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FULL-LENGTH ORIGINAL RESEARCH

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Assessment and treatment of childhood epilepsy in Haiti

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Abstract

Objective: The global burden of pediatric epilepsy is disproportionately concentrated in low- and middle-income countries (LMICs). However, little is known about the effectiveness of current treatment programs in this setting. We present the outcomes of children who were assessed and treated at the Clinique D'Épilepsie de Port-au-Prince (CLIDEP), the only pediatric epilepsy referral center in Haiti.

Methods: A 10-year retrospective review of children consecutively assessed and treated at CLIDEP was performed. The primary outcome was seizure control following treatment for epilepsy. The secondary outcome was an accurate determination of the diagnosis of epilepsy. A data-driven principle component regression (PCR) analysis was used to identify variables associated with outcomes of interest.

Results: Of the 812 children referred for evaluation, most children (82%) underwent electroencephalography to investigate a possible epilepsy diagnosis. Very few children (7%) underwent cranial imaging. Although many patients were lost to follow-up (24%), most children who returned to clinic had less frequent seizures (51%) and compliance with medication was relatively high (79%). Using PCR, we identified a patient phenotype that was strongly associated with poor seizure control which had strong contributions from abnormal neurological examination, higher number of antiepileptic drugs, comorbid diagnoses, epileptic encephalopathy or epilepsy syndrome, and developmental delay. Head circumference also contributed to epilepsy outcomes in Haiti with smaller head sizes being associated with a poor seizure outcome. A dissociable phenotype of febrile seizures, suspected structural abnormality, epileptic encephalopathy or epilepsy syndrome, and higher seizure frequency was associated with a diagnosis of epilepsy.

Significance: We describe the current landscape of childhood epilepsy in Haiti with an emphasis on diagnosis, treatment and outcomes. The findings provide evidence for the effectiveness of programs aimed at the diagnosis and management of epilepsy in LMICs and may inform the allocation of resources and create more effective referral structures.

KEYWORDS

Caribbean, Global health, low- and middle-income countries, Pediatric

1 | INTRODUCTION

Epilepsy affects more than 50 million people worldwide.[1,2] Cumulatively, seizure disorders account for 13 million disability-adjusted life years (DALY), or the number of years lost due to ill-health, disability, or early death.[1,2] Young children, particularly those less than one year of age, represent the most affected age group.[2-4] In addition, low- and middle-income countries (LMICs) are disproportionately affected and have a higher severity of disease and greater years of life lost (YLL) as a result of epilepsy.[1] Epilepsy leads to significant medical and psychiatric morbidity[5,6] and mortality.[7,8] It also imposes a substantial burden on caregivers, carries social stigma, and contributes to the propagation of the cycle of poverty.[9,10] These factors further impede adequate treatment of epilepsy in LMICs, where the treatment gap is estimated to be up to 75%.[11-13] In order to address this important global health problem, the World Health Organization (WHO) has called for urgent, coordinated action to treat epilepsy and its causes at the global, regional, and national levels.[13]

Haiti is the most impoverished country in the Western Hemisphere with 23% of the population living in severe multidimensional poverty.[14] While recent efforts have focused on the delivery of neurological care in Haiti, namely for the treatment of infantile hydrocephalus,[15-17] epilepsy remains a medical and societal epidemic in the country. Epilepsy is estimated to affect roughly 24 000 Haitians.[1] This estimate however was based on very limited data and may not be indicative of the true scope of the illness. Several risk factors for epilepsy are endemic in Haiti including intracranial infections, such as neurocysticercosis[18-21] and neonatal meningitis.[22,23]

The treatment of epilepsy in Haiti is limited by several factors. First, there are almost no healthcare providers specialized in disorders of the nervous system.[15,16] Second, health infrastructure is lacking. For example, at last count, the entire country had only three functioning computed-tomography (CT) scanners and one trauma hospital.[15] Additionally, there are significant barriers in access to medications due to unavailability or prohibitive costs and formulations available may vary considerably in their composition. Furthermore, poor understanding and social stigma surrounding the illness limit access to potentially available and low-cost treatments. In recent years, the treatment of neurological diseases in Haiti has gained increasing emphasis in various global health forums.[15,16,24] Several residency and fellowship training initiatives and new infrastructure projects have generated capacity and increases in treatment availability.[15-17]

Further efforts at mitigating the burden of pediatric epilepsy in Haiti and other LMICs must be informed by relevant evidence.[13] Given the high prevalence of epilepsy and the paucity of data regarding the challenges of diagnosis and treatment, we sought to characterize the assessment and effectiveness of treatments in Haiti.

Key points

- Haitian children with epilepsy had a high disease burden at presentation and were often evaluated by EEG with few children undergoing any brain imaging
- Patients at CLIDEP had significant seizure improvement and a low rate of medication side effects or noncompliance although 26% did not return for follow-up
- PCR analysis identified factors associated with poor seizure outcome in Haiti including several established risk factors as well as a small adjusted head circumference
- Febrile seizures, structural abnormality, epileptic encephalopathy, or syndrome were associated with a future diagnosis of epilepsy in Haiti

We reviewed all the records of patients treated from 2008 until 2018 at the only pediatric epilepsy referral center in Haiti, the Clinique D'Épilepsie de Port-au-Prince (CLIDEP). The primary outcome of interest was the assessment of clinical outcomes following the evaluation and treatment of epilepsy. The secondary outcome of this study was the evaluation of patient characteristics leading to a diagnosis of epilepsy.

2 | METHODS

2.1 | Study covariates

Approval was obtained from the administration of CLIDEP to collect and digitize all paper records from 2008 to 2018 from CLIDEP. Once digitized, the charts were anonymized and analyzed by three independent reviewers (GC-S., TB-C., and EM). Patient demographics, anamnesis, physical examinations, diagnostic tests, diagnosis, prescribed treatments, medication adherence, side effects of treatment, and seizure frequency at follow-up were extracted. The variables collected were established a priori and derived from recommended guidelines for the evaluation and referral of epilepsy.[25] Drug-resistant epilepsy was defined as treatment failure with ≥2 antiepileptic medications.[13] Percentiles for head circumference based on age and sex were generated from clinical measurements using the sds function of the "childsds" package in R statistical software.[26] The reference data for that package were the WHO child growth standards 2012.[27]

2.2 | Principal component regression

A data-driven method, principle component regression (PCR), was used to identify associations between clinical covariates and outcomes of interest. This method, based on principal component analysis (PCA), allows all clinical variables to be decomposed into principal components. Principal components represent linear combinations of all variables that represent unique or orthogonal dimensions of the variance.[28] Each principal component can be conceptualized as a combination of correlated variables that make up a singular patient phenotype.[28] PCR allows us to correlate patient phenotypes with outcomes of interest.[29]

The data were organized such that variables with fewer than 10 instances were either concatenated or excluded from the analysis to provide adequate variance to model. For example, epilepsy etiology was comprised of multiple sparse descriptions which were concatenated into structural vs. acquired subgroups.

The data were comprised of categorical, ordinal, and continuous variables; therefore, the Factor Analysis of Mixed Data (FAMD) function in the "FactoMineR" package of R was used to perform the analysis.[30] FAMD can decompose mixed-data types into dimensions representing linear recombinations of the original covariates, providing unique (orthogonal) patient phenotypes. Dimensions with eigenvalues greater than 1 were considered meaningful.

Missing data were imputed using the imputeFAMD function of the "missMDA" package in R.[31] The number of dimensions to be included in the principle component analysis was estimated using the estim_ncpFAMD function of the "FactorMineR" package.[30] The threshold for statistical significance was set at $P < .05$.

2.3 | Primary and secondary outcomes

The primary outcome of this study was to determine patient phenotypes associated with improved seizure symptoms following assessment and treatment for children diagnosed with epilepsy at CLIDEP. Improvement in seizure symptoms was defined as a patient or caregiver reported decrease in seizure frequency and/or improvement in comorbid epilepsy symptoms such as epileptic encephalopathy and developmental or motor delay.

Given that a large proportion of children are referred for evaluation but did not have epilepsy, the secondary outcome of interest was the determination of patient phenotypes associated with a diagnosis of epilepsy following evaluation at CLIDEP. A PCR analysis of variables available to referring physicians for all patients evaluated at CLIDEP was used to identify those which had a strong association with the diagnosis of epilepsy.

3 | RESULTS

3.1 | Descriptive analysis

Eight hundred and twelve children were evaluated at CLIDEP over a 10-year period. Only two thirds of all patients (542/812) referred to the epilepsy clinic for assessment and management of epilepsy were diagnosed with a seizure disorder. The male-to-female ratio was roughly equal at 1.15. The mean age at the initial visit to the clinic was 7.5 years while the mean age of symptom onset was 4.4 years.

History and physical examinations revealed that patients treated in Haiti had a heavy epilepsy burden, which was associated with comorbid conditions on presentation in 40% of children. The most common comorbid diagnosis was developmental delay, which in this context implied a combination of language delay and/or a delay in expected primary school achievement. A substantial portion of patients had more than one seizure per month at presentation (Table 1). Seizure semiology most often consisted of loss of awareness, and events were frequently considered disabling by the patient or their family. One third of patients diagnosed with epilepsy had an abnormal neurological examination (Table 1).

The primary diagnostic evaluation consisted of a one-time electroencephalography (EEG) in the majority of cases (Table 1). A small minority of children, only 7% of all patients diagnosed with epilepsy, underwent brain imaging. A single patient underwent MRI, whereas the remainder had CT imaging. Because of the lack of imaging, the majority of children did not have a documented etiology for their seizures (Table 2).

During the course of their treatment, nearly all children diagnosed with a seizure disorder were treated with antiepileptic drugs (AEDs) (Table 3). The most commonly prescribed AED was carbamazepine, followed by phenobarbital. While 26% of patients were lost to follow-up, the majority of those with multiple visits had a documented reduction in seizure frequency and reported an improvement in symptoms. Most patients remained on a single AED at last follow-up with high treatment adherence rates (76%) for those for which this outcome was recorded. Few medication side effects were reported, and drug-resistant epilepsy was notably uncommon in this population (Table 3).

3.2 | Clinical phenotypes associated with seizure control

The primary outcome of interest was patient phenotype associated with improvement in epilepsy at last follow-up in patients with epilepsy. The data underwent PCR for dimensionality reduction, yielding five meaningful components with eigenvalues greater than 1. When these components were

TABLE 1 Anamnesis and physical examination data for children diagnosed with epilepsy

	Number of patients	% of epilepsy patients
Seizure frequency at baseline:		
>12/y	209	39
1-12/y	176	32
<1/y or seizure-free	17	3
Not specified	140	26
Worst seizure type		
Impaired awareness	439	81
Motor	55	10
Not specified	48	9
Seizure severity		
Disabling	424	78
Nondisabling	60	11
Not specified	58	11
Epilepsy duration		
>1 y	236	44
<1 y	235	43
Not specified	71	13
Comorbid diagnosis	224	41
Developmental delay	149	28
Febrile seizures	66	12
Perinatal insult	61	11
Motor delay	41	8
Other medical disease	40	7
Global developmental delay	19	4
Attention disorder	17	3
Microcephaly	16	3
Headache	15	3
Other	15	3
Abnormal neurological examination	196	36
EEG result		
Abnormal	390	72
Normal	53	10
Not performed	99	18
Neuroimaging result		
Abnormal	26	5
Normal	13	2
Not performed	503	93

TABLE 2 Seizure etiology and presence of epileptic encephalopathy in children diagnosed with epilepsy

	Number of patients	% of epilepsy patients
Epileptic encephalopathy[a]		
Yes	24	4
No	253	47
Not specified	265	49
Epilepsy syndrome		
Yes	67	12
No	244	45
Not specified	231	43
Etiology		
Structural	67	12
Acquired	52	10
Not specified	423	78

[a]Defined as progressive psychomotor dysfunction attributable to epilepsy, as best as can be gleaned from retrospective chart review.

entered into a logistic regression model with improvement in seizure outcomes as the dependent variable, two significant dimensions associated with outcome were identified (Dim 1: estimate = −0.44, $P < .001$, variance explained = 4.2%; Dim 2: estimate = 0.24, $P < .01$, variance explained = 3.0%). A biplot of these two dimensions is presented in Figure 1.

The first dimension was associated with a lack of improvement in seizure symptoms (OR 0.64; $P < .001$), whereas the second dimension was associated with improvement in seizure symptoms (OR 1.25; $P = .009$). The first dimension had large contributions from abnormal neurological examination, developmental delay, higher number of AEDs, epilepsy syndrome or epileptic encephalopathy, and comorbid diagnoses. The second dimension had strong contributions from febrile seizures. Head circumference by percentile adjusted for age and sex had a strong contribution from both Dim 1 and Dim 2. This suggests that a smaller head circumference was associated a lesser likelihood of seizure improvement compared to a normal or larger head circumference.

3.3 | Clinical phenotypes associated with diagnosis of epilepsy

A second PCR of all children evaluated at CLIDEP was performed to determine patient phenotypes associated with a subsequent diagnosis of epilepsy. Five meaningful components were derived with eigenvalues greater than 1. On logistic regression, two of these were significantly associated with a diagnosis of epilepsy (Dim 2: estimate = −0.81, $P < .001$, variance explained = 8.9%; Dim 3: estimate = 0.48, $P < .001$, variance explained = 6.2%). A biplot of these dimensions is presented in Figure 2.

The first of these dimensions was associated with a diagnosis other than epilepsy (OR = 0.44; $P < .001$), whereas the

TABLE 3 Seizure outcomes in patients treated for epilepsy

	Number of patients	% of epilepsy patients
Antiepileptic drug (AED) use	533	98
Type of AED prescribed		
Carbamazepine	251	47
Phenobarbital	191	36
Valproate	136	26
Clonazepam	36	7
Levetiracetam	24	5
Phenytoin	10	2
Other	18	3
No documented follow-up	142	26
Seizure frequency at last follow-up		
>12/y	79	15
1-12/y	97	18
<1/y or seizure-free	161	30
Not specified	205	38
Improvement in seizure symptoms		
Yes	279	51
No	50	9
Not specified/No follow-up	213	39
Number of AEDs per patient		
1	402	74
2	97	18
≥3	28	5
None/Not specified	15	3
Medication adherence		
Good	206	38
Poor	53	10
Not specified/No follow-up	283	52
Medication side effects		
Yes	30	6
No	385	71
Not specified	127	23
Drug-resistant epilepsy		
Yes	45	8
No	416	77
Not specified	81	15

second was associated with the final determination of a seizure disorder (OR = 1.61; $P < .001$). Seizure type and seizure severity contributed significantly to the former. Conversely, the presence of febrile seizures, a suspected structural etiology, suspected encephalopathy or epilepsy syndrome, and a higher seizure frequency at baseline collectively comprised a phenotype that was associated with the latter.

4 | DISCUSSION

This study is the first to examine the assessment and treatment of pediatric epilepsy in Haiti. We report several encouraging trends. Most children who returned for follow-up had improvement in associated epilepsy symptoms such as reduced seizure frequency on AEDs, as well as improvement in developmental delay or epileptic encephalopathy. These children also demonstrated high rates of medication compliance with few side effects. We also identified patient phenotypes associated with poor seizure control and various challenges to the assessment and treatment of epilepsy in Haiti. Many of the referred children did not have a diagnosis of epilepsy. In addition, those who were determined to have epilepsy rarely underwent cranial imaging and an etiology for the epilepsy was often elusive. Finally, many patients were lost to follow-up.

4.1 | Seizure control in Haiti

The primary goal of this study was to identify patient phenotypes associated with improvements in seizure symptoms at follow-up in the LMIC setting. Results of the PCR indicated that several variables contribute to poor seizure outcome in Haiti. These characteristics, which are all well-established risk factors for drug-resistant epilepsy, included the following: abnormal neurological examination, suspected epileptic encephalopathy, suspected epilepsy syndrome, developmental delay, drug-resistant epilepsy, and higher number of AEDs.[32-34]

This provides support for the use of tools developed for high-income countries in a low-resource setting.

Although PCR does not yield independent associations between individual coavariates and outcomes, head circumference was prominently featured in both PCR components. This suggests that a smaller adjusted head circumference contributes to a lack of improvement in seizure symptoms. Alternatively, normo- or macro-cephalic children were associated with an improvement in seizure symptoms. Although this association has not been established in developed countries,[32-34] these findings are broadly consistent with an Egyptian study which demonstrated that smaller head circumference was associated with both developmental delay and epilepsy.[35] Indeed, these two conditions are highly collinear on PCR in the current study population. Furthermore, a Sudanese study also reported a strong association between severe growth restriction and childhood epilepsy compared to control patients.[36] The authors hypothesized that the social stigma and added caregiver burden of epilepsy resulted in worsening poverty and malnutrition for those patients in Sudan. This association is well documented in other LMICs.[9,10]

Alternatively, we speculate that there may be an underlying association with undiagnosed postinfectious hydrocephalus and patients with larger head circumference. This may

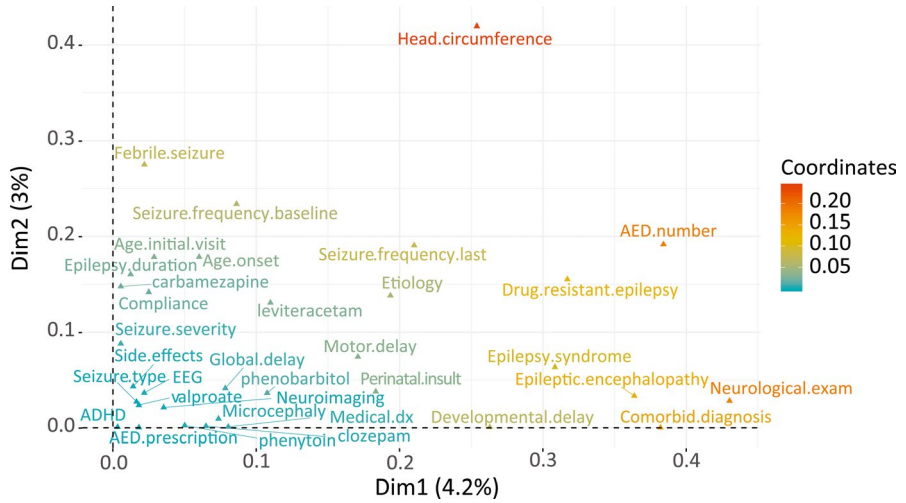
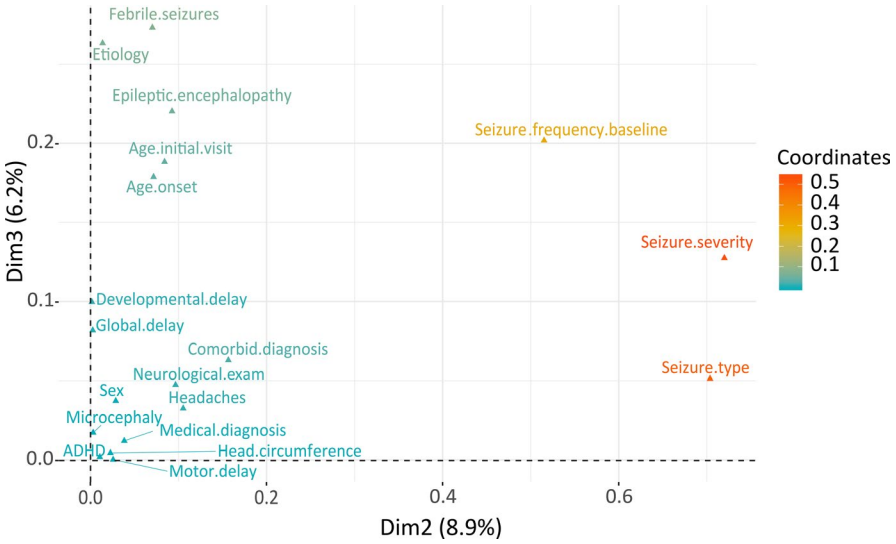


FIGURE 1 Associations with seizure outcome. Biplots demonstrating latent variables associated with seizure outcome for children treated for epilepsy in Haiti. The first dimension had large contributions from abnormal neurological examination, developmental delay, higher number of AEDs, epilepsy syndrome or epileptic encephalopathy, and comorbid diagnoses. The second dimension had strong contributions from febrile seizures. Head circumference by percentile adjusted for age and sex had a strong contribution from both Dim 1 and Dim 2

FIGURE 2 Associations with an accurate diagnosis of epilepsy. Biplots demonstrating latent variables associated with an accurate diagnosis of epilepsy. The first of these was dominated by seizure type and severity. The second had large contributions from the presence of febrile seizures, a suspected structural etiology, suspected encephalopathy or epilepsy syndrome, and a higher seizure frequency at baseline



portend the presence of a postinfectious or other lesional epilepsy etiologies which may have a better response to medical treatments than generalized pathology. Future studies assessing the relationship between head circumference, nutritional status, and intracranial findings in Haitian children with epilepsy are needed to inform targeted interventions.

4.2 | Diagnosis of epilepsy in Haiti

Our findings demonstrated a three-year mean gap between symptom onset and initial evaluation at CLIDEP. Although wait-time data were not directly available, this discrepancy suggests that access to basic neurological care for epilepsy patients is severely lacking in Haiti. In addition, approximately one third of patients evaluated at CLIDEP were not found to have a seizure disorder. Together, these findings provide evidence for the need for more robust referral infrastructures within the medical community.

In the current report, we identified several factors that contributed to a subsequent diagnosis of epilepsy. Results from PCR suggest that referring physicians should pay special consideration to frequently reported seizures (≥ one per month) as well as to anamnesis and physical examination findings which may suggest a structural etiology, epileptic encephalopathy, or the presence of an epilepsy syndrome. These findings should inform the urgent referral of patients for assessment and treatment.

A significant challenge identified in the current study was the near complete lack of basic intracranial imaging, likely related to limited access to scanners in this region.[15] Only 7% of patients received a CT scan, and a single patient from over

800 analyzed records underwent an MRI. Inequities in access to imaging may explain the discrepancy between the large number of patients with abnormal examination findings and the small proportion who were diagnosed with a specific etiology for their epilepsy. This diagnostic uncertainty is likely detrimental to the evaluation and proper treatment of patients with epilepsy. Interventions aimed at improving the imaging infrastructure would likely benefit most epilepsy patients in Haiti.

A third challenge related to the substantial proportion of patients who were lost to follow-up after evaluation. Possible explanations for this include the following: treatment abandonment, spontaneous improvement in seizure symptoms, death from epilepsy, poor documentation, prohibitive distance to clinic, poor access to prescribed medicines, inaccessible second-line medications, severe poverty, and seeking alternative treatments. It is possible that the high treatment response rate, low rates of side effects, and modest proportion of patients diagnosed with drug-resistant epilepsy are biased by the failure of this cohort to return for reassessment. A prospective analysis aimed at simplifying these complex relations is required to promote care for children with epilepsy in Haiti.

4.3 | Clinical implications

In the developing world, there is increasing recognition of the need for a comprehensive epilepsy strategy, including surgical treatments to address the burden of uncontrolled seizures. Surgery in the developing world could indeed prove to be a valuable tool in the clinician's armamentarium. Surgical treatment is often a curative, single intervention with a reasonable safety profile even in LMICs.[37-39] In addition to being feasible and effective, surgical treatment reduces stigma and improves quality of life in the LMIC setting.[39] Furthermore, epilepsy surgery may be a cost-effective treatment alternative[40] which can obviate certain challenges such as medication access, adherence, and potentially follow-up. Given increasing emphasis on inequities in access to surgical care and Haiti's growing neurosurgical capacity,[15] a national epilepsy surgery strategy may improve the care of affected children.

4.4 | Limitations

This study has several important limitations. Firstly, the study suffers from the limitations of a retrospective review, including selection bias, whereby candidates who benefit the most may be more likely to return for follow-up. The dataset also did not allow for the assessment of important determinants of health such as accessibility and affordability of care, poverty, and malnutrition. Furthermore, the large number of missing data values limited the variance explained by the regression models. Better documentation of patient interactions especially regarding seizure improvement at follow-up, treatment side effects, and barriers to accessing health care and medications would help provide a clearer picture of the challenges which still need to be addressed in Haiti.

5 | CONCLUSIONS

This study provides an overview of the landscape of pediatric epilepsy in Haiti. The results presented here have identified encouraging trends, established patient characteristics associated with epilepsy outcomes, uncovered variables that may inform the referral process, and revealed important challenges for the treatment of childhood epilepsy in the LMIC setting. This work is intended to be an impetus for future research and development of effective interventions for the care of epilepsy patients in Haiti and in other LMICs.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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