Herbal Medicine-Induced Seizures in Children: Single-Center Experience Over 18 Months

Many common household herbal preparations may have seizurogenic ingredients. We report 15 children with seizures following exposure to such compounds: oral ingestion of liquid preparation in 13, and local application of balm and Eucalyptus oil ingestion in one each. All children, except one, had generalized seizures. This study highlights the need to address this history during evaluation of first seizure, and increase awareness of seizurogenic potential of such preparations.

Keywords: *Adverse effects, Complementary and alternative medicines, Epilepsy.*

It is common practice in Indian households to treat minor ailments with herbal preparations. They are considered natural and safe, and are easily available as over-the-counter medications. The herbal preparations have ingredients like camphor, eucalyptus oil, menthol and other aromatic compounds. All these compounds have adverse effects, with the most serious being their tendency to provoke epileptic seizure. The objective of the present study was to highlight the seizurogenic potential of these components and increase awareness among pediatricians.

This is a case record review, with cases having been evaluated between December, 2018 and June, 2019 at a tertiary care pediatric center in Southern India. All children (up to 18 years) with first afebrile (apparently unprovoked) seizure presenting to emergency room were evaluated and treated as per standard protocol [1]. The necessary investigations like blood sugar, serum electrolytes, electroencephalography (EEG) and neuroimaging were done, with extent of evaluation varying on case-to-case basis, and treating physician's discretion. Children with confirmed acute symptomatic seizures (due to fever, hypoglycemia, electrolyte disturbances, systemic infections) and those with remote symptomatic etiology were excluded. All the children in whom no cause could be identified, but had an antecedent exposure to any of the seizurogenic compounds and/or herbal preparations in any form (enteral, inhalational or local application) were included. Children with unprovoked seizures who were evaluated at other medical centers, but had come for neurological consultation later, were also included if all the inclusion criteria were met. The details of dose, route of exposure, time between exposure and seizure onset, type and duration of seizures were noted.

A total of 15 children (8 girls) met the inclusion criteria, with median (range) age of 4.8 years (6 months-14 years) – 10 were younger than 5 years (**Table I**). All children were with typical development except one child with pre-existing ischemic stroke and left hemiparesis due to mineralizing angiopathy. There was no past history or family history of febrile seizures or epilepsy in any of the subjects. All these herbal medicines were used by the caretakers for treatment of minor ailments like nose block, cold and cough in young children, and headache in older kids.

The most commonly used preparation was a liquid formulation Zinda Tilismath (Karkhana Zinda Tilismath) (13, 86.7%); menthol plus was locally applied for one child and eucalyptus oil ingestion in one child. For Zinda tilismath, drinking after dilution with water was the commonest mode of exposure (n=10), while three children had local application as well. Its ingredients include eucalyptus oil, camphor, menthol, thymol and alkanet root as mentioned in the package insert. One child was exposed to herbal balm with similar composition. The quantity of the liquid preparation used was 2-5 drops (6 of 13 children) and 0.5-2.0 mL (6 of 13 children). One child drank 5 mL of preparation.

Of 15 children, 8 were hospitalized. Two children were admitted for status epilepticus (eucalyptus oil ingestion, 5 mL of liquid formulation); one child was ventilated for 1 day for poor respiratory efforts, and one child was admitted for two days in view of prolonged post-ictal encephalopathy. Five children were admitted for unprovoked seizures for one day each. Mean duration of stay was 2.6 days. Later in the study, children were managed on an outpatient basis if there was unequivocal history of antecedent exposure to one of these compounds, and other causes of acute symptomatic seizures were ruled out. History of previous exposure to the herbal medicine was present in 10 children. The median (range) interval between exposure and onset of seizures was 49 (15-120) minutes. The median (range) seizure duration was 3 minutes (30 seconds-5 minutes). Investigations like blood sugar, serum calcium, magnesium, and serum electrolytes were done in all children to rule out other causes of acute symptomatic seizures, and were normal. EEG was done in ten children and was normal. Five children underwent neuroimaging (computerized tomographic scan, 3; magnetic resonance imaging, 2), which was normal in all. This included two children with status epilepticus and one child with focal seizures. During follow-up of 6-12 months, one child had afebrile seizure and one had febrile seizure after one month and 20 days, respectively; the rest of the children were normal.

To the best of our knowledge, this is the largest case series in children till date, highlighting the seizurogenic potential of herbal medications/compounds. The list of toxic compounds/drugs that can cause acute symptomatic seizures is exhaustive and include compounds like industrial chemicals, pesticides and natural toxins [2]. Among these, natural plant toxins are the main ingredients of many herbal medicines, and encephalo-pathy, seizures, hallucinations, coma and death have been reported [3].

Few animal studies in rats have proven the seizurogenic effects of camphor and 1,8-cineole, which is an ingredient of

Table I Characteristics of Study Subjects

No.	*Age (mo)/ sex*	*Amount ingested* [a]	*Indication*	*Seizure onset (min)*	*Seizure type*	*Seizure duration (min)*	*Hospitalization (d)*
1	24/F	1 mL	URI	90	GTCS	2	None
2	35/M	1 mL	URI	20	GTCS	2	1
3	168/M	1 mL	Headache, body pain	60	GTCS	1	1
4	31/F	2 drops+LA	URI	30	GTCS	5	None
5	6/M	2 drops+LA	URI	20	GTCS	5	None
6	45/F	4-5 drops	For general well being	90	GTCS	0.5	None
7	36/F	Topical[c]	URI	30	GTCS	2	None
8	21/F	5 drops	URI	15	GTCS	2	None
9	18/M	2 mL	URI	60	GTCS	4	2
10	66/M	2 drops	For digestion	120	Focal[b]	3	1
11	20/M	3 drops	URI	30	GTCS	5	None
12	79/M	2 mL	URI	120	GTCS	1	2
13	36/F	5 mL	Accidental ingestion	15	GTCS	30	6
14	118/F	3 drops[d]	Coryza	30	GTCS	45	4
15	73/F	2.5 mL	URI	15	GTCS	5	2

GTCS: Generalized tonic clonic seizures; LA: Local application, [a]of liquid preparation taken orally; [b]with behavioral arrest; [c]Menthol plus balm; [d]Eucalyptus oil.

eucalyptus and other essential oils. They have shown that epileptiform activity is induced by blockade of K^+ channels and upregulation of Ca^{2+} inward currents [4-6]. The toxic effects of these compounds are more pronounced in children due to immature brain. Some of them have dose-related effects and some are idiosyncratic responses. When multiple compounds are present in a preparation, the complex interplay of all ingredients can cause toxic effects [7]. In a similar study by Mathew, et al. [8] on eucalyptus oil inhalation and seizures, 10 patients (5 children) were studied [8]. The mean duration for seizure onset and type of seizures were similar to our study. However, all the patients in that study were evaluated with EEG and imaging, whereas these were done in only a few of the children in this study. This was so because during the later part of the study duration, we could limit our investigations when an unequivocal temporal relation was found with herbal compound exposure.

In previous case reports of camphor poisoning in 4 children (age range 15-36 months), the interval between exposure and seizures was 40 minutes to 2 hours, similar to our study [9,10]. Duration of seizures in this study ranged from 2 minutes to 1 hour, with all requiring admission and observation. Dose was mentioned for only one child (750 mg). In our study, the amount of preparation taken had no correlation with either onset of seizures or duration of seizures (excluding status epilepticus). This is highlighted by the oldest case (case 14) developing seizure after ingesting 3 drops of herbal substance. There were no unique clinical, biochemical, imaging or electrographic findings associated with herbal compound induced seizures in our cohort.

Seizures occurring in association with minor infections without fever, and underlying genetic predisposition for epilepsy could not be ruled out. Two children in our study had seizure recurrence within a month, and that is less likely to be due to single exposure to herbal compounds. Long-term, prospective studies should be done to answer this.

Despite the previous case reports in literature quoting seizurogenic potential of the herbal compounds, this awareness is lacking in both clinicians and parents. This was the reason five children in our study were admitted (and underwent neuroimaging) as either the history was taken later or exposure was not considered causative initially.

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Pertussis Epidemic in Lower-Grade Schoolchildren Without Preschool Vaccination Boosters

We investigated the characteristics of patients with pertussis who did not receive preschool vaccination boosters. Fifteen patients with laboratory-confirmed pertussis and 29 pertussis-negative patients were compared. All pertussis-positive patients, but only 17% of pertussis-negative patients, were elementary school age and older. There is a need to study the utility of routine preschool pertussis vaccine booster in Japan.

Keywords: *DPT, Immunization, LAMP, Seroprevalence*.

The pertussis vaccine is effective in preventing *Bordetella pertussis* infection and death, and the risk is high in young infants who do not receive the vaccine [1]. *B. pertussis* infection in siblings is considered a common route of transmission to young infants [2]. Currently, three brands of DPT-IPV (acellular pertussis, diphtheria and tetanus toxoids, and inactivated polio combined) are used in Japan. All contain pertussis toxin and filamentous hemagglutinin (6-23.5 and 23.5-51.5 µg/0.5 mL, respectively), and one contains additional pertactin and fimbriae (5 and 1 µg/0.5 mL, respectively) [3]. Children receive a total of four doses of DPT-IPV: three primary doses at the ages of 3, 4, and 5 months, and one booster dose at 18 to 23 months as a national routine vaccination. In 2018, vaccine coverage for the four doses was 95.0%, 95.7%, 96.2%, and 96.2%, respectively [4]. The preschool pertussis vaccination booster is used in some Asian countries like India, but not in Japan [5]; even though Japan has one of the highest primary pertussis vaccination rates in the world [6]. We, herein present data from an outbreak of pertussis, which occurred mainly in lower-grade school children without preschool vaccination boosters.

A retrospective chart-based study was conducted on patients who visited the Saiwai Pediatric Clinic, Tokyo, Japan, with persistent cough. Patients were examined by board-certified pediatricians for suspected pertussis and received a laboratory diagnosis between August and September, 2018. In accordance with the Pediatric Respiratory Infection Practice Guidelines in Japan [7], diagnostic tests for pertussis were defined as positive by either nasal swab loop-mediated isothermal amplification (LAMP) or anti-pertussis IgM/IgA in sera. The positive and negative predictive rates of LAMP are 100% and 97%, respectively (Loopamp Pertussis Detecting Reagents D; Eiken Chemical Corporation). The sensitivity of anti-pertussis IgM and IgA are 29-56% and 25-44%, respectively and the specificities are 93% and 99%, respectively (Novagnost *Bordetella pertussis* IgM/IgA; Siemens Healthcare Diagnostics KK). The patient background (sex, age, and vaccination history), and diagnosis method were collected.

Statistical analyses included a bar graph review and Fisher exact test of age-distribution comparisons. We used SPSS Statistics 25 (IBM Corp.) and BellCurve for Excel for Windows (Social Survey Research Information Co. Ltd.) software programs.

Of the 44 patients (age distribution: 0-21 years, median: 6 years), data of 15 patients who were diagnosed with laboratory-confirmed pertussis (age: 7-21 years, median: 8 years) and 29 patients who were pertussis-negative (age: 0-11 years, median: 5 years) were compared. All patients (n=15) who were pertussis-positive but only 17% (n=7) of patients who were pertussis-negative were elementary school age and older (P< 0.001) (**Fig. 1**). All 16 preschool children were negative. Excluding serodiagnosis cases (3 positive cases, 1 negative case), a significant difference in age distribution (P<0.001) was also observed. When a 2 × 2 table was prepared with 7 years of age as the cut-off value, the sensitivity, specificity, positive predictive rate, and negative predictive rates were 100%, 83%, 75%, and 100%, respectively.

None of the 44 patients had a history of preschool vaccination booster at around 5 years of age. Of 15 children who were positive, 14 patients had received four routine vaccinations and the booster history was uncertain in 1 patient. Of 29 children who were negative, 26 patients had received four routine vacci-

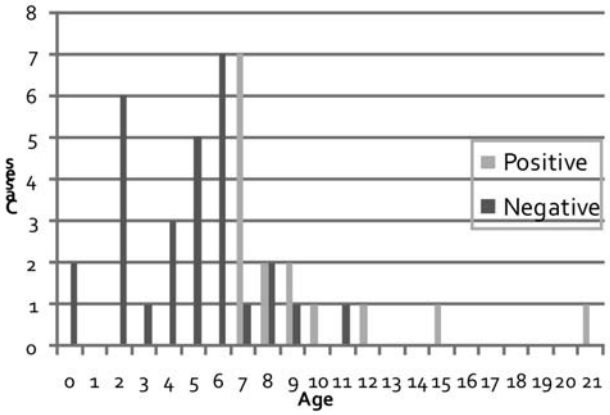

Fig. 1 Pertussis test results and age distribution.

nations, but two patients who were a few months old were vaccinated 0 and 2 times, and the booster history was uncertain in another patient.

The absence of pertussis in preschool children and the presence of pertussis in lower-grade schoolchildren suggest the need of additional preschool vaccinations. It has been reported that the prevalence of anti-pertussis toxin titer in individuals aged 4 to 7 years declines to 26-38% even among regular vaccines [8]. During our research period, the Japanese Society of Pediatrics began to recommend that preschool children aged 5 to 6 years receive a DPT vaccination, but this is on a voluntary basis [9].

This report covers a limited number of cases in a single institution, and the question remains of whether the data on sensitivity and specificity for pertussis at age 7 years or older can be generalized. However, the all-Japanese pertussis cases reported indicate that over 60% of cases are between the ages of 6 and 15 years, peaking at the age of 7 years [10], which is consistent with the age distribution reported herein.

We experienced a pertussis epidemic in elementary school-age children, all of whom had been immunized with at least three doses of primary DPT-IPV immunization. We believe that popularizing the preschool pertussis vaccination is important in order to eliminate the infection source for young infants. Consideration should be given to routine preschool pertussis vaccination boosters in Japan if larger community-based studies confirm our findings.

Ethics approval: Keio University School of Medicine Ethical Committee, Tokyo, Japan; No. 20190205, dated December 26, 2019.

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Impact of Coronavirus Disease 2019 Pandemic and Lockdown on Mental Health Symptoms in Children

Pediatric symptom checklist (PSC)-youth self-report short version was administered telephonically to children between 11-15 years to study the impact on mental health. Out of 423 children, 130 (30.7%) had psychosocial problems, of which 107 (25.2%) had anxiety or depressive symptoms. The common reasons were fear of acquiring COVID-19 infection (60%), not able to attend school (56%), and not able to meet friends (80%).

Keywords: *Psychosocial wellness, COVID-19.*

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During the coronavirus disease (COVID-19) pandemic-induced nationwide lockdown, children were staying indoor (home confinement) and limited online teaching was provided by some schools. The impact on children may not be only because of the virus but also due to psychological effects created by exposure to verified/unverified information through various sources. Our primary objective was to study the effects of pandemic and lockdown (home confinement) on mental health symptoms in children aged 11 to 15 years.

The study period was from 15, April, 2020 to 15 May, 2020 in Pune, India. We included children aged between 11-15 years in whom medium of instruction in schools was English. Children receiving neuropsychiatric medicines/treatment were excluded from the study. Telephonic interview of children was conducted after obtaining prior informed verbal consent from one of the parents. Approval was taken from institutional ethics committee.

Children were identified from our hospital records. Friends/ relatives and other contacts of researchers were contacted to identify more children in that age group who would be willing to participate. The information about the survey was put on personal Facebook pages of investigators and interested people were asked to contact a dedicated telephone number. Children who participated in the survey were also asked to suggest contacts that would be willing to participate.

Pediatric symptom checklist (PSC) – youth, self-report shorter version consisting of 17 questions was used [1,2]. This is a validated method for screening for psychosocial problems of school-aged children. A cut-off more than 15 was considered abnormal. Subscale scores were also calculated for anxiety or depressive problems, and a subscale score of 5 or more was considered significant. In addition to PSC, 13 questions exploring adaptation to lockdown and post-lockdown expectations were also administered. The complete questionnaire was administered to the children by three researchers in a uniform and standardized format.

We calculated that with a confidence level of 95% and acceptable margin of error 5%, we would need a sample size of 384 respondents. Assuming a 10% drop out rate, a sample size of 422 was chosen. We used SPSS version 23 (IBM Inc,) for statistical analyses. Linear regression analysis was used to determine effect of various parameters on mental health. P value of less than 0.05 was considered significant.

Overall, we telephoned 486 children, of which 36 phone calls were not answered despite repeated attempts. Twenty-seven parents declined participation. Finally, 423 (87%) children [mean (SD) age, 12.3 (1.6) year; 54.4% boys] completed the questionnaire and were included in the study. Of these 70% belonged to nuclear families, 25% had no siblings and 10.8% had one/both parents in healthcare profession. Mothers of 34% and 18% were employed full-time or part-time, respectively. The source of information on the pandemic was from news (51.3%), parents (27.4%), both of these in 6% and friends in 7.5%.

Of these, 130 (30.7%) children had psychosocial problems, of which 107 (25.2%) had anxiety or depressive symptoms, the common reasons being fear of acquiring COVID-19 infection (60%), not able to attend school (56%), and not able to meet friends (80%). Of others, 23 (5.4%) were feeling hopeless, 107 (25.2%) seemed to be having less fun, and 99 (23.4%) were feeling sad or unhappy. Around a quarter (24.3%) were worrying a lot and 12.5% were 'down on oneself.'

Of the remaining, 246 (58%) children were happy to spend more time with family, 140 (33%) did not feel any anything unusual, while 32 children (7.6%) children were annoyed by the constant presence of parents.

The topic of discussion with friends was COVID-19 pandemic in 43 (10%) children and 103 children (23.2%) kept a daily count of patients suffering and dying from COVID-19. All children responded that they had not anticipated this

Table I Coping With the Pandemic and Long Term Outlook

Responses	*No. (%)*
Measures taken to reduce anxiety[a]	
Music	88 (21)
Talking to friends	73 (17.3)
Talking to parents	51 (12)
Hobbies	123 (29)
Physical exercise	35 (8.3)
What are you missing most?[b]	
Freedom to move out	140 (33)
School	79 (18.7)
Friends	133 (31.5)
Sports	48 (11.4)
What is the first thing you do once the lockdown is over?[c]	
Meet friends	279 (66)
Stay at home	66 (15.6)

[a]*Reading and playing games on mobile phone in 4.7% each, and sleeping more in 3%;* [b]*shopping (3%) and movies in theater (2.4%);* [c]*Go shopping (6.6%), and organize a party or go to watch movie in 5.9% each.*

happening, and 267 (63%) children felt that this lockdown will change their habits, mind set or outlook towards other people.

Binary regression analysis showed that duration of lockdown, family size, siblings, working status of parents, healthcare status of parents, source of information of pandemic etc did not have any significant effect on mental health (anxiety or depression). However, increased use of social media was associated with higher risk of anxiety or depressive symptoms [OR (95% CI) 1.83 (1.21 to 3.96); *P*=0.001]

We found that anxiety or depressive symptoms were seen in nearly 25% of all surveyed children as a result of lockdown. We started the survey after completing 4 weeks of lockdown and finished by 8 weeks after which the lockdown restrictions were relaxed. Completing the study within lockdown time ensured that children were able to answer all questions with complete clarity and lack of memory lapses. We did not find any relation between duration of lockdown and impact on mental health symptoms. Nearly half of this lockdown period coincided with the regular summer break for most children. So, it is possible that the impact is less due to this overlap.

Interestingly, we found that higher usage of social media platforms was associated with anxiety or depressive symptoms. However, it can also be argued that children with mental health issues were more likely to access social media rather than use of social media being the cause of mental health issues. We restricted to children age 11 years or more of age since the cognitive function and social skills are better developed in this age group [4], and proxy-reporting is avoided [3].

The data is self-reported and hence subject to reporting bias. Also, the children may have been influenced by other family members though they were requested to not seek help while answering questions. This is not a truly representative sample since the children interviewed are from private English-medium schools, which typically represents upper-middle socioeconomic strata. None of the interviewed children had COVID-positive patients in the family. We do not know if this effect on mental health is a temporary phenomenon but these children will need to be followed up for long term effects. Majority of the children were optimistic about long term outlook, leading us to believe that adverse impact on mental health may be short-lived.

The study results are important to healthcare providers, parents as well as policy makers. Policy makers should devise ways to minimize these effects while implementing a lockdown (home confinement) on children. Parents and health providers should recognize these problems early and treat if necessary.

Contributors: SS: designed the questionnaire, data interpretation and analysis. Critical appraisal of the manuscript was done by him; AK: conceptualized this study, designed the questionnaire and interviewed the children, assisted in the data interpretation and analysis, and drafted the manuscript. RS: gave inputs on the questionnaire, interviewed the children, did the data entry and drafted the manuscript. SM: helped in interviewing the children, data entry, and in drafting of the manuscript. All authors approved the final manuscript.
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CLIPPINGS

Hydroxychloroquine to prevent recurrent congenital heart block in fetuses of anti-SSA/Ro-positive mothers *(J Am Coll Cardiol. 2020;76:292-302)*

Untreated congenital heart block (CHB) has significant morbidity and mortality both before and after birth. The risk of recurrence of fetal atrioventricular block in subsequent pregnancies is reported to be as high as 18%.This study (PATCH trial) was a multicenter, single-arm, 2-stage clinical trial evaluating efficacy of hydroxychloroquine (HCQ), a Toll-like receptor antagonist, in preventing recurrence of antibody (SSA/Ro) mediated congenital heart block.

Anti-SSA/Ro–positive mothers with a previous pregnancy complicated by CHB were started on daily therapy with 400 mg HCQ, prior to completion of 10th gestational week and were continued throughout pregnancy. The primary outcome was second or third degree heart block in utero or at birth.The authors found that the recurrence rate of CHB was reduced by more than 50%; 18% to 7.4%, by intention-to-treat (ITT) as well as per protocol analysis. The authors suggested prescription of HCQ for secondary prevention of CHB in all anti-SSA/Ro-exposed pregnancies.

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