Unintentional Cannabis Intoxication in Toddlers

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abstract

BACKGROUND AND OBJECTIVES: In France, cannabis consumption is illegal. The health impact of its increasing use and higher tetrahydrocannabinol (THC) concentrations is still poorly documented, particularly that of unintentional pediatric intoxications. We sought to evaluate the French national trend of admissions for unintentional cannabis intoxication in children over an 11-year period (2004–2014).

METHODS: A retrospective, national, multicenter, observational study of a pediatric cohort. All children aged <6 years admitted to a tertiary-level pediatric emergency department (PED) for proven cannabis intoxication (compatible symptoms and positive toxicological screening results) during the reference period were included.

RESULTS: Twenty-four PEDs participated in our study; 235 children were included, and 71% of the patients were 18 months old or younger. Annual admissions increased by a factor of 13. Hashish resin was the main form ingested (72%). During the study period, the evolution was characterized by a national increase in intoxications, younger intoxicated children (1.28 ± 0.4 vs 1.7 ± 0.7 years, $P = .005$), and more comas ($n = 38$) ($P = .05$, odds ratio 3.5 [1.02–11.8]). Compared with other intoxications, other PED admissions, and the same age population, cannabis-related admissions were greater. There was a potential link between the increased incidence of comas and increased THC concentration in resin seized in France over the period.

CONCLUSIONS: Children are collateral victims of changing trends in cannabis use and a prevailing THC concentration. Intoxicated children are more frequent, are younger, and have intoxications that are more severe. This raises a real issue of public health.

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Dr Claudet conceived the project and the study design, analyzed results, interpreted data, and drafted the initial manuscript; Dr Labadie performed all the data extraction and analysis from the national database of French poison control centers; Drs Mouvier, Manin, Michard-Lenoir, Eyer, and Dufour collected data and critically reviewed and revised the manuscript; all authors contributed to data collection and substantially participated in data analysis; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: The outbreak of pediatric cannabis intoxication has been recently published in relation to decriminalization in several states in the United States. In France, consumption is illegal. Unintentional pediatric intoxications related to increasing use are poorly documented.

WHAT THIS STUDY ADDS: In this national, retrospective, multicenter study, we included 235 intoxications. During the 11-year period, the evolution of intoxications was significant for younger children, and an increase in severe presentations potentially correlated to the increase in cannabis resin potency.

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France, where cannabis is illegal, is the highest drug-consuming country in Europe.[1] Users are mainly young adults and teenagers aged 15 to 16 years old with rates of 22% and 39%, respectively. Among ninth graders, this rate was 24% among girls and 28% among boys in 2014.[2,3] Whereas the herbal cannabis market changes with increased French production, most cannabis resin is imported from Morocco via Spain by air or sea and moves through France toward the Netherlands and Northern Europe by road using "go fast or go slow" vehicles. The resin form has changed to smaller, olive-shaped pellets rather than traditional 250 g bars.[1] Another major change is increased Δ9-tetrahydrocannabinol (THC) concentrations in both marijuana and hashish (9.3% in 2004 and 20.7% in 2014 in France).[4] The health impact of these trends remains poorly documented, particularly that of the evolution of unintentional intoxication in young children.

The primary objective was to analyze the national evolution of pediatric admissions for unintentional cannabis intoxication in the main French pediatric emergency departments (PEDs) over an 11-year period (2004–2014). The secondary objectives were to detail clinical presentations and analyze the evolution of severe intoxications (coma, respiratory depression, and apnea) and the resulting social and legal measures.

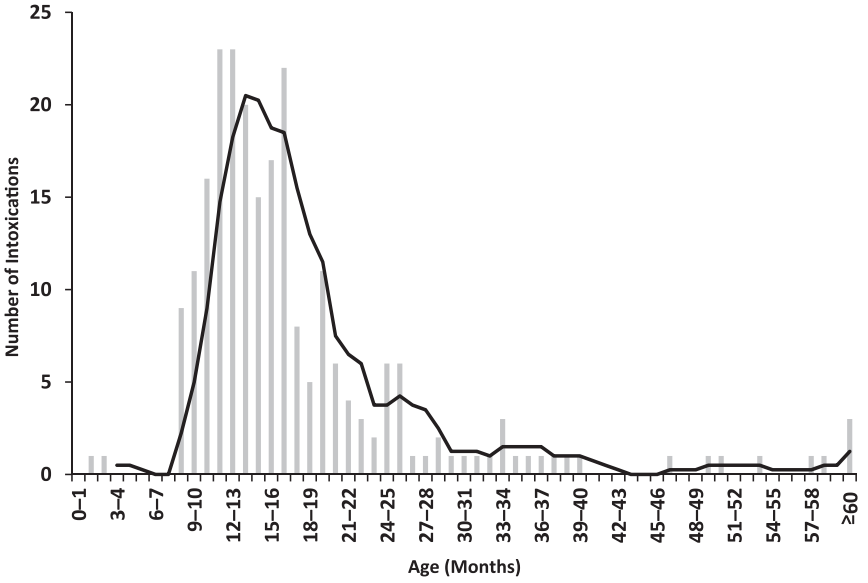

FIGURE 1
Pediatric cannabis intoxication distribution by age.

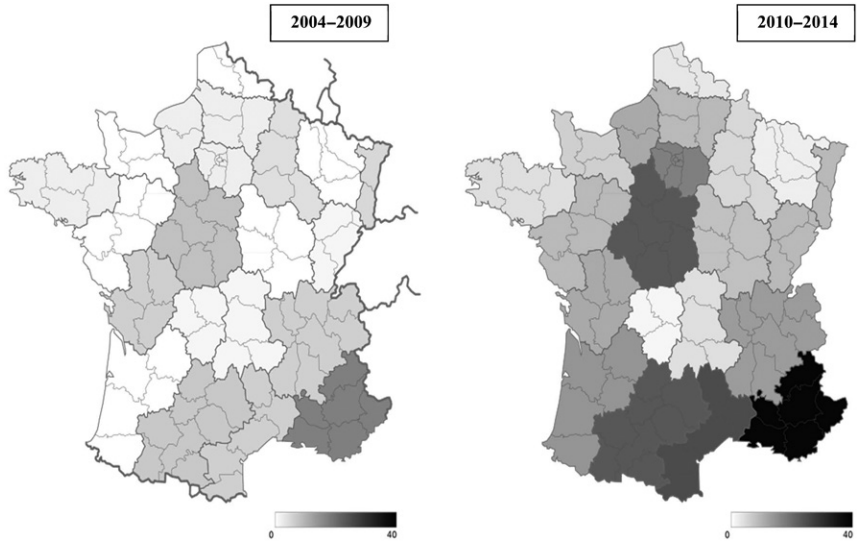

FIGURE 2
French geographical distribution of cannabis unintentional intoxication from 2004 to 2009 and 2010 to 2014 in children aged <6 years (number of cases).

METHODS

Study Design

This was a national, multicenter, retrospective, observational study of a pediatric cohort.

Setting and Study Participants

All children <6 years of age who were admitted with proven cannabis intoxication (compatible clinical symptoms and positive toxicological screening results) in a tertiary-level PED during the reference period were eligible. Compatible clinical symptoms that defined "intoxicated" children were any acute neurologic symptom(s) (eg, drowsiness, ataxia, hypo- or hypertonia, seizures, comatose status, altered consciousness, agitation, euphoria, and/or mydriasis) occurring in a previously healthy, afebrile toddler with no antecedents. Patients >6 years of age, asymptomatic patients (those who were exposed but not intoxicated), and those with suspected but unproven cannabis intoxications were not included. Since 2000, French hospital medical records have progressively switched from paper charts to electronic records. Two-thirds of French hospitals have electronic medical records. Laboratory results are also electronically linked to medical

TABLE 1 Comparison of Demographic Characteristics Between the 2010–2014 and 2004–2009 Periods

Characteristics	Total, *n* (%)	2010–2014, *n* (%)	2004–2009, *n* (%)	*P*	OR (95% CI)
Number of admissions	235	187	48	—	—
Male sex	127 (54)	101 (54)	26 (55)	.98	1.0 (0.6–1.9)
Seasonal distribution					
Summer (June to August)	55 (23)	44 (24)	11 (23)	.93	1.0 (0.5–2.2)
Spring (March to May)	29 (12)	18 (9)	11 (23)	.015	0.4 (0.2–0.8)
Autumn (September to November)	93 (40)	82 (44)	11 (23)	.009	2.6 (1.3–5.5)
Winter (December to February)	58 (25)	43 (23)	15 (29)	.24	0.7 (0.3–1.9)
Weekly distribution					
Weekend admission	61 (26)	48 (26)	13 (27)	.84	0.9 (0.5–1.9)
Mode of admission					
Family	165 (70)	128 (68)	37 (77)	—	—
Sanitary (ambulance, firefighters) and medicalized transport	44 (19)	39 (21)	5 (10)	.11	2.3 (0.8–6.1)
NS	26 (11)	20 (11)	6 (13)	.86	—
Time of admission					
8:00 AM–11:00 AM	28 (12)	24 (13)	4 (8)	.39	1.6 (0.5–4.9)
12:00 AM–5:00 PM	88 (37)	72 (39)	16 (34)	.51	1.3 (0.6–2.4)
6:00 PM–11:00 PM	103 (44)	79 (42)	24 (50)	.34	0.7 (0.4–1.4)
12:00 PM–7:00 AM	16 (7)	12 (6)	4 (8)	.67	0.7 (0.2–2.5)
Mean delay of admission, min (SD)	270 (190)	293 (209)	176 (99)	.08	—
Age, mo					
0–11	61 (26)	51 (27)	10 (21)	.36	1.4 (0.7–3.1)
12–23	136 (58)	109 (59)	27 (56)	.79	1.1 (0.6–2.1)
24–35	25 (11)	19 (10)	6 (13)	.55	0.7 (0.3–1.9)
≥36	13 (5)	8 (4)	5 (10)	.11	0.4 (0.1–1.2)
Mean age, y (SD) [range]	1.5 (0.6) [0.1–5.8]	1.4 (0.5) [0.1–5.3]	1.7 (0.7) [0.2–5.8]	.17	—
Location of intoxication					
Home	156 (66)	127 (68)	29 (60)	.33	1.4 (0.7–2.7)
Public area	28 (12)	23 (12)	5 (10)	.72	1.2 (0.4–3.4)
With friends	24 (10)	13 (7)	11 (33)	.002	0.3 (0.1–0.6)
Others[a]	7 (3)	7 (4)	0 (0)	—	—
NS	20 (9)	17 (9)	3 (7)	.53	1.5 (0.4–5.3)
Cannabis type					
Resin (hashish)	169 (72)	136 (73)	33 (69)	.82	1.1 (0.5–2.1)
Marijuana (herbal)	16 (7)	14 (7)	2 (4)	.54	1.9 (0.4–17.4)
NS	50 (21)	37 (20)	13 (27)	.27	0.7 (0.3–1.4)
Severity of intoxication					
PSS 1	170 (72)	130 (70)	40 (83)	.06	0.5 (0.2–1.0)
PSS 2	25 (11)	20 (11)	5 (10)	.96	1.0 (0.4–2.9)
PSS 3	40 (17)	37 (19)	3 (7)	.03	3.7 (1.1–11.8)
Parental consumption					
Yes	105 (45)	89 (48)	16 (33)	.08	1.8 (0.9–3.5)
No	41 (17)	32 (11)	9 (20)	—	—
NS	89 (38)	77 (41)	12 (25)	.04	2.1 (1.0–4.3)
Social measures					
No report	54 (23)	41 (22)	13 (27)	.45	0.7 (0.4–1.6)
Simple referral to CPS	162 (69)	132 (71)	30 (63)	.28	1.4 (0.7–2.8)
Report for special concern to CPS	39 (17)	31 (17)	8 (17)	.98	1.0 (0.4–2.3)
Foster care placement	5 (0)	4 (2)	1 (2)	—	—
Complaint to the police department	4 (0)	3 (2)	1 (2)	—	—
NS	10 (4)	9 (5)	1 (2)	—	—

NS, nonspecified. —, not applicable.

[a] Others = grandparent, uncle, aunt, or nanny.

files. For each hospitalized patient, the diagnostic code is electronically assigned through the medical information system program by using the *International Classification of Diseases, 10th Revision*. The medical files were selected by cross referencing the associated *International Classification of Diseases, 10th Revision* diagnostic codes (T407 and F120-F122) and positive cannabis screening results in urine and/or blood at the toxicology laboratories affiliated with each hospital.

The data collected per patient were as follows: demographic data (age, sex, weight, date and time of admission, and mode of transportation); clinical data (vital parameters on admission, Glasgow Coma Score, heart rate, blood pressure, respiration rate, and body temperature); neurologic symptoms (dizziness, coma, convulsions, agitation, and euphoria); respiratory symptoms (bradypnea and apnea); ophthalmologic symptoms (mydriasis and conjunctival hyperemia); cardiovascular symptoms (hypotension, hypertension, and tachycardia); intoxication-related data (time and mode of exposure, estimated ingested amount, place of intoxication, form of cannabis [resin, joint, edible products ("space cakes" or "space cookies," candies, and chocolate bars), or liquid (e-cigarettes)]); data related to examinations (blood tests, lumbar puncture, head computed tomography scans, electrocardiograms, EEGs, toxicological tests [blood, urine, and hair]); disposition (home, general pediatric ward, intensive care or resuscitation unit [mechanical ventilation required]); and a notion of parental consumption and evolution (date and time of discharge from the emergency unit, total hospitalization duration, social measures [Child Protective Services (CPS), alert information, reporting to the judge of juvenile or family

TABLE 2 Clinical Manifestations of Cannabis-Intoxicated Patients Aged <6 Years Admitted Between 2004 and 2014 in French PEDs and Compared With Published Series (Percentage in Columns)

	Present Study			*P*[a]	Spadari et al[6]	Onders et al[7]	Cao et al[8]
Type of unit, location	PEDs, France				PCC, France	PCC, United States	PCC, United States
Study design	Retrospective, multicenter				Retrospective, single center	Retrospective, multicenter	Retrospective, multicenter
Years	2004–2009	2010–2014	2004–2014	—	1993–2008	2000–2013	2013–2015
Patients,[b] *n*	46	183	229	—	93	1969[c]	92
Symptoms, % (*n*)							
Neurologic	80.4 (37)	87.4 (160)	86.0 (197)	.22	57.0 (53)	45.5	85.8 (79)
Drowsiness	63.0 (29)	60.1 (110)	60.7 (139)	.72	48.4 (41)	29.5	66.3 (61)
Hypotonia	34.8 (16)	35.5 (65)	35.4 (81)	.93	10.7 (10)	0.7	—
Coma	4.35 (2)	16.9 (31)	14.4 (33)	.03	<1 (1)	0.9	—
Agitation	6.52 (3)	10.9 (20)	10.0 (23)	.58	8.6 (8)	3.3	5.4 (5)
Ataxia	17.4 (8)	7.10 (13)	9.17 (21)	.04	3.2 (3)	5.4	14.1 (13)
Convulsions	6.52 (3)	5.46 (10)	5.24 (12)	.77	2.2 (2)	0.5	—
Euphoria	6.52 (3)	4.37 (8)	4.80 (11)	.46	3.2 (3)	NS	NS
Cardiovascular	30.4 (14)	29.5 (54)	29.7 (68)	.90	6.5 (6)	4.1	—
Hypertension	17.4 (8)	9.28 (17)	10.9 (25)	.12	—	0.3	—
Tachycardia	6.52 (3)	14.2 (26)	13.5 (31)	.22	5.4 (5)	3.1	9.8 (9)
Hypotension	2.17 (1)	1.09 (2)	1.31 (3)	.49	<1 (1)	0.3	—
Ophthalmologic	45.6 (21)	52.4 (98)	51.1 (117)	.34	10.7 (10)	5.9	—
Mydriasis	41.3 (19)	46.9 (88)	45.8 (105)	.41	8.6 (8)	3.4	9.8 (9)
Conjunctival hyperemia	2.17 (1)	12.0 (22)	10.0 (23)	.05	2.2 (2)	1.2	8.7 (8)
Respiratory	4.35 (2)	10.4 (19)	9.17 (21)	.26	5.4 (5)	1.2	—
Hypoventilation	6.52 (3)	6.01 (11)	6.11 (14)	.89	5.4 (5)	—	—
Apnea	0.00 (0)	3.27 (6)	2.62 (6)	.60	—	0.7	3.3 (3)
Assisted ventilation	0.00 (0)	4.37 (8)	3.49 (8)	.36	—	NS	2.2 (2)
Temperature							
Hyperthermia (≥38.5°C)	4.34 (2)	2.73 (5)	3.06 (7)	.57	<1 (1)	0.3	—
Hypothermia (<36°C)	2.17 (1)	2.73 (5)	2.62 (6)	.83	<1 (1)	—	—
Disposition					—	—	—
Hospitalization, % (*n*)	86.9 (40)	88.5 (162)	88.2 (202)	.77			
ICU, % (*n*)	4.34 (2)	14.7 (25)	12.1 (27)	.08			

NS, nonspecified. —, not applicable.

[a] Compare years 2010–2014 and 2004–2009.

[b] Exclusion of patients with cointoxications.

[c] Percentages have been calculated out of the number of exposures (symptomatic and asymptomatic patients) and not out of the number of symptomatic patients (intoxicated).

court, and foster care]). Each center sent its confidential database to the study coordinator. The severity criteria were as follows: coma status (unarousable or unresponsive), seizures, respiratory failure (apneas and/or respiratory rate <10th percentile for age and/or tracheal intubation), hypotension (systolic blood pressure <fifth percentile for age), hypertension (systolic blood pressure >95th percentile for age), bradycardia (pulse rate <80 beats per minute [age ≤1 year]), pulse rate <60 beats per minute [1–6 years]), and a Poisoning Severity Score (PSS) value of 3.[5] To depict the evolution of unintentional pediatric cannabis intoxication, our data were compared with French poison control centers (PCCs) data concerning calls for cannabis exposure or intoxications (in symptomatic patients) and calls for other intoxications in the same age group.

Statistical Analysis

For statistical analysis, data were entered in Microsoft Excel tables (Microsoft Corporation, Redmond, WA). Analysis was performed with StatView 5.1 (SAS Institute Inc, Cary, NC) and EpiInfo 6.04fr (VF, ENSP-Epiconcept, Paris, France). In the descriptive analysis, data are presented as a mean ± SD, a median with extreme values, or with 95% confidence intervals (CIs) when appropriate unless otherwise indicated. To compare qualitative variables, a χ^2 test (Cochran-Mantel-Haenszel) was used, and a 2-tailed Fisher's exact test was used if the expected value was <5. For quantitative independent variables, a paired Student's *t* test was applied. A nonparametric Kruskal-Wallis test was performed in cases of non-normal distribution. Statistical significance was considered at $P < .05$.

Ethical and Regulatory Considerations

The data recorded during this research were subject to electronic processing at the Toulouse University Hospital PED in accordance with law

TABLE 3 Comparison of Comatose and Noncomatose Intoxicated Children (Percentage in Columns)

	Comatose[a] *n* (%), (*n* = 32)	Noncomatose, *n* (%), (*n* = 197)	*P*	OR (95% CI)
Mean age, y	1.5 ± 0.4	1.5 ± 0.6	.24	—
Age group, mo				
0–5	0 (0)	2 (1)	.99	1.02 (0.05–21.6)
6–11	7 (18)	52 (26)	.59	0.78 (0.32–1.91)
12–17	12 (37)	89 (45)	.42	0.73 (0.34–1.57)
18–23	8 (25)	21 (11)	.03	2.79 (1.11–7.00)
≥24	5 (16)	33 (17)	.87	0.92 (0.33–2.56)
Autumn admission	14 (44)	93 (47)	.72	0.87 (0.41–1.35)
Weekend admission	7 (22)	61 (26)	.30	0.62 (0.26–1.52)
Nonreferred by a physician	20 (63)	141 (82)	.30	0.66 (0.30–1.44)
Time of admission				
8:00 AM–11:00 AM	6 (19)	21 (11)	.19	1.93 (0.71–5.23)
12:00 AM–5:00 PM	8 (25)	79 (40)	.11	0.49 (0.21–1.16)
6:00 PM–11:00 PM	14 (44)	85 (43)	.95	1.02 (0.48–2.17)
12:00 PM–7:00 AM	4 (11)	12 (6)	.25	2.19 (0.48–7.91)
Tachycardia	5 (16)	24 (12)	.57	1.33 (0.37–3.99)
Hypertension	5 (16)	84 (43)	.004	0.27 (0.10–0.67)
Hypotension	7 (22)	14 (7)	.01	3.66 (1.35–9.93)
Hypoventilation	22 (69)	87 (44)	.01	2.78 (1.25–6.18)
Mydriasis	24 (75)	82 (42)	.001	4.20 (1.80–9.83)
High glycemia	3 (9)	8 (6)	.19	2.43 (0.39–10.9)
Hyponatremia	3 (9)	3 (12)	.04	6.59 (1.28–34.7)

—, not applicable.

[a] Cointoxications with molecules of neurologic effects are excluded (*n* = 6).

number 78-17 of January 6, 1978, regarding information technology, files, and liberties amended by law 2004-801 of August 6, 2004. The research protocol (number 15.1019a) received a favorable opinion of the National French Institutional Board (Advisory Committee on Health Research Information Processing).

RESULTS

Descriptive Analysis

Twenty-four PEDs (80% of national PEDs) in 20 French districts and 21 regions took part in the study. During the study period, 235 children matching the inclusion criteria were admitted. Seventy-one percent were aged 18 months old or younger (Fig 1). Figure 2 illustrates the national geographical distribution of these admissions from 2004 to 2009 and 2010 to 2014. The main demographic characteristics are summarized in Table 1 and compared between the 2 periods. Annual admissions increased by a factor of 13 over 11 years (+133%). Between 2004 and 2014, the number of severe cases increased by a factor of 20 and by a factor of 4 between 2013 and 2014. The estimated time of ingestion had a bimodal distribution with 2 peaks (10:00 AM–1:00 PM and 06:00 PM–10:00 PM). The average delay between ingestion and admission was 4 hours 24 minutes ± 3 hours 6 minutes. The main place of intoxication was the parental home (72%). Ingestion was the main route of intoxication (75%). Resin sticks, balls, and cones were the principal form ingested (72%), and the most frequent amount (80%) was 1 stick (average weight of 2–3 g) (data came from the French Office for Drugs and Drug Addiction) or 1 ball (average weight of 2–4 g). The clinical signs at admission are shown in Tables 2 and 3 and were predominantly neurologic symptoms (86%). Eighty-three (35%) children had at least 1 severity criteria. Fifty-three percent of all children with comas were admitted during 2014 (Fig 3). Fourteen patients were diagnosed with respiratory failure, and 8 required assisted ventilation for 24 hours or less. Basic metabolic panel blood tests that were performed on 178 patients (76%) revealed abnormalities (*n* = 40). These included high blood sugar levels (*n* = 14), hyponatremia (≤130 mmol/L) (*n* = 8), metabolic acidosis (*n* = 5), and functional kidney failure (*n* = 5). Additional procedures included the following: electrocardiograms (*n* = 63), head computed tomography scans (*n* = 39), abdominal ultrasounds (*n* = 39), lumbar puncture (*n* = 24), and EEGs (*n* = 24). In addition to cannabis detection, blood and/or urine toxicological screenings (for benzodiazepines, barbiturates, opiates, amphetamines, methamphetamine, cocaine, buprenorphine, norbuprenorphine, methadone, codeine, lysergic acid diethylamide, ethanol, tricyclic antidepressants, paracetamol, and tramadol) were performed in 205 cases. Eight other molecules were isolated in 8 children (4%) (Table 4). None of these patients required assisted ventilation. Paracetamol was allegedly being given to treat hyperthermia (*n* = 2). Benzodiazepines were detected in children who had received diazepam to stop seizures. Most of the children were hospitalized (88%), of whom 27 were in a resuscitation unit or ICU. Parental cannabis consumption was indicated in 146 cases (62%), and 72% declared to be regular users. Social or legal measures included a referral to CPS for 162 cases, a written report for special concern for 39 children, 5 children were placed in foster care by court order, and 4 families were subject to a complaint filed with a police department.

Comparative Analysis

Table 2 shows the comparison of clinical manifestations between the 2004–2009 and 2010–2014 periods. The most recent period was marked by the number of comas (excluding patients with cointoxications) (16.9% vs 4.4%, *P* = .03, odds ratio 4.9,

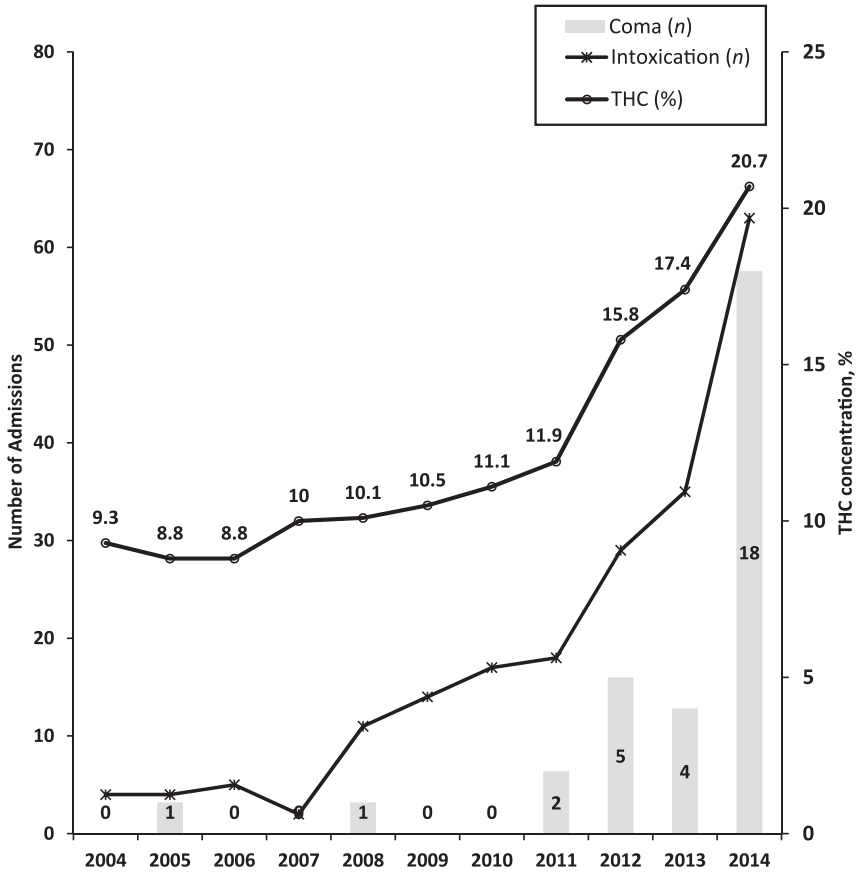

FIGURE 3

Distribution of pediatric cannabis intoxications and comatose presentations and THC concentration in hashish resin (results obtained from the analysis of products seized by French customs) during the study period (2004–2014).

95% CI 1.03–19.5). The comparison of PSS distribution (excluding patients with cointoxications) indicated more severe presentations (PSS 3) (18.5% vs 4.3%, OR 5.0, 95% CI 1.2–21.7, $P = .02$). When 2004 was compared with 2014, the average age of intoxicated patients revealed younger children ($P = .005$) (Table 1). The increase in intoxications and comas was compared with the concentration of THC in resin seized by French customs over the same period (Fig 3). Data were compared with cannabis-related calls and other toxic exposure-related calls (in symptomatic and nonsymptomatic patients) received by French PCCs during the same period. Patients included in this study represented 84% of national cannabis-related calls for symptomatic children.

Between 2004 and 2014, the rate for cannabis exposures in children aged <6 years progressed from 5.4 to 15.4 per 10 000 toxic exposures. The number of cannabis-related calls to French PCCs increased by 312%, 8.3% for noncannabis exposures and 3.3% for the pediatric population younger than 6 years old between 2004 and 2014 in the same geographical areas (data came from the French National Institute of Statistics and Economic Studies). Compared with the French population of children <6 years old in 2004 and 2014, the overall national rate per capita for cannabis-related calls progressed from 0.7 to 3.6 per 100 000. Compared with PED admissions for children aged <6 years between 2004 and 2014, cannabis-related PED visits increased from 1.7 to 16.1 per 100 000 admissions per year.

DISCUSSION

The evolution of unintentional pediatric cannabis intoxications is remarkable because of increased admissions throughout the country and an increase in severe presentations (Fig 3). Between 2004 and 2014, the evolution of PED visits for cannabis intoxication in toddlers increased 133%, and cannabis exposure-related calls to French PCCs increased 312%. Calls for other toxic exposures increased by only 45%. The phenomenon was not related to an equivalent increase in the French pediatric population for the same age group. Between 2000 and 2013, the evolution of similar calls to American PCCs showed a variation of 147% for pediatric exposure to cannabis.[7] In France, Spadari et al[6] of the Marseille PCC raised an initial alert in 2009 when they reported 93 calls for pediatric intoxications. They suspected a link between higher THC concentrations in cannabis products and more severe cases. Since this warning, 1 French series of 8 pediatric intoxications was reported in 2015.[9] Contrary to other European countries, hashish (resin) is the most popular cannabis form in France. Increased THC concentration in resin has been demonstrated and is related to a change in production. Cannabis hybrids that allow higher resin yields and THC content[10,11] have replaced the traditional Moroccan plants. In France, Dujourdy and Besacier recently published that almost three-quarters of records corresponded to a mean THC content >20% per gram (cannabis potency).[12] European data on cannabis potency are based on forensic analysis of seized materials. This is not necessarily representative of the market, especially in countries with significant domestic cultivation (eg, the Netherlands).[13] Detailed data on cannabis product potency have been studied in the Netherlands,

TABLE 4 Characteristics of Pediatric Patients With Cointoxications

Patients	1	2	3	4
Year	2005	2007	2010	2011
Age, mo	10	19	13	22
Symptoms	Hypotension, tachycardia, agitation, seizures, and altered consciousness	Tachycardia, comatose, apneas, and hypoventilation	Hypertension, comatose, and hypothermia	Tachycardia and ataxia
Mydriasis	No	No	Yes	Yes
GCS	10	6	6	14
Cointoxicants	Cocaine	Buprenorphine	Cocaine and tramadol	Levorphanol
LOS, d	7	1	3	NS
PICU	No	No	Yes	Yes
Social measures	Foster care placement	Simple CPS report	Special concern CPS report	None
Patients	5	6	7	8
Year	2013	2013	2014	2014
Age, mo	13	9	17	14
Symptoms	Tachycardia, hypothermia, hyperventilation, hypertonia, and hyponatremia	Tachycardia, hypotonia, and altered consciousness	Comatose, nystagmus, and hyponatremia	Tachycardia, hypoventilation, altered consciousness, and hyperthermia
Mydriasis	Yes	No	Yes	No
GCS	7	13	6	12
Cointoxicants	Benzodiazepines	Paracetamol	Benzodiazepines	Paracetamol
LOS, d	2	2	2	1
PICU	Yes	No	Yes	No
Social measures	Simple CPS report	Simple CPS report	Simple CPS report	Special concern CPS report

GCS, Glasgow Coma Scale; LOS, length of stay; NS, nonspecified.

the United Kingdom, France, the United States,[14] and Australia.[15] In the Netherlands, the THC content of resin is higher than herbal products of the same origin (local or imported), and Dutch products are more potent than imported ones (local resin 29.6% vs 14.3%).[13,16] In the United Kingdom, cannabis seized by law enforcement showed no change in the mean potency of resin (5.9%) or imported herbs (8.5%) in 2008.[17] In the United States, ElSohly et al,[14] focusing on seized products, published a mean cannabis potency of 12%. In Australia, Swift et al[15] found the same evolution toward a higher potency of herbal cannabis (a mean THC content of 14.9%). Cannabis decriminalization also seems to contribute to the progression of moderate to severe pediatric intoxications. In the United States, these clinical forms are significantly more represented in states where cannabis has been decriminalized.[18–21] In these states, the ingestion of food products containing cannabis is of concern.[22] The risk of exposure is high because of attractive packaging and naming that is phonetically similar to the original candy (eg, "Beef-Kat" or "Oeo").[10,22–24] In France, the ingestion of resin sticks or balls is the main source of intoxication.[6,8,9,25–29] Intoxication in infants through passive inhalation has also been described.[30] The main compounds in cannabis have a plasma peak between 1 hour for inhalation and 3 to 4 hours for ingestion. The effects last between 6 and 24 hours.[30] More prolonged neurologic effects have been published.[31] The comparison of the evolution of clinical manifestations of pediatric intoxications presented by Spadari et al[6] or Cao et al[8] to the current study indicates a higher proportion of neurologic and cardiovascular symptoms in our cohort (Table 2). We believe this difference could be related to an elevated resin potency. The occurrence of seizures was described by several authors.[6–8,25] The proconvulsive effect of cannabis is not unanimous. Some authors advocate the opposite effect because of the physiopathology of cannabinoids and the capacity to reduce the release of neurotransmitters, such as γ-aminobutyric acid or glutamate, and therefore neuronal excitability.[31,32] Seizures would be related to possible adulterants of the resin (eg, anticholinergic substances, cocaine, or methamphetamine) or a concomitant ingestion of another toxin instead.[33] The adulteration of cannabis resin was previously alleged. Moroccan hashish is cut mainly with a range of inert or active substances (eg, soil, henna, paraffin or bee wax, glue, licorice, or coffee).[34] There is little data on adulterants in cannabis resin, and the existing data are controversial. The presence of adulterants in cannabis resin could not been confirmed by studies conducted in France by the French Office for Drugs and Drug Addiction (2007) or the French Reitox focal point.[34] Therefore, positive results for cannabis and other drugs or molecules through a blood and/or urine screening are more likely because of separate poisonings. Because other drugs or toxic molecules may not be detected by classic enzyme immunoassays, more sophisticated techniques (such as gas chromatography and mass spectrometry) should be requested for their isolation, especially when clinical presentation is unusual or severe. The existence of mydriasis associated with other neurologic signs is a decisive element suggesting cannabis intoxication in children, but

its presence is inconsistent (Table 2). This inconsistency explains the diagnostic uncertainty in cases of coma and the use of additional tests (eg, head computed tomography scans, lumbar puncture, EEGs, and metabolic tests).[35] Cardiovascular symptoms are the result of the stimulation of type 1 cannabinoid receptors located in the heart. This stimulation generates an orthostatic and parasympathetic imbalance and the activation of the sympathetic system and potential blockage of the parasympathetic system.[36–38] These transitory manifestations, which are dominated by sinus tachycardia, do not usually require any specific therapy.[38,39] Adulterants should also be considered in the presence of severe cardiovascular manifestations (eg, myocardial infarction, coronary syndrome, and rhythm disorder). Hyponatremia may be explained by the direct effect of THC on the hypothalamic-pituitary axis (the release of vasopressin)[23] or the effects of an adulterant, such as methamphetamine.[40] In our cohort, 6 of 8 patients with hyponatremia were screened. Results were negative for methamphetamine.

The increase in severe pediatric patients admitted to a pediatric intensive care or resuscitation unit was identified in France by Le Garrec et al.[35] Because of the current prevalence of cannabis intoxication in young children, this diagnosis should be considered when an afebrile comatose child is admitted to a French emergency unit.[29,35] Given the increased frequency, it could also be assumed that physicians investigated cannabis intoxication more often, and this may have contributed to the increase in prevalence in the last 2 years.

No pediatric deaths because of cannabis intoxication have been reported. The systematic postmortem toxicological detection in a pediatric cohort of 730 children <19 years of age showed that 38% tested positive for toxic drugs or medications, but none of them were for cannabis.[41]

The variation in social measures accounts for the difficulty (in legal terms) of such cases in which the intoxicated person is not the user of the illicit drug but is vulnerable and subjected to the environment and parental or caregiver supervision.[42]

Because of the retrospective character of the study, some data available were insufficient (eg, parental cannabis consumption). Some children could have been admitted to non-PEDs, but usually (because of the alarming clinical presentation), they are transferred to the nearest regional PED. Extensive toxicological screening was not performed for all children. Cointoxications could have been underestimated for 30 patients. Cointoxication was detected in 4% (n = 8) of the screened patients (n = 205), making the risk of underestimation low for the unscreened patients. Most molecules known to produce false-positives for THC in urinalysis were not taken by our pediatric population (eg, dronabinol, efavirenz, naproxen, pantoprazole, and tolmetin). Concerning ibuprofen, a false-positive result for cannabinoids in urine tests has been shown only in 2 of 24 adult patients with chronic treatment.[43] Niflumic acid can cause false-positive urine test results in some commercial immunoassays for cannabinoids,[44] but it is not recommended in France for fever management. The risk of false-positive urine detection because of niflumic acid use was therefore limited in nonscreened patients.

CONCLUSIONS

In France, the increase of cannabis-related PED admissions seems obviously linked to changing consumption trends and a higher potency of the predominant form on the market (hashish). In countries where marijuana has been decriminalized, this increase is related to greater availability and the growing lucrative market of edible products containing marijuana. In countries where cannabis potency has remained low, this pediatric health issue has not been reported. In the Netherlands, cannabis has been culturally smoked in coffee shops for some time. This could explain the absence of published pediatric intoxication. The most recent trends (2015–2016) provided by French PCCs confirm our results, showing an increase in the phenomenon and raising a real public health issue. Unintentional intoxication should be tightly monitored, and it should be mandatory to report such cases. Our data demonstrate incomplete reporting to CPS, especially when clinical presentation is not severe. Intervention by social services must also be mandatory and homogeneous across the country.

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ABBREVIATIONS

CI: confidence interval
CPS: Child Protective Services
PCC: poison control center
PED: pediatric emergency department
PSS: Poisoning Severity Score
THC: tetrahydrocannabinol

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