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A survey on the association of seizure disorders with asthma and allergies in children

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Impact statement

Little is known about the relationship between allergic diseases and seizure disorders. The number of comorbid allergic diseases is more related to the development of types of seizures than types of allergic disease.

Summary

Background. *Little is known about the relationship between allergic diseases and seizure disorders including epilepsy. It is hypothesized that inflammation from allergic diseases may predispose children to seizures. The aim of this study is to investigate the frequency of seizure disorder in children with asthma and allergy.* ***Methods.*** *This is a cross-sectional survey study of parents of 1,300 children and adolescents under 20 years of age referred to the Allergy and Asthma Clinic of Imam Ali Hospital (Karaj) who were asked to complete a screening questionnaire for seizures in their children. Parents who reported any history of seizures in their children were contacted to answer a second in-depth questionnaire to determine more detail of type, triggers, and treatment of seizures.* ***Results.*** *A total of 705 males (62%) and 433 females (38%) participated in this study, with a mean and standard age of 6.62 ± 4.57 years. Among them, 70.6% had asthma, 15.2% had allergic rhinitis, 5.6% had atopic dermatitis, 3.5% had urticaria, 2.7% had food allergies, 1% had drug allergies, and 1.4% had other allergic diseases. Additionally, 88 patients (7.7%) had a history of doctor-diagnosed seizures, 57 patients (5%) had febrile convulsions, and 15 patients (1.31%) had idiopathic epilepsy. There was no significant relationship found between febrile convulsions, seizures, and epilepsy with the type of allergic diseases. However, a significant association was observed between the number of comorbid allergic diseases in patients with febrile convulsions (OR 1.4, 95%CI 1.07-1.83, p = 0.013). There was also an association between the epilepsy and comorbid allergic diseases number with an OR 1.84, 95%CI 0.28-12, however the risk of epilepsy was increased by 0.84% but this increase was not significant. Regarding the relation between the number of allergic diseases in parents and idiopathic epilepsy in their children, a significant association was found only for mothers (OR 1.28, 95%CI 1.04-2.23, p = 0.024), but not for fathers (p > 0.05).* ***Conclusions.*** *Febrile convulsion is associated with the number of comorbid allergic diseases in children and the mother's number of allergic diseases is more related to idiopathic epilepsy in children than the father's.*

Introduction

Allergic diseases including asthma, allergic rhinitis, atopic dermatitis and food allergy are the most common chronic health conditions in the world. These diseases affect approximately 20% of the global population worldwide now (1), only respiratory allergic diseases, namely asthma and allergic rhinitis, affect approximately seven hundred million people (2).

Allergic diseases such as atopic dermatitis (AD) and asthma are associated with multiple neuropsychiatric and mental health disorders in children and adults, including depression, anxiety, attention deficit hyperactivity disorder and autism (3-6). Despite growing evidence of such a connection, little is known about the relationship between allergic diseases and other neurological disorders, including epilepsy. Seizures are one of the most common neurological disorders in children. In Iran, the lifetime prevalence of childhood seizure has been reported to be 3.2%, and approximately 60% of these cases were related to convulsions caused by fever (7).

Many adults with epilepsy experience the onset of seizures in childhood. Almost a quarter of children with epilepsy are drug-resistant, and the exact pathophysiology of epilepsy is still unknown, but research has determined the importance of neuroinflammation and related cytokines in this regard (8, 9). A meta-analysis revealed a positive link between several different epilepsy etiologies and elevated levels for IL-1ra, IL-1β, IL-6 and CXCL8/IL-8. It is also reported the increased levels of IL-1α, IL-7, and IL-13, as well as the chemokines CCL2-5, -19, and -22, exclusively in brain tissue (9). Other studies have also shown the importance of the relationship between microglial cells and mast cells in nervous system inflammation (5).

Animal studies show that the inflammatory pathways involved in allergic diseases may also be activated in the brain and contribute to the development of epilepsy (10). Previous epidemiological studies have shown an association between epilepsy and asthma in adults (11, 12), but the mechanism of association between allergic disease and seizures is still unclear. Perhaps inflammation caused by allergic disease exposes children to seizures. Overall, there are very few studies on the relationship between epilepsy and allergic diseases, especially in childhood, and research on the relationship between these two diseases is new. The aim of this study is to investigate the frequency of seizure disorder in children with asthma and allergy.

Materials and methods

This study was done in a cross-sectional manner. The method in this study was availability sampling. The patients were selected from allergy clinics of Imam Ali Hospital in Karaj. The code of ethics (IR.ABZUMS.REC.1398.138) was obtained from the Ethics Committee of Alborz University of Medical Sciences.

In this study, 1,300 patients with asthma and other allergic diseases under 20 years of age who referred to the allergy clinics of this center in 2017-2018 and met the inclusion criteria and did not have the exclusion criteria were selected. Inclusion criteria included age below 20 years, parental and patient consent to participate in the study, and diagnosis of allergic disease/asthma by an asthma and allergy specialist. Exclusion criteria included lack of consent of the patient or their parents to participate in the study and the reason for referral was other than allergic diseases. After obtaining the consent form from these 1,300 patients and explaining the plan by the researcher, the questionnaire was completed for the patients. In this questionnaire, you will be asked about demographic information including age, gender, and place of residence. Then, you will be asked about the reason for the referral and the type of allergic disease or diseases, including asthma, nasal allergy, eye allergy, eczema, urticaria, food allergy, drug allergy, and pruritus. The diagnosis of allergic disease or asthma is confirmed by an asthma and allergy specialist. Then, the patients or their parents were asked about the "history of mentioned allergic problems in first-degree relatives" and "history of seizure diagnosis by doctor in the child". If the patient had a positive history of seizures, a second questionnaire was given to the patients, asking questions such as the age of the first onset of seizures, recurrence of seizures, accompanying seizures with or without fever, states during seizures, cause of them, history of drug use, drugs currently used, the history of drug sensitivity following the use of anticonvulsant drugs, other neurological diseases and the developmental status.

In this study, if a patient with normal neurologic physical exam and brain MRI had more than one seizure without an underlying cause such as fever, metabolic or infectious diseases, it was classified as idiopathic epilepsy, and if there was an identifiable cause for repeated and recurring seizures, it was classified as chronic symptomatic epilepsy. If the onset of convulsions in a child was accompanied by fever and in the age range of 6 months to 6 years without central nervous system infection or other predisposing disorders, it would be classified febrile convulsions. After completing the questionnaires, the type of seizures in children was categorized based on the information recorded by the parents, the consultation, and opinion of a pediatric neurology specialist. At the end, the data were collected and subjected to statistical analysis, and the obtained statistics were finally compared with the global average statistics of childhood seizures.

Statistical analysis

Continuous baseline demographic and clinical data are presented as mean ± standard deviation and grouped data as frequencies and percentages. The comparison of means between the groups, for quantitative variables with approximately normal distribution, was performed using paired or independent t-tests

and one way ANOVA as appropriate. Chi-square test or Fisher's exact test were used to determine the independence of the two categorical variables. P-value less than 0.05 was considered as significant. All analysis ere done using SPSS software version 24.

Results

Out of 1,300 patients, 45 patients were excluded due to lack of proper cooperation and 52 patients due to repetition, 35 patients due to incomplete and unreliable information, 10 patients due to declaration of lack of consent to participate in the study, and 20 patients due to immunodeficiency; after completing the questionnaires they were excluded from the study, and we obtained the results from the information of 1,138 patients. The average age of the patients was 6.62 with a standard deviation of 4.57, and the minimum and maximum age was 0.5 and 20 years (**table I**).

In terms of gender, 705 patients (62%) were boys, and 433 patients (38%) were girls, which were significantly different in Fisher's exact test ($p < 0.05$).

Regarding the reason for visiting the clinic, 803 patients (70.6%) had asthma/airway hyperreactivity, 173 patients (15.2%) had allergic rhinitis, 64 patients (5.6%) had eczema, 40 patients (3.5%) with urticaria, 31 patients (2.7%) with food allergy, 11 patients (1%) with drug allergy, 8 patients (0.7%) with chronic itching, 7 patients (0.6%) with ocular allergic disease and 1 (0.1%) patient had anaphylactic reaction. 719 patients (63.2%) had one allergic disease, 272 patients (24.1%) had two allergic diseases, 85 patients (7.5%) had three allergic diseases, and 60 patients (5.3%) had 4 allergic diseases.

In terms of the history of atopy in the parents, in 596 patients (52.4%) no history of allergic disease was reported in any of the parents, in 542 patients (47.6%) the history of atopy was seen in the parents of the patients.

The frequency of seizure history in patients according to the history of atopy in parents had no statistically significant difference in Fisher's exact test ($p > 0.05$).

Regarding the history of seizures in the patient's relatives, 166 people (14.6%) had a positive history and 972 people (85.4%) had a negative history.

Out of 166 people with a history of positive seizures in the patient's relatives, 86 people (7.6%) had first degree, 55 people (4.8%) had second degree and 25 people (2.2%) had third degree.

In terms of history of seizures in patients, 88 patients (7.7%) had a positive history and 1,050 (92.3%) had a negative history of seizures, and the frequency of history of seizures in patients according to the history of seizures in relatives according to Fisher's test had a significant difference ($p < 0.05$).

Regarding the number of seizures, 58 patients (65.9%) had only one seizure and 30 patients (34.1%) had more than one seizure.

Regarding the occurrence of seizures in the last 5 years, 57 patients (64.8%) had seizures in the last 5 years and 31 patients (35.2%) did not have seizures in the last 5 years.

Regarding anticonvulsant drug use in patients with a positive history of seizures, 64 patients (72.7%) were not currently taking any anticonvulsant drug, 13 patients (14.8%) were taking an anticonvulsant drug, 9 patients (10.2%) were taking at least two anticonvulsant drugs, and their seizures were controlled, and 2 patients (2.3%) were taking at least two anticonvulsant drugs and their seizures were not controlled.

In terms of accompanying fever with seizures in patients with a history of seizures, in 57 patients (64.8%) seizures were always accompanied by fever, in 27 patients (30.7%) seizures were without fever and in 4 patients (4.5%) seizures were sometimes with fever.

In patients with a positive history of seizures, in 57 patients (64.8%) seizures accompanied by fever, in 3 patients (3.4%) with head trauma, in 2 patients (2.3%) with meningitis/encephalitis, in 1 patient (1.1%) with metabolic diseases, in 1 patient (1.1%) with drug poisoning, in 1 patient (1.1%) with brain tumor, in 1 patient (1.1%) with vaccine, in 1 patient (1.1%) with neonatal seizures and 21 patients (23.9%) had epilepsy. Of the 21 patients with epilepsy, 15 patients (1.31%) had

Table I *- The frequency of patients with seizure history according to age group.*

	Positive history number (percentage)	Negative history number (percentage)	P-value
Age			0.246
Less than 1 year	6 (4.3%)	134 (95.7%)	
Between 1 and 2 years	5 (4.7%)	101 (95.3%)	
2 to 5 years	19 (7.4%)	237 (92.6%)	
6 to 12 years	46 (9.1%)	458 (90.9%)	
More than 12 years	12 (9.1%)	120 (90.9%)	

Table II *- Frequency of patients in terms of history of seizures according to gender.*

	Positive history number (percentage)	Negative history number (percentage)	P-value
Gender			0.005
Boys	66 (9.4%)	639 (90.6%)	
Girls	22 (5.1%)	411 (94.9%)	

idiopathic epilepsy (occurrence of seizures more than once and without any underlying factors) and the other 6 patients were classified as chronic symptomatic epilepsy.

Therefore, in general, the frequency of history of seizures with fever in the population of allergic children referring to Imam Ali Clinic was 50 per 1,000 people, and the frequency of idiopathic epilepsy in this population was 13 people per 1,000 people.

Regarding the change of anticonvulsant medication in patients with a history of seizures, 23 patients (95.8%) did not change or stop taking the medication due to an allergic reaction, and 1 patient (4.2%) stopped taking the anticonvulsant medication due to an allergic reaction without requiring hospitalization.

The frequency of history of seizures in patients according to the gender of the patients is shown in **table II**, which had a significant difference in Fisher's exact test ($p < 0.05$).

The frequency of seizure history in patients according to the allergic disease of the patients is shown in **table III**, which had no significant difference with each other ($p > 0.05$).

The frequency of seizure history in patients was checked according to the number of allergic diseases of the patients, which did not have significant differences with each other ($p > 0.05$).

Also, the frequency of idiopathic epilepsy in the patients according to the type of allergic disease was not significantly different from each other ($p > 0.05$).

There was an association between the epilepsy and allergic disease number with an odds ratio OR 1.84, 95%CI 0.28-12, however the risk of epilepsy was increased by 0.84%, but this increase was not significant.

The frequency of idiopathic epilepsy in patients according to the number of comorbid allergic diseases of the patients' fathers had no statistically significant difference ($p > 0.05$).

Table III *- The frequency of patients in terms of seizure history according to the allergic disease of the patients.*

	Positive history of seizure number (percentage)	Negative history of seizure number (percentage)	P-value
Disease			0.602
Asthma/Airway hyperreactivity	64 (8%)	739 (92%)	
Allergic rhinitis	15 (8.7%)	158 (91.3%)	
Eye allergy	0 (0%)	7 (100%)	
eczema	1 (1.6%)	63 (98.4%)	
Urticaria	5 (12.5%)	35 (87.5%)	
Chronic itching	0 (0%)	8 (100%)	
Food allergy	2 (6.5%)	29 (93.5%)	
Drug allergy	1 (9.1%)	10 (90.9%)	
Anaphylaxis	1 (100%)	0 (0%)	

Table IV *- The frequency of patients in terms of idiopathic epilepsy according to the number of comorbid allergic diseases.*

	Positive Idiopathic epilepsy number (percentage)	Negative Idiopathic epilepsy number (percentage)	Total
Number of allergic diseases in patients			
One	13 (1.81%)	706 (98.19%)	719
Two	0 0%)	274 (100%)	274
Three	0 (0%)	85 (100%)	85
Four	2 (3.33%)	58 (96.67%)	60

Table V - *The frequency of idiopathic epilepsy in patients according to the number of allergic diseases of the patients' parents.*

	Number of allergic diseases in mothers		Number of allergic diseases in fathers	
	Positive idiopathic epilepsy number (percentage)	**Negative idiopathic epilepsy number (percentage)**	**Positive idiopathic epilepsy number (percentage)**	**Negative idiopathic epilepsy number (percentage)**
No allergy	12 (1.49%)	791 (98.51%)	13 (1.55%)	827 (98.45%)
One allergic disease	1 (0.36%)	273 (99.64%)	2 (0.77%)	258 (99.23%)
Two allergic diseases	0 (0%)	32 (100%)	0 (0%)	23 (100%)
Three allergic diseases	1 (5%)	19 (95%)	0 (0%)	10 (100%)
Four allergic diseases	1 (11.11%)	8 (88.89%)	0 (0%)	5 (100%)
P-value	0.024		> 0.05	

But the frequency of idiopathic epilepsy in patients according to the number of allergic diseases of the patients' mothers had a statistically significant difference in the Chi-square test (p = 0.024, OR 1.28, 95%CI 1.04-2.23) (**table IV**).

Next, the frequency of febrile convulsion in patients according to the allergic disease of the patients is shown in **table V**, which were not significantly different from each other in the chi-square test (p > 0.05).

Next, the frequency of febrile convulsion in patients according to the number of allergic diseases of patients is shown in **table VI**, which had a significant association between the number of comorbid allergic diseases in patients with febrile convulsions (OR 1.4, 95%CI 1.07-1.83, p = 0.013).

The frequency of febrile convulsions in children had no significant relationship with the number of allergic diseases of neither father nor mother.

Discussion and conclusions

In this study, in terms of history of seizures in patients, 88 patients (7.7%) had a positive history, and 1,050 patients (92.3%) didn't have, and regarding the subgroups of seizures, 21 patients had epilepsy (15 of them had idiopathic epilepsy) and 57 patients had febrile convulsion. Therefore, the prevalence of epilepsy, idiopathic epilepsy, and febrile seizures were 18.4/1,000, 13/1,000, and 50/1,000, respectively.

In Iran, the lifetime prevalence of epilepsy has been reported 16.6 per 1,000 people with an average age of onset of 21.1 ± 19.1 years, and 50.6% of patients had an underlying cause (13). Although this study was not limited to the age group of children, the prevalence of idiopathic epilepsy was lower than in the present study.

Some studies have been conducted on the prevalence of epilepsy in the population of children in our region. In a study from Bahrami Hospital in Tehran (7), which was reported in 2009,

Table VI - *The frequency of patients in terms of febrile convulsion according to the number of comorbid allergic diseases.*

	Positive history of febrile convulsion number (percentage)	**Negative history of febrile convulsion number (percentage)**	**Total**	**P-value**
Number of allergic diseases in patients				0.013
One	20 (2.78%)	699 (97.22%)	719	
Two	30 (10.95%)	244(89.05%)	274	
Three	4 (4.71%)	81 (95.29%)	85	
Four	3 (5%)	57 (95%)	60	

the history of seizures in 2,500 children under the age of 12 was questioned, and the prevalence of history of seizures in this population was 32/1,000, the prevalence of history of epilepsy was 4.4 in 1,000, and the prevalence of febrile convulsion was 19/1,000, which is significantly lower than the present study. Part of the difference between the results of this study and ours is due to the target population of the study. In Alizadeh *et al.*'s study (7), the prevalence of seizures in school children was evaluated, and thus, a part of the population of children who are unable to go to school, such as cerebral palsy patients (who are at a higher risk for seizures) were excluded from the study. But this problem does not exist in the case of children referred to the allergy clinic. Considering the very small number of these patients in the allergy clinic, it seems that the reason for this significant difference in the prevalence of seizures between the two studies is beyond this issue.

In another study from Turkey, the prevalence of epilepsy in 4,288 children aged 0-17 years was investigated, and the prevalence of epilepsy in this population was reported as 8.6 per 1,000 people (14). Another study from Egypt, among 36,195 children and adolescents under 18 years of age, the overall prevalence of epilepsy was 9.7/1,000, but the prevalence of idiopathic epilepsy in this population was 5.7/1,000 (15). Therefore, compared to regional studies on the general population of children, it seems that the history of seizures and idiopathic epilepsy are more frequent in allergic children. However, it would be better to evaluate the frequency of history of seizures and epilepsy in the general population of children and adolescents under 20 years of age in Karaj to make more reliable comparisons and conclusions.

On the other hand, the frequency of history of epilepsy in patients with at least one allergic disease in 2014 in America out of 91,605 patients was reported as 1.37%, which is equivalent to 13.7/1,000 (16), and in our study, the prevalence of idiopathic epilepsy was about 13 per 1,000 people, which is very close to this study. In Strom *et al.*'s study (17), according to their evidence, they have come to the conclusion that there is a positive association between allergic disease and seizures, which the present study could not show and the reason for this difference can be due to the difference in the sample size, the geographical area and the difference in some definitions in the two studies.

In this study, the frequency of males in patients with a history of seizures was significantly higher than that of females, and the results of Silverberg *et al.*'s study (16) show the same relationship. On the other hand, in the Strom *et al.*'s study (17), the most frequent patients with a history of seizures were seen in patients with food allergies, while in the present study, it was seen in patients with urticaria (not statistically significant). Of course, it should be noted that in children urticaria can be related to food allergies, and therefore, from this aspect, patients need more careful follow-up to identify the cause of urticaria. Also, in the present study 5.6% of the patients had eczema, and among the 64 patients with eczema, one patient had history of seizures, while in Strom *et al.*'s study, 9.5% of the patients had eczema and among 19,647 patients with eczema, 263 patients had a history of seizures (prevalence 1.4%) (17). In Silverberg's study (16), the prevalence of epilepsy in children with eczema was 1.73%. Also, in the Taiwan study, the prevalence of epilepsy in atopic dermatitis patients compared to the control group was 0.94 to 0.27 cases per 1,000 people per year (18). The estimation of seizure prevalence in the atopic dermatitis population participating in our study has low statistical power due to the limitation of the sample size. In addition, since many children with asthma and allergic rhinitis also have a past history of atopic dermatitis and food allergy, and in this study only the current allergic diseases of the patients were recorded, maybe if the past history of atopic diseases was also taken into account, the results would be different.

In terms of the prevalence of epilepsy in the population with asthma, in the current study, out of 803 patients with asthma, 9 cases have idiopathic epilepsy, which is a prevalence of 11.2/1,000, which is higher than the statistics calculated in Castaned's study (19). A recent cohort study including 150,827 patients with asthma showed that the probability of developing epilepsy in patients with asthma was 1.39 times higher than in healthy controls (11).

In a Mendelian randomization (MR) study whether asthma causally contributes to epilepsy susceptibility was investigated and they reported asthma is associated with an increased risk of epilepsy independent of the age onset of asthma (20). The potential reasons for the association between asthma and epilepsy could be due to anoxia and hypocapnia caused by frequent asthma attacks, or perhaps chronic inflammation is a common pathological feature of asthma and epilepsy.

Silverberg *et al.* (16) reported that as the number of comorbid allergic diseases increased, so did the odds of both lifetime and point prevalence of epilepsy. It was reported by Strom *et al.* (17) that childhood seizures were associated with 1, 2, and 3 comorbid allergic diseases but were most strongly associated with 4 comorbid allergic diseases.

In the current study, there was an association between the epilepsy and number of comorbid allergic diseases, with an odds ratio of 1.84, 95%CI 0.28-12. The frequency of idiopathic epilepsy was 3.3% in patients with four comorbid allergic diseases but it was 1.8% in patients with one allergic disease, and despite the risk of epilepsy was increased by 0.84% in patients with four comorbid allergic diseases, this increase was not significant due to limitation of patients number.

It is undetermined why seizures are associated with the number of comorbid allergic disease in patients. Perhaps multisystem allergic inflammation predisposes children to seizures. On the other hand, since there are different differential diagnoses for

each allergic disease such as asthma, rhinitis, and eczema, and these manifestations can be seen in a wide range of diseases with different pathophysiologies, and the allergic phenotype is only one of the diverse phenotypes of these diseases, co-existence of the several allergic diseases in one person increases the possibility that all these manifestations have occurred in the context of a single genetic background (atopy).

Also, our results showed a significant relationship between epilepsy and the number of allergic diseases in mothers ($p = 0.024$) and not fathers, which suggests the connection between the genetic background of allergies, especially from the mother's side, with the occurrence of idiopathic epilepsy in children.

On the other hand, we found a highly significant relationship between the frequency of febrile convulsion and the number of comorbid allergic diseases in the patients ($p = 0.013$). Because respiratory allergies are considered a risk factor for frequent and febrile respiratory infections due to allergic secretions and inflammation and partial obstruction in some parts of the airways, it is predictable that the prevalence of febrile convulsion in the population of patients with respiratory allergies be higher; but the fact that febrile convulsion are related to the number of allergic diseases in patients indicates that there is a relationship beyond the mentioned case between these two diseases, and maybe the same genetic or inflammatory background is the cause of the emergence and occurrence of these two different diseases in this population of patients.

In addition, in another large retrospective study based on the data of the Taiwan National Health Insurance Research Database, more than 67,000 children with allergic rhinitis and 67,000 people in the control group were compared in terms of the risk of developing epilepsy during a 12-year period and concluded that a group who had allergic rhinitis have a higher incidence of epilepsy compared to the control group (6.84 people *vs* 3.94 people per 10,000 people per year, $p < 0.001$) and the age of onset of epilepsy in this group was lower than the control group, and in the total incidence allergic rhinitis increases the risk of epilepsy by 76% in children, and the risk of epilepsy in boys is 21% higher than in girls. In our study, out of 173 patients with allergic rhinitis, 15 patients had a history of seizures, and 4 patients had a history of idiopathic epilepsy. The prevalence is equal to 23 people per 1,000 people, which although the prevalence is very high, but due to the small size of the sample, it cannot be discussed, and studies with a higher sample size are needed for a more accurate interpretation of the issue.

Finally, it is recommended to conduct more studies with larger sample size in this field, because the most important limitation of the present study was the limitation of the sample size and the lack of integrated information of patients in the Iranian health system.

The limitations of the study are the limited population, no control group, no record of history of atopic diseases in patients; the strengths of the study are the correct and accurate selection of patients based on the physical examination and history taken by asthma and allergy specialists and not on the parents' self-report; attention to the family history of atopy and the division of subgroups of common childhood seizures and determining the relationship of each of these subgroups with the context atopy and not just an allergic disease.

In conclusion, the findings of the current study demonstrated that number of comorbid allergic diseases in the patients is more related to development of some types of seizures than the type of allergic disease and the number of allergic diseases of mothers is related to idiopathic epilepsy in their children.

Fundings

None.

Contributions

HS: conceptualization, investigation, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review & editing. AM: investigation, writing – original draft, writing – review & editing. NT: investigation, data curation, writing – original draft. MB: formal analysis, writing – review & editing. HME: methodology, validation, writing – review & editing. EZ: methodology, writing – review & editing. AZ: validation, writing – review & editing. MT: investigation, resources, supervision, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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