on a biweekly basis throughout the entire duration of the project. Completed data record sheets were cross-checked with patient charts to ensure accuracy and completeness. In addition, the completeness of patient enrollment was determined by cross-checking it with the hospital patient registration book on a biweekly basis.

Statistical analysis. Quantitative data were double entered using Microsoft Office Excel 2007 (Microsoft, Redmond, WA). The prevalence of ANI was calculated as number of cases divided by the total number of admissions during the study period. Analysis were stratified by location. χ^2 or Wilcoxon rank sum test was used to compare categorical and continuous variable as appropriate. All analysis were performed using SPSS version 23 (IBM corporation, New York City, NY).

RESULTS

Over a 12-month period, 471 children with ANI were admitted at both sites, including 276 in Kinshasa and 195 in Lodja. In the same period of time, 5,387 children were admitted in Kinshasa and 1,176 children were admitted in Lodja. Thus, the hospital-based prevalence of children with ANI was 51/1,000 in the urban site and 169/1,000 in the rural site. Furthermore, children with a diagnosis of ANI made up 35% of all admissions to the intensive care unit at the urban site (251 cases with a total of 720 admissions).

The demographics, physiological variables, Blantyre coma scores, basic laboratory results, and treatments of the entire cohort are shown in Table 1. Cerebrospinal fluid analysis was not indicated in children classified into Group 1, given that their diagnosis could be reached with clinical certainty without it ($N = 37$). Similarly, for 11 cases in Groups 3 and 4, CSF analysis would not have added significantly to the clinical

TABLE 1

Demographics, physiological variables, Blantyre coma scores, laboratory results, treatments, and neurological outcomes of cohort by location (N = 471)

Variable	Result			
	Total (N = 471)	Urban (N = 276)	Rural (N = 195)	P value*
Age in months: median (range)	37 (1–236)	37 (1–236)	37 (1–216)	0.82
Male: n (%)	241 (51)	147 (53)	94 (48)	0.26
Days to presentation: median (range)	4 (1–30)	4 (1–30)	4 (1–21)	0.97
Seizures before arrival: n (%)	424 (90)	245 (89)	179 (92)	0.28
Respiratory rate on admission (/min): median (range)	34 (6–66)	33 (6–70)	36 (6–66)	0.06
Cardiovascular rate on admission (/min): median (range)	133 (18–200)	133 (55–200)	132 (18–190)	0.50
Blantyre coma score: median (range)	3 (1–6)	3 (1–6)	3 (1–6)	0.43
Rapid malaria test positive: n (%)	345 (74)	201 (73)	144 (76)	0.56
Parasite density/mm ³ median (interquartile range)	31,568 (14,500–186,50)	28,700 (15,200–180,00)	35,515 (14,900–187,000)	0.97
Hemoglobin (g/dL)	8 (2–13)	8 (2–12)	8 (2–13)	0.55
White blood cell count (wbc/ μ L): median (interquartile range)	11,600 (3,600–68,600)	7,800 (4,350–23,450)	8,275 (4,800–32,800)	0.46
CSF examinations performed: n (%)	178 (38)	111 (40)	67 (35)	0.23
CSF white cell count: median (range)				
Bacterial meningitis	110 (8–1,200)	148 (8–1,200)	150 (64–1,200)	0.69
Tuberculous meningitis	75 (24–125)	–	75 (24–125)	–
Cerebral malaria	5 (0–44)	5 (2–44)	5 (0–42)	0.97
Other CNS infection	10 (3–125)	10 (3–125)	13 (3–65)	0.70
Medications received: n (%)†				
Quinine	130 (28)	71 (26)	59 (30)	0.28
Artusenate	293 (62)	175 (63)	118 (62)	0.52
Ceftriaxone	381 (81)	222 (80)	159 (82)	0.76
Chloramphenicol	321 (68)	188 (68)	133 (68)	0.98
Dexamethasone	104 (22)	61 (22)	43 (22)	0.99
Benzodiazepines	254 (54)	141 (51)	113 (58)	0.14
Phenobarbital	145 (31)	87 (32)	58 (30)	0.68
Other anticonvulsant	16 (3)	8 (3)	8 (3)	0.48
Neurologic outcomes: n (%)				
Death (total)	102 (22)	52 (19)	50 (27)	0.29
Bacterial meningitis	6 (6)	3 (6)	3 (6)	–
Cerebral malaria	19 (19)	12 (23)	7 (14)	–
Presumed CNS infection	73 (72)	37 (71)	36 (72)	–
Other etiology	4 (4)	0	4 (8)	–
Spastic quadriplegia: n (%)	69 (15)	47 (17)	22 (11)	–
Other neurological deficits: n (%)	74 (16)	44 (16)	30 (15)	–
Normal: n (%)	212 (45)	124 (45)	88 (45)	–
Unknown: n (%)	14 (3)	9 (3)	5 (3)	–

CNS = central nervous system; CSF = cerebrospinal fluid; /min = per minute; n = number.

* P value for χ^2 (categorical variables) or Wilcoxon rank sum test (continuous variables).

† Patient could receive more than one drug at a time.

impression and, therefore, lumbar puncture (LP) was not performed. For the remaining 423 children in Group 2 whose clinical scenario was thought to likely represent central nervous system (CNS) infection, 178 (38% of total cohort and 42% of those where analysis was clinically indicated) had LP performed for CSF analysis as part of confirmatory testing and 245 did not (58%). In those children without confirmatory CSF analysis, 12 LPs were not performed because of documented clinical indication, 67 children died within 6 hours of hospitalization and before LP could be completed, and 81 families lacked the resources necessary to pay for laboratory investigations of the spinal fluid. The reason for lack of confirmatory CSF testing was the clinician's choice in an additional 85 cases.

The number of cases within each diagnostic group and the hospital-based prevalence of each diagnosis are noted in Table 2. In Group 1, febrile seizures were the leading cause of admission. Notably, most (82%) were complex in nature with recurrent seizures or prolonged convulsions requiring benzodiazepines and/or phenobarbital for the cessation of

seizures. Nine children in the group were admitted with a diagnosis of traumatic brain injury. Two were passengers on a motorbike involved in an accident, three were pedestrians on the roadside struck by a motorbike, two fell from trees, and two were struck by objects. Neurological impairment in this group ranged from temporary loss of consciousness to deep coma. Without cerebral computed tomography, a definite diagnosis regarding the origin of the neurological signs could not be reached. The other seven cases in Group 1 carried a known diagnosis of epilepsy and were admitted with afebrile status epilepticus. Six of the seven children (86%) did not have access to their standard antiepileptic medications and had, therefore, not been taking them before their admission. The distribution of each of these causes as a proportion of ANI did not vary by location but varied substantially as a proportion of all admissions by hospital (Table 2).

Group 2 was subdivided into groups based on diagnostic certainty, which was largely reached based on results of LP. Group 2a comprised 151 cases. Of the 38 children with bacterial meningitis, the causative organism was *Neisseria meningitidis*

TABLE 2
Neurological disorders by group and location (N = 471)

	Total	Urban	Rural	Prevalence/1,000*	
	n (%)	n (%)	n (%)	Urban	Rural
Group 1	37 (7.9)	19 (6.9)	18 (9.2)	3.5	15.3
Febrile seizures	21 (56.8)	12 (63.2)	9 (50.0)	2.2	7.7
Traumatic brain injury	9 (24.3)	4 (21.1)	5 (27.8)	0.7	4.3
Epilepsy	7 (18.9)	3 (15.8)	4 (22.2)	0.6	3.4
Group 2a	151 (32.1)	102 (37.0)	49 (25.1)	18.9	41.7
Bacterial meningitis	38 (25.2)	22 (21.6)	16 (32.7)	4.1	13.6
Tuberculous meningitis	3 (2.0)	1 (1.0)	2 (4.1)	0.2	1.7
Cerebral malaria	109 (72.2)	79 (77.5)	30 (61.2)	14.7	25.5
Herpes simplex encephalitis	1 (0.7)	0	1 (2.0)	0.0	0.9
Group 2b	272 (57.8)	149 (54.0)	123 (63.1)	27.7	104.6
Presumed CNS infection					
CSF not examined	243 (89.3)	137 (92.0)	106 (86.2)	25.4	90.1
Parasitemia+	198 (72.8)	109 (73.2)	89 (72.4)	20.2	75.7
Rapid malaria–	45 (10.7)	28 (18.8)	17 (13.8)	5.2	14.5
CSF examined and –for bacterial infection and rapid malaria–	29 (10.7)	12 (8.1)	17 (13.8)	2.2	14.5
Group 3	5 (1.1)	2 (0.7)	2 (1.5)	0.4	1.7
Hydrocephalus	1 (20)	0	1 (33.3)	0	0.9
Guillain–Barre syndrome	1 (20)	0	1 (33.3)	0	0.9
Neurotoxicosis	1 (20)	1 (33.3)	0	0.2	–
Shigella with convulsions	1 (20)	0	1 (33.3)	0	0.9
Stroke associated with CHD	1 (20)	1 (33.3)	0	0.2	0
Group 4	6 (1.3)	4 (1.5)	2 (1.0)	0.7	1.7
Medication-induced seizures	2 (33.3)	1 (25.0)	1 (50.0)	0.2	0.9
Electrolyte abnormality–induced seizures	3 (50.0)	2 (50.0)	1 (50.0)	0.4	0.9
Encephalopathy	1 (16.7)	1 (25.0)	0	0.02	0

CHD = congenital heart disease; CNS = central nervous system; CSF = cerebrospinal fluid; n = number. Group 1: disorders without diagnostic uncertainty based on medical history and clinical examination alone. Group 2a: disorders identified based on medical history and clinical examination together with basic confirmatory tests, including cerebrospinal analysis. Group 2b: disorders identified based on medical history and clinical examination but for which basic laboratory elements that were available were not performed. Group 3: disorders that are known in which a presumptive diagnosis can be reached based on medical history and clinical examination, but in which there remains some diagnostic uncertainty, given lack of confirmatory testing. Group 4: syndromes that were unknown with major diagnostic uncertainties.

* Number of cases divided by the total number of admission during the study period.

in 16 (42%), *Streptococcus pneumoniae* in 14 (37%), *Haemophilus influenza* in three (8%), *Staphylococcus aureus* in four (9%), and *Listeria monocytogenes* in one (3%). Three children were diagnosed with disseminated tuberculosis based on clinical history, examination, and chest X-ray findings. Furthermore, tuberculous meningitis was confirmed by acid-fast bacilli positive smears on CSF analysis in these cases. One hundred and nine children met the WHO definition and our diagnostic criteria for cerebral malaria. One neonate in Group 2a had skin lesions consistent with herpes simplex virus, shock, and seizures. Tzanck smear of CSF was positive for multinucleated giant cells, consistent with a diagnosis of herpes encephalitis.

Group 2b included a total of 272 cases. Twenty-nine had rapid blood tests negative for malaria and CSF examinations negative for bacterial or fungal elements. These cases, therefore, could not be classified as cerebral malaria or bacterial or tuberculous meningitis. No advanced testing, for example, with molecular analysis, is available at either site to aid in the diagnosis of viral CNS infection. The largest percentage of this group (243 cases, 89%) was those with clear clinical signs of CNS infection such as fever, convulsions, and altered mental status but in whom no CSF was taken for analysis. Rapid malarial testing, evidence of peripheral parasitemia, and coma was present in 198 cases. Peripheral parasitemia was absent in 45 cases. Similarly to Group 1, the distribution of each of these Group 2 diagnoses as a proportion of all ANI did not vary by location but varied substantially as proportion of all admissions by hospital (Table 2).

Groups 3 and 4 comprised small patient numbers fitting each diagnosis. One child in Group 3 presented at the age of

3 months with 2 months of enlarging head circumference and downward eye deviation. He lacked any infectious or other history. A clinical diagnosis of congenital obstructive hydrocephalus was made but could not be confirmed with computed tomography. Another 4-year-old child with a recent history of gastrointestinal illness presented with diffuse and progressive weakness. Physical examination was notable for absent tendon reflexes. A clinical diagnosis of Guillain–Barre syndrome was made but no confirmatory testing with electromyogram or nerve conduction study testing was possible. One child with known congenital heart disease (unrepaired truncus arteriosus on previous cardiac echography) presented with acute-onset dense hemiplegia that did not improve with treatment. She was felt to have likely suffered embolic stroke, but computed tomography was not available to confirm the diagnosis. Three patients in Group 4 presented with gastroenteritis complicated by repeated bouts of emesis and diarrhea. Convulsions ensued and resolved rapidly with the administration of sodium chloride bolus and, therefore, presumptive diagnosis of hyponatremic seizures was made. However, no electrolyte testing is available at either site to have confirmed sodium values at the time of the seizures. The distribution of diagnosis in both Group 3 and Group 4 as a proportion of all ANI also did not vary by location but varied substantially as proportion of all admissions by hospital (Table 2).

Overall mortality rate for the entire cohort was 21% (97/471) (Table 1). A total of four cases from Groups 1, 3, and 4 died (two with traumatic brain injury, one with Guillain–Barre syndrome, and one with encephalopathy). Mortality in Group 2a was

similar between children confirmed to have bacterial meningitis (21%) and cerebral malaria (18%). Those children classified in Group 2b with likely CNS infection but who did not have confirmatory testing performed experienced a mortality rate of 29%. There was no significant mortality difference between the urban and rural sites. In addition, 15% of children (69/471) were left with severe neurological deficits that rendered them incapable of interacting with their families or environment. When considering death and severe sequelae together, 44% of all participants had poor neurological outcomes. Another 16% had residual neurologic deficits such as ataxia, visual impairments, hearing impairments, or developed epilepsy. Only 45% of the cohort were found to have normal neurological examinations on completion of the study. Two percent were lost to follow-up and their neurologic outcomes are unknown.

DISCUSSION

Many neurologic diseases affecting pediatric patients in developing countries are of acute onset and their course may be rapidly lethal. Early and adequate treatment may prevent neurologic damage, decrease the morbidity and mortality, and improve the patient's and their families' quality of life. In addition, understanding the prevalence and impact of these diseases is imperative to plan effective preventative strategies in these settings with limited resources. Yet, to date, the impact of neurological disorders affecting children in these regions has been underestimated and often overlooked. Therefore, the aim of this study was to describe, in a prospective fashion, the prevalence, diagnostic strategies used, treatments given, and outcomes of children affected with acute neurological diseases in both an urban and rural African hospital.

Overall, we found that acute neurologic conditions made up 5% of hospital admissions to the urban site and 17% of admissions to the rural site. However, cases did not differ across sites for their demographics, severity, or neurological outcomes, suggesting that the prevalence difference might be related to prevalence of etiological conditions in the catchment population of the two sites. One limitation to the study is that included patients were identified on ward rounds by study personnel. These patients were cross-checked with the hospital registry to ensure all patients thought to have ANI were included. However, patients may have died in triage before inclusion in the registry and before arrival to the hospital ward, so the true overall prevalence may be underreported.

Most of the cases in the study were classified into Group 2b ($N = 272$). All of these cases exhibited clear signs of CNS infection such as fevers, decreased mental status, and seizures. Despite this, most of the patients did not have further diagnostic testing with CSF analysis to determine the definitive etiology of their symptoms. In most cases, clinician preference was noted as the reason to not perform further diagnostic testing for these children. As this was an observational study, education regarding appropriate evaluation and treatment of various neurological disorders was not given before or during the study. One key point identified by this study, therefore, is that significant gaps in knowledge exist in appropriate and necessary diagnostic and treatment strategies for children with acute neurologic illness. Improving education in this area is of paramount importance as studies

have shown that following specific diagnostic algorithms and treatment plans in resource-poor settings improves childhood mortality and is either cost-saving or cost-effective.^{10,11} Furthermore, appropriate diagnosis could potentially limit exposure to unnecessary and potentially harmful therapies. For example, in our study, we found that 80% of children received complete treatment courses of antibiotics with ceftriaxone and 67% with chloramphenicol, whereas the hospital prevalence of confirmed bacterial meningitis in our cohort was only 8/1,000. A major problem in addressing this issue is the lack of neurological expertise in African nations. In sub-Saharan Africa, the average ratio of neurologist to general population is 1:3.4 million, with at least 11 nations reporting no neurologist at all. By comparison, the ratio of population to neurologist in the United States is on the order of 1:26,200.^{12,13} Thus, training of more neurologists who can provide both clinical care and education to other practitioners seems to be critical for improving the health of children suffering from neurologic illness or injury in African countries.

A smaller percentage of the children in Group 2b (6%) lacked evidence of peripheral parasitemia and had CSF investigations that did not represent bacterial infection. These cases could, therefore, not be classified as having cerebral malaria or bacterial meningitis. Therefore, these children were thought to likely represent cases of viral meningoencephalitis or other CNS infections such as Human African trypanosomiasis, schistosomiasis, or opportunistic infections. However, confirmatory molecular testing for these types of infections is not widely available in sub-Saharan Africa.¹⁴ In addition, evaluating CSF for acid-fast bacilli is an insensitive diagnostic test, so some of these children may have had tuberculous meningitis. This group is important for two reasons. Viral infections most often can be managed with supportive care alone and making an accurate diagnosis would minimize the need for antibiotic usage and potentially reduce antibiotic resistance in these areas. Furthermore, most of the other CNS infections noted previously can be cured with inexpensive drug regimens, but without accurate diagnostic testing, life-saving care is often not given.¹⁵ Our study, therefore, supports the development and accessibility of field-proven rapid diagnostic tests to aid in definitive classification of these illnesses.

The second largest group identified in our study were those with a confirmed CNS infection (Group 2a). Most of the children in this group met WHO criteria for cerebral malaria (109/151, hospital-based prevalence of 14.7/1,000 and 25.5/1,000 for urban and rural sites, respectively) followed by a smaller group of children definitively diagnosed with bacterial meningitis (38/151, hospital-based prevalence of 4.1/1,000 and 13.6/1,000 for urban and rural sites, respectively). In the retrospective studies in Nigeria evaluating neurologic illness in children, they described cerebral malaria as the culprit of neurologic symptoms in 21–28% of children and bacterial meningitis in 18–27%.^{2,3} The slightly lower numbers we report likely are secondary to the high number of children who had to be classified into Group 2b because of lack of confirmatory testing. In that group, there were 198 children who presented with fever, altered mental status, convulsions, and had peripheral parasitemia. A significant proportion of these children would have likely been classified as having cerebral malaria, had CSF analysis been performed and found to be negative for bacterial infection. Similarly, there were an additional 45

children who had a rapid malaria test that was negative and likely represented a significant number of children with bacterial meningitis. Overall, this would make our hospital-based prevalence of cerebral malaria much higher (as high as 66%) than what has been previously described in retrospective studies and our prevalence of bacterial meningitis similar (as high as 17%). Regional differences in malaria prevalence are not surprising as endemicity is dependent on a range of climatic, physical, and population characteristics.^{16,17} Implementation of basic programs to improve community awareness and steps to reduce malaria transmission have the potential to avert hundreds of thousands of cases of cerebral malaria and significantly reduce childhood morbidity and mortality.^{18,19} This makes reliable surveillance data imperative to best inform public health policy and outreach programs in regions such as ours with high burden of disease.

Surprisingly, relatively few children were classified into Group 1, which included diseases such as febrile convulsions, traumatic brain injury, and epilepsy. The hospital-based prevalence for each of these disease entities was much lower than previously reported in retrospective studies on this topic. The reasons for this are not completely clear but are likely multifactorial and related to country-specific factors such as extreme poverty, lack of developed transportation infrastructure, and armed conflict. For example, poverty and conflict often leads families to rely on the more inexpensive and readily available local traditional treatments for various conditions or to not seek care at all for their children. In this scenario, a simple febrile convulsion with rapid return to consciousness or a seizure in a child with epilepsy would not likely lead to presentation at a medical center for treatment or hospitalization. This is supported by the fact that the vast majority of children ultimately classified as having had febrile convulsions in our study experienced complex episodes before presentation. The relatively low prevalence of traumatic brain injury found in our study is likely due, at least in part, to the nearly completely collapsed road system in the DRC.²⁰ Motor vehicle use is extremely limited, and even when used, travel speeds are quite low because of road conditions. This would limit the number of children suffering traumatic brain injury compared with other African nations with better transportation infrastructure. This is important to note because as development occurs, public education and outreach on avoiding crowding on public transportation and the use of safety belts must occur or the prevalence of traumatic brain injury may rise.

Overall mortality in our cohort was quite high at 21%. Another 31% had modest to severe neurologic deficits at the time of testing, leaving only 45% of children with a normal neurological outcome following hospitalization for ANI. We found no significant mortality difference between the urban and rural sites. Most of the deaths and disability occurred in children with presumed or proven CNS infections. Whereas mortality for CNS infections in developed countries ranges from 5% to 8%, reported mortality in developing countries ranges from 15% to 35%.^{21–23} This mortality rate is comparable to our findings and highlights the handicaps of caring for children with acute neurological conditions in settings such as the DRC. Certainly, poverty leading to delayed presentation and educational gaps in terms of following diagnostic and treatment algorithms contribute to the poor outcomes of these children. Beyond these factors, significant resource limitations

stand as extremely important barriers to improving the outcomes of these children. Globally low access to radiologic evaluations such as computed tomography or magnetic resonance imaging or to advanced laboratory examinations leads to difficulties in diagnosis and treatment of neurological conditions and their complications. Many medications that are readily available to aid in the treatment of these diseases in western pharmacies are not on hospital formularies throughout Africa. Moreover, even if desired treatments are available, their administration is often limited by cost as families are required to pay out of pocket for all treatments given. Last, a suboptimal level of availability and functionality of important medical equipment that is used routinely in the management of neurologic conditions in developed countries limits the care of children in less-developed settings. Given the relatively high prevalence of acute neurologic diseases in children identified in this study and the poor prognosis associated with these conditions, improving access to resources may serve as an important step to reduce the significant burden on childhood health of acute neurologic diseases in Africa. One limitation of our study that should be noted is that resource limitations did not allow for detailed neurodevelopmental testing or for longer term neurologic follow-up. Although mortality differences would not change, perhaps those children identified as having neurologic deficits in the short term may have had improvements in functional status over time that we did not capture. Future studies should focus on the longer term neurologic outcomes of these children.

CONCLUSION

This study shows that neurological disorders are highly prevalent in children hospitalized in an urban and rural setting in the DRC. Most of the children were diagnosed with presumed or confirmed CNS infection, which carried a high rate of morbidity and mortality. Socioeconomic realities in the region clearly handicap daily care of these pathologies. Improving provider education and access to crucial diagnostic and therapeutic options are paramount to reducing the impact of these diseases.

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