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Brain Imaging in Normal Kids (BRINK): Community-Based MRI Study in Malawian Children

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Abstract

Objective—To collect normative MRI data for effective clinical and research applications. Such data may also offer insights into common neurologic insults.

Methods—We identified a representative, community-based sample of children aged 9–14 years. Children were screened for neurodevelopmental problems. Demographic data, medical history and environmental exposures were ascertained. Eligible children underwent the Neurologic Examination for Subtle Signs (NESS) and a brain MRI. Descriptive findings and analyses to identify risk factors for MRI abnormalities are detailed.

Results—102/170 households screened had age-appropriate children. 2/102 children had neurologic problems—one each with cerebral palsy and epilepsy. 96/100 eligible children were enrolled. Mean age was 11.9 years (SD 1.5), 43 (45%) were male. No acute MRI abnormalities were seen. NESS abnormalities were identified in 6/96 (6%). Radiographic evidence of sinusitis 29 (30%) was the most common MRI finding. Brain abnormalities were found in 16 (23%): mild diffuse atrophy in 4 (4%), periventricular white matter changes/gliosis in 6 (6%), multi-focal punctuate subcortical white matter changes in 2 (2%), vermian atrophy in 1 (1%), empty sella in 3 (3%), and multifocal granulomas with surrounding gliosis in 1 (1%). Having an abnormal MRI was not associated with age, sex, antenatal problems, early malnutrition, febrile seizures, an abnormal neurologic examination or housing quality (all p's > 0.05). No predictors of radiographic sinusitis were identified.

Conclusion—Incidental brain MRI abnormalities are common in normal Malawian children. The incidental atrophy and white matter abnormalities seen in this African population have not been reported among incidental findings from US populations, suggesting Malawi-specific exposures may be the cause.

Keywords

Sinusitis; abnormal brain MRI; developmental delay

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Introduction

Neurologic disorders contribute substantially to the global burden of disease, but we know little about the pathophysiology of many common tropical conditions. Our insights into tropical diseases have often been elucidated through autopsy studies, but such insights are only available for fatal conditions and fatal cases offering limited insights into brain injury among survivors. Advanced neuroimaging technology can elucidate mechanisms of brain injury *in vivo* but such technologies are generally not available in low income settings. For example, in Africa only 1 of every 5 countries has even a single MRI scanner and in 2004, 40% of African countries surveyed had no functioning CT scanner.

When the Malawi MRI Facility opened in July 2008, the absence of normative data complicated interpretation of brain MRI studies substantially. Difficulties were that (1) Images obtained for evaluation of acute illnesses frequently revealed abnormalities associated with a chronic condition or pre-existing injury. (2) Structural abnormalities, such as unusual cortical nodules and severe vermian atrophy, were seen in pediatric populations. These are not well described in the radiologic literature and the significance of such findings was unclear. (3) Other findings of unclear significance, such as subclinical hydrocephalus, were frequently evident.

In low income, tropical settings individuals may experience CNS insults associated with trauma and infections more frequently than in developed regions. Exposures not generally encountered in developed populations, such as CNS parasitic infections and malnutrition also occur. As a result of these exposures, people from low income, tropical settings who undergo neuroimaging may have unexpected findings which are unrelated to their acute presentation. Without normative data, there is substantial risk of falsely attributing coincidental findings to acute clinical conditions. In the absence of normative data, MRI technology could contribute more confusion than clarification in the tropics. Therefore we undertook a study of brain MRIs in a community-based, representative sample of normal children in Malawi.

Methods

Study Population

From July 2010 to December 2011, a representative, community-based sample of youths 9–14 years old were identified in the Blantyre catchment area using a pseudo-snowball referral technique, the Ten Questions. Using the homes of children enrolled in a previous longitudinal cohort study as a reference point, the research nurse used random directional sampling methods to identify an adjacent household to seek potential participants. Random directional sampling tables were developed for use during community recruitment visits. After identifying the reference household, the research nurse consulted the directional sampling table to determine which adjacent household to select. In the selected household, she then approached the head of household in residence to determine whether there are any children in the appropriate age range residing in the home. If more than one potential participant was identified, a modified Kish grid (1, 2) was used to select a specific youth. If the selected child or their parent declined participation or if no eligible child resided in the home, the declining household was used as the next point of reference and using the same technique as described above, another adjacent household was identified and similarly approached. Once identified, potential normative study subjects were then screened using the Ten Questions and assessed for information regarding their demographic details, socioeconomic status and exposures they have previously had that might result in CNS injuries. Inclusion criteria included being a resident of the sampled household, being 9–14

years old, no neurologic problems identified on the Ten Questions, parental consent, and youth assent. Menstruating females also underwent a urine pregnancy test prior to MRI. This study was approved by the Malawi College of Medicine Research Ethics Committee and Michigan State University's Biomedical Institutional Review Board.

Participant Assessments

Structured interviews were conducted in the local language to ascertain demographic details, socioeconomic characteristics, and environmental assessments and to obtain key aspects of the medical history. Study participants, all of whom had normal neurodevelopment based upon the Ten Questions, underwent the Neurologic Examination for Subtle Signs (NESS) by a pediatric neurologist (Denckla 1985). They then underwent a brain MRI (0.35T GE Signa Ovation, Sag T1, Ax T2, Ax DWI). See Appendix 1 for the full scanning protocol. Two interpreting radiologists used *NeuroInterp,* a web-based multi-variable tool of potentially relevant data points, which was developed and used for this and other ongoing studies using the Malawi MRI. *NeuroInterp* is a computer-based MRI reading program that requires the interpreting radiologists to evaluate and quantify MRI findings based upon the presence of normal structures and/or the scaled rating of any abnormality. The radiologists used *NeuroInterp* to provide independent reviews of the images; any discrepancies between the two radiologists were identified and adjudicated. A panel of physicians, including the QECH neurologists and the physician investigators from the team reviewed each case when a clinical or structural abnormality was noted and categorized each identified structural abnormality as (1) clinically relevant but asymptomatic (2) clinically relevant and symptomatic, (3) clinical significance unknown, or (4) not clinically relevant. Where clinical assessments reveal an examination abnormality without an associated structural abnormality, the team reviewed the images as a group for confirmation.

Data Management & Analysis

A full code book was developed and data (except for NeuroInterp) were initially entered onto paper forms before entry for importation into EPI INFO for analysis. Descriptive data were presented for the prevalence and characteristics of NESS and MRI findings. Due to the range and prevalence of abnormalities identified, we conducted an analysis to identify risk factors for any brain MRI abnormality (all abnormalities combined excluding sinusitis and normal variants) as well as for risk factors for sinusitis. For age, the only continuous variable, Student's t-test was used. Otherwise, the Pearson's chi-square test was used unless sample size required Fisher's Exact test. P-values of <0.05 were considered statistically significant. The sample size of 100 was chosen because it was feasible both logistically and financially. The power yielded by a chi-square test with 1 degree of freedom, alpha=0.05 and n=100 is 0.61, 0.89 and 0.97 for X2 of 5, 10 and 20, respectively.

Results

Of 170 households screened, 102 had an eligible child. Nine of 102 screened positive on the Ten Questions for possible developmental problems. Seven had simple febrile seizures and were eligible. One child had cerebral palsy and one had epilepsy and these were excluded. Thus 96 eligible children were enrolled. Mean age was 11.9 years; SD=1.5 years, 42/96 (44%) were male. All were in school except one child whose parents reported being unable to pay school fees.

Study subject characteristics included: 4/96 problem pregnancies (4.2%), 6/96 problem births (6%), 5/96 with a history of coma in the context of an acute illness (5%), 2/96 with a history of underweight status or growth problems (2%), 30/96 with history of prior hospitalization (31%), and 8/96 with a history of prior provoked seizures (8%).

On the NESS, 6/96 (6%) children had clinical exam abnormalities. See Table 1. These individual findings included poor fine motor control especially on the left, intellectual disability, poor fine motor and balance, saccadic smooth pursuit and vestibular ocular reflex (VOR), isolated saccadic smooth pursuits and poor coordination of left hand.

No acute MRI changes were seen. A normal variant MRI was seen in 5/96 (5%) (Table 2). Radiographic evidence of sinusitis was the most common finding - occurring in 28 (29.2%) children. Abnormal brain structures were found in 16/96 (17%) children and comprised the following: mild diffuse atrophy, mild periventricular white matter changes/gliosis, multifocal punctuate subcortical white matter changes, vermian atrophy and empty sella, and multifocal granulomas with surrounding gliosis (Table 3). Having an abnormal MRI was not associated with age, sex, history of problem pregnancy, history of problem birth, history of illness with coma, history of growth/weight problems, history of prior hospitalization, history of seizures, abnormal physical exam or housing quality (Table 4).

Factors evaluated for an association with the radiographic evidence of sinusitis were age, sex, history of growth/weight problems, housing quality and fuel for cooking (electricity, charcoal or wood) (Table 5). None show significance but trends were seen in fuel for cooking with the use of charcoal or wood being associated with higher rates of sinusitis.

Conclusions

Many of the impressive advances in the clinical and basic neurosciences over the past two decades were made possible through ever-evolving imaging technologies. Critical advances in treatments for common conditions (e.g., disease modifying agents for multiple sclerosis, “clot busters” for acute stroke, more refined surgical resections for epilepsy) are predicated on access to imaging. As imaging becomes more available, at least at a small minority of research facilities in low income tropical settings, MRI technology may offer critical insights into the nature, progression, and clinicopathologic natural history of CNS infections and infestations common in tropical and developing country settings. Neuroimaging also has the potential to allow researchers to better understand clinical differences in disease etiology for neurologic problems that are globally ubiquitous but which exhibit unique epidemiologic parameters in different geographical settings.

A substantial proportion of healthy Malawian children have evidence of structural brain abnormalities in the absence of clinical symptoms. These included atrophy and empty sella. Radiographic “sinusitis” with no clinical correlate is also common. To our knowledge, these are the first normative brain MRI data from Africa and the first report of incidental findings from an African population. Incidental findings in healthy individuals have been reported from Western populations. A study of 2,536 young men in the German military found low rates of abnormalities such as arachnoid cysts in 1.7%, and vascular abnormalities and intracranial tumors in 0.5%. A review of 1000 MRIs obtained from healthy volunteers participating in research at the US National Institute of Health in Bethesda, MD included mostly adults. Incidental findings were dominated by age-related changes but did include sinusitis in 13.2%. (Katzman et al. 1999). Among pediatric populations a study of 225 children in Cali-fornia also identified sinusitis as being a common finding—seen in 9.3% of children. None of the children in this California-based sample exhibited the atrophy and white matter abnormalities seen in our Malawian cohort, suggesting that a factor or factors innate to Malawi may be the underlying cause.

This study is primarily limited by the small sample size and the field strength of the MRI. Due to the limited number of individuals with any specific MRI abnormality, we had limited power to identify risk factors for specific abnormalities. Furthermore, the MRI field strength

may have led to an underestimation of structural abnormalities further limiting our analytic capacity. Patients were selected using a snowball sampling mechanism based upon the households of children from a prior study who were admitted to the hospital with cerebral malaria. The 80/20 urban/rural distribution of the sample population in the BRINK study reflects the QECH Blan-tyre referral population, but this was not a systematic, population-based sample. The sampling frame may have favored children from areas with more expeditious hospital referral routes or it may have preferentially selected for children residing in more malarial regions. Nonetheless, this report provides important normative data for clinicians and researchers using neuroimaging in Malawi and similar regions.

Incidental brain MRI abnormalities are common in normal Malawian children. The incidental atrophy and white matter abnormalities seen in this African population have not been reported among incidental findings from US populations suggesting Malawi-specific exposures may be the cause.

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Table 1

Abnormalities identified by the Neurologic Examination for Subtle Signs (n=96)

Subject ID	Finding
BR009	Poor fine motor control especially on the left
BR044	Intellectual disability
BR063	Poor fine motor and balance
BR064	Saccadic smooth pursuit and saccadic vestibulo-ocular reflex
BR070	Saccadic smooth pursuits
BR073	Poor coordination of left hand

Table 2

Normal Variant Brain MRI Findings (n=96)

Subject ID	MRI Finding
BR041	Peritrigonal cyst
BR015	3mm left peritrigonal cyst
BR079	Posterior fossa (3.5 cm) arachnoid cyst
BR068	Left temporal (3 cm) arachnoid cyst
BR032	Bilateral hippocampal cystic changes (right > left)
BR063	Cavum septum pellucidum
BR095	

Table 3

Brain MRI Abnormalities Identified (n=96)

Subject ID	MRI Finding
BR001	Vermian atrophy and empty sella
BR004	Mild Diffuse atrophy
BR005	Periventricular white matter changes (mild - moderate) and mild diffuse atrophy
BR007	Empty sella
BR012	Periventricular white matter changes (mild)
BR022	Mild diffuse atrophy
BR027	Periventricular white matter changes (mild) and s multifocal punctate subcortical white matter changes
BR032	Mild diffuse atrophy
BR034	Periventricular white matter changes (mild)
BR036	Empty sella
BR039	Right hippocampal cystic changes with surrounding gliosis
BR048	Periventricular white matter changes (mild - moderate)
BR051	Empty sella
BR073	Very small right frontal white matter cystic focus with high T2 signal
BR084	Periventricular white matter changes (mild - moderate) and multifocal punctate subcortical white matter changes
BR095	Cystic lesion and solid areas of localized edema consistent with a granulomatous process

Table 4

Risk Factor Analysis for Brain MRI Abnormalities

Characteristics	Abnormal MRI (n=15)	Normal MRI (n=81)	p-value
Age	12.1 (mean yrs)	11.9 (mean yrs)	0.71
Sex (male)	8 (53%)	34 (42%)	0.42
History of problem pregnancy	0	4 (5%)	0.76
History of problem birth	2 (13%)	4 (5%)	0.23
History of illness with coma	1 (14%)	4 (5%)	0.32
History of growth/weight problems	0	2 (3%)	0.71
History of Hospitalization	5 (33%)	25 (31%)	0.53
History of seizure	2 (13%)	6 (7%)	0.36
Abnormal NESS	1 (7%)	6 (7%)	0.70
Housing quality	7.5	6.3	0.23

Table 5

Risk Factor Analysis for Radiographic Sinusitis

Characteristics	Sinusitis	No sinusitis	p-value
Age (mean)	11.9 (SD 1.5)	12.6 (SD 1.5)	0.26
Sex (male)	3 (43%)	39 (44%)	0.28
History of growth/weight problems	0	2 (2%)	0.86
Housing quality (mean score)	6.5 (SD 3.7)	4.6 (SD 3.4)	0.28
Fuel for cooking (n=95)			0.62
-Electricity	1 (3.6%)	3 (4.5%)	
-Charcoal	19 (67.9%)	51 (76.1%)	
-Wood	8 {28.6%}	13 (19.4%)	