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Posterior Reversible Encephalopathy Syndrome in Clinical Toxicology: A Systematic Review of Published Case Reports

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Background: Posterior reversible encephalopathy syndrome (PRES) is a rare clinical and radiological entity characterized by a typical brain edema. Although several case reports have described PRES in a context of poisoning, to our knowledge, a comprehensive assessment has not been performed. The aim of this systematic review was to raise awareness on poisoning-specific PRES features and to encourage consistent and detailed reporting of substance abuse–and drug overdose–associated PRES.

Methods: Medline/PubMed, Web of Science, and PsycINFO were screened through May 31, 2019, to systematically identify case reports and case series describing PRES associated with poisoning (i.e., alcohol, drugs, illicit drugs, natural toxins, chemical substances) in accidental context, intentional overdose, and substance abuse. The methodological quality of eligible case reports/series was assessed. Patients and exposure characteristics were recorded; relevant toxicological, radiological, and clinical data were extracted.

Results: Forty-one case reports and one case series reporting 42 unique cases were included. The median time to PRES onset from the start of exposure was 3 days (IQR 2–10). Acute high blood pressure, visual disturbance, and seizure were reported in 70, 55, and 50% of patients, respectively. The initial clinical presentation was alertness disorders in 64% of patients. Nine patients (21%) required mechanical ventilation. One-third of patients had at least one risk factor for PRES such as chronic hypertension (17%) or acute/chronic kidney failure (24%). The main imaging pattern (67%) was the combination of classical parieto-occipital edema with another anatomical region (e.g., frontal, basal ganglia, posterior fossa involvement). Vasogenic edema was found in 86% of patients. Intracranial hemorrhage occurred in 14% of patients. Both brain infarction and reversible cerebral vasoconstriction syndrome were diagnosed in 5% of patients. Three patients (12%, 3/25) had non-reversible lesions on follow-up magnetic resonance imaging.
INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a rare radiological and clinical entity characterized by a typical brain edema and various symptoms such as high blood pressure (75–80%), encephalopathy (50–80%), headache (50%), visual disturbances (33%), focal neurological deficits (10–15%), seizures (60–75%), and status epilepticus (5–15%) (1). Kidney injury is highly prevalent during PRES (up to 55%), and more than half of patients have chronic hypertension (1). PRES can occur in a number of complex clinical conditions, classically dichotomized into iatrogenic (e.g., antineoplastic therapy, calcineurin inhibitors) and PRES-associated medical conditions (e.g., eclampsia, sepsis, autoimmune disorders), requiring mechanical ventilation for 3–7 days in 35–40% of patients (2). Although there is currently no unified diagnostic algorithm, neuroimaging usually yields bilateral cortical–subcortical vasogenic edema according to three anatomic patterns: dominant parieto-occipital involvement, variant atypical PRES, and combination of different patterns. Variant atypical PRES gathers superior frontal sulcus, holohemispheric watershed, cerebellum, basal ganglia, brainstem, and spinal cord involvements (3, 4). The atypical or combined patterns are more common than the typical PRES with isolated parieto-occipital involvement.

The pathophysiology of PRES is still debated through hypoperfusion and hyperperfusion theories. Impaired cerebral autoregulation responsible for disruption of the blood–brain barrier (BBB) is one of the two main hypotheses, the other one being endothelial dysfunction (5). A recent review suggests that arginine vasopressin (AVP) axis stimulation could precipitate PRES development through an increase in AVP secretion or AVP receptor density. Activation of vasopressin V1a receptors leads to cerebral vasoinconstriction, endothelial dysfunction, and subsequent brain edema (5).

Thus, PRES is a syndrome whose circumstances of occurrence and radiological features are associated with significant clinical and radiological polymorphism, making it difficult to characterize. Drug toxicity is one of the potential etiologies. Data are available in the literature regarding PRES occurring at therapeutic drug doses, but to the best of our knowledge, no review focused specifically on cases of accidental or intentional poisoning-associated PRES.

In order to investigate the occurrence of PRES in poisoned patients, the authors systematically reviewed the scientific literature of case reports and case series concerning PRES associated with poisoning (i.e., alcohol, drugs, illicit drugs, natural toxins, chemical substances) in accidental context, intentional overdose, and substance abuse. The authors did not include cases of calcineurin inhibitor overexposure, which has already been covered (6). The purpose of this study is to raise awareness of the features of PRES in poisoned patients and encourage consistent and detailed reporting of PRES in a context of overdose and substance abuse.

METHODS

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (7).

Eligibility Criteria

All language case reports and cases series were eligible if they concerned human subjects and included full-text. Records were screened if they were explicitly labeled as PRES based on head MRI (magnetic resonance imaging) or CT (computed tomography) scans. Case reports were included if PRES occurred in temporal connection with poisoning (i.e., alcohol, drugs, illicit drugs, chemical substances, natural toxins) in accidental context, intentional overdose, or substance abuse and/or a causal relationship was assumed by the authors of the report.

Data Sources, Search Strategy, and Data Extraction

A search using Medline/PubMed, Web of Science and PsycINFO was performed without any limits through May 31, 2019. The search terms in Medline were a combination of medical subject heading (MeSH) terms and keywords. The search strategy consisted of using the health multi-terminology portal HeTOP (8) for each term (i.e., text words OR MeSH OR title/abstract) with the following search algorithm: [(posterior leukoencephalopathy syndrome) AND (poisoning) OR (overdose) OR (intoxication) OR (substance abuse) OR (solvents) OR (organophosphates) OR (licorice) OR (venoms) OR (scorpion) OR (mushroom) OR (lysergic acid) OR (cathinone) OR (coca) OR (amphetamine) OR (heroin) OR (natural toxins)].
[cannabis] OR [alcohol]). A manual search and screening of the bibliographies of selected articles was performed, in addition to the computerized search. The search strategy is summarized in Supplementary Figure 1.

Extracted data included the following clinical and toxicological considerations: age, gender, risk factors of PRES occurrence, and exposure characteristics to the causative agent. Clinical and radiological data on PRES, its time course, and outcomes were also extracted. Unreported data were considered absent. Neuroimaging results were classified according to three different patterns. Briefly, the classical PRES pattern, involving only parieto-occipital lobes; the variant, including isolated various anatomical regions (e.g., frontal, cerebellum, brainstem, basal ganglia); and finally, the combined pattern, which includes combination of various regions.

Methodological Quality Assessment

The methodological quality of case reports and cases series was assessed using the tool proposed by Murad et al. (9) modified to adapt it to the analysis of toxicological exposures associated with PRES. The selected items were based on scores used for causality assessment in drug overdose (10, 11). This new tool converges into 10 items that can be categorized into six domains: selection, ascertainment, diagnosis, causality, follow-up, and reporting (Supplementary Table 1). Briefly, items included time to onset of PRES, exposure characteristics (e.g., dose, drug detection, identification of species), radiological features, clinical data (e.g., symptoms, risk factors), dechallenge phenomenon, differential diagnosis, pharmacological properties of the causative agent, and clinical/radiological follow-up. The results of this modified tool have been summarized by summing the scores of the 10 binary responses into an aggregate score (Supplementary Tables 1, 2).

RESULTS

Case Selection

The literature search revealed a total of 149 non-duplicate records of which 95 were excluded because they did not report poisoning-associated PRES or were not case reports or case series. Out of 54 full-texts assessed for eligibility, 13 were excluded because they did not report poisoning-associated PRES or outcomes of interest (i.e., symptoms, brain edema features, follow-up). Finally, 40 case reports and 1 case series reporting a total of 42 unique cases were included (Supplementary Figure 1).

Synthesized Findings

Demographic Characteristics and Clinico-Biological Findings

Demographic data, substances involved, and clinico-radiological characteristics are summarized in Supplementary Table 3. Out of 42 patients included, 22 were female (52%); median age was 41 years (IQR 27–55, range 3–73). Four children were included (12–15). The median time to PRES onset from the start of exposure or intoxication diagnosis was 3 days (IQR 2–10) and ranged from 2 h (13) to 4 months (16, 17). The initial clinical presentation was alertness disorders in 64% of patients (13–15, 18–40). Visual disturbances were reported in 55% of patients (23/42) (12, 13, 15, 16, 19–21, 23, 25–27, 29, 34, 35, 37, 39, 41–47) including photophobia (19, 20, 35), visual hallucination (21, 23, 26, 27), and cortical blindness (15, 16, 24, 29, 34, 37). Four patients had concurrent acute kidney failure with PRES (13, 19, 44, 48). When performed (33, 39, 43), hypomagnesemia was found in one patient (39). Cerebral spinal fluid (CSF) analysis (20, 21, 23, 24, 34, 36, 37, 45, 47, 49) showed elevated CSF protein in one patient (34). Nine patients (21%) required mechanical ventilation (14, 21, 28, 33, 38, 46–48). The median time required to hospital discharge was 14 days (IQR 7–18). Mortality and neurological recurrence rate were null.

Radiological Features

Radiological diagnosis was based on brain MRI and CT scans in 91% (38/42) and 9% (4/42) (35, 38, 40, 43), respectively. The neuroimaging findings, including anatomical pattern, diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), edema type, symmetry, and arterial characteristics, are summarized in Supplementary Table 3. Five patients (19, 24, 26, 34, 44) had normal initial brain CT (5/9, 56%) (19, 20, 24, 26, 34, 42, 44, 48, 50). All patients exhibited cortical and/or subcortical edema, characterized by hyperintensities in T2-weighted and/or T2 fluid-attenuated inversion recovery (FLAIR) imaging, which was consistent with PRES diagnosis in MRI. Symmetrical lesions were reported in 76% of patients (25/33) (12–15, 19, 22–25, 27, 29, 32–34, 36, 37, 39, 40, 43, 44, 46, 47, 49, 50). The combined pattern, which includes combination of various regions, was the most frequent with 67% of patients (13, 14, 17–22, 24–26, 28, 30–35, 38, 39, 41, 44, 46–49, 51). The classical PRES pattern, involving only parieto-occipital lobes, was found in 19% (8/42) of patients (12, 16, 23, 27, 30, 40, 42, 45). The variant pattern of PRES (6/42, 14%), including isolated anatomical region such as occipital (29, 36, 43, 50) and cerebellum (15, 52), occurred in 9 and 5%, respectively. In five reports, angiography (by contrast-enhanced arteriography in CT, or MRI sequences including non-contrast time-of-flight and angio-MRI or digital subtraction angiography) showed narrowing of the cerebral arteries (16, 28, 36, 37, 49). Reversible cerebral vasoconstriction syndrome (16, 49) was diagnosed in 5% of patients (2/42).

DWI was positive in 60% of patients (12/20), totally or partially in correspondence with T2/FLAIR hyperintensities, with focal or larger extent (20, 25, 26, 29, 30, 36, 37, 39, 47–49). When data related to ADC were provided, positive DWI due to vasogenic edema (i.e., no restricted ADC) (16, 17, 19, 21, 23, 25, 26, 28–31, 33, 34, 36, 45, 47–49) and cytotoxic edema (i.e., restricted ADC) (20, 24, 39, 49) were found in 86 and 19% of cases, respectively. T2* (gradient echo) or susceptibility weighted imaging revealed intracranial hemorrhage in 14% of patients (16, 20, 30, 31, 36, 43). The median time of follow-up imaging was 21 days (IQR 11–60). Out of 25 patients with follow-up imaging, 22 (88%) showed complete resolution of brain edema (12–14, 16, 21, 22, 24, 26, 29–31, 33, 38, 43–47, 50, 51).

Characteristics According to the Causative Agent

Exposure characteristics, clinico-radiological features, and follow-up data of the included cases are shown in Table 1.
| References           | Substance/context            | Sex/age | Comorbidities                  | Time to onset | Blood pressure | Diagnosis                                      | Follow-up                                      | Imaging                  |
|----------------------|------------------------------|---------|--------------------------------|---------------|----------------|-----------------------------------------------|-----------------------------------------------|--------------------------|
| Bhagavati et al. (22) | Acute alcohol intoxication   | M/57    | Chronic alcohol abuse          | 2 days        | 131/88         | Confusion                                      | Complete clinical resolution                 | Complete resolution after 2 weeks |
| Coppens et al. (23)  | Acute alcohol intoxication   | M/43    | Chronic alcohol abuse on disulfiram | 3 weeks after daily alcohol consumption | 150/100       | Disorientation, delirium, visual hallucination, paraparesis | Slight improvement of lower limb paresis over several months | Almost complete resolution at day 14 |
| Srikrishna et al. (24)| Acute alcohol intoxication   | M/68    | Chronic alcohol abuse on disulfiram | 3 h after alcohol consumption | 160/100       | Vomiting, headache, confusion, cortical blindness, seizure | Clinical improvement after 15 days Walk without any assistance after 21 days | Complete resolution at day 21 |
| Kim et al. (25)      | Acute alcohol intoxication   | M/59    | Chronic alcohol abuse          | 1 day         | 191/100        | Confusion, disorientation, visual hallucination, seizure | Discharge at day 14 Only slight resolution after 2 months | Complete resolution at day 16 |
| Ishikawa et al. (26) | Alcohol withdrawal and acute pancreatitis | F/28 Ø | Chronic alcohol abuse           | 2 days        | 112/82         | Confusion, disorientation, visual hallucination, seizure | Combined pattern, positive DWI General condition improved at day 7 Discharge at day 17 Complete resolution at day 18 | Combined pattern at day 2 |
| Mengi et al. (27)    | Alcohol withdrawal           | M/53    | Ø                              | 3 days        | 150/90         | Disorientation, visual hallucination           | Clinical resolution at day 7 Significant regression at day 7 Resolution (date unknown) | Clinical resolution at day 16 |
| Gill et al. (28)     | Alcohol withdrawal after admission for acute alcohol intoxication and AKI | M/15    | Ø                              | Concomitantly with acute pancreatitis | 130/80        | Confusion, disorientation                       | Combined pattern, no restricted ADC Subacute infarct in the right parietal lobe Mental status improved after 2 days Able to walk around at day 5 Discharge at day 14 Signs of hemorrhage reabsorption after 2 months | Complete resolution after 1 month |
| Kimura et al. (29)   | Chronic alcohol abuse        | M/51    | Amphetamine abuse              | Not applicable | 170/100       | Confusion, disorientation, cortical blindness  | Clinical symptoms resolved in 4 days No permanent neurological abnormalities after 1 month Complete resolution, except few microbleeds in cerebellum after 1 month | Complete resolution after 1 month |
| Baek et al. (30)     | Chronic alcohol abuse with acute pancreatitis | M/49 Ø | Concomitantly with acute pancreatitis | 1 week after acute pancreatitis | Not available | Headache, vomiting, confusion, seizure          | Combined pattern, no restricted diffusion Subacute hemorrhage in the right frontal lobe | Complete resolution after 2 months |
| Magno Pereira et al. (31)| Chronic alcohol abuse       | M/33    | Ø                              | Not applicable | 190/100        | Combined pattern, no restricted diffusion      | Discharged at day 15 Lesions improved after 2 months | Complete resolution after 2 months |
| Murphy et al. (41)   | Chronic alcohol abuse with acute pancreatitis | F/40 Ø |                                   | 1 week after acute pancreatitis | Not available | Visual loss                                    | Combined pattern Visual recovery after 2 months Lesions improved after 2 months | Complete resolution after 2 months |
| John et al. (32)     | Severe acute alcoholic hepatitis | F/40    | Hepatic encephalopathy         | 3 weeks after alcholic hepatitis diagnosis | 114/78        | Headache, psychomotor retardation, seizure     | Combined and symmetrical patterns Not available Not available | Not available |
| Fitzgerald et al. (33) | Lithium withdrawal after lithium intoxication with AKI | F/50    | Chronic HTN                    | 9 days after intoxication | 140/80        | Headache, bladder/bowel incontinence, seizure  | Combined and symmetrical patterns, no restricted diffusion Discharged at day 22 Complete resolution 5 months later | Complete resolution after 2 months |

(Continued)
| References                        | Substance/context                        | Sex/age | Comorbidities        | Time to onset | Blood pressure | Diagnosis                                                                 | Follow-up                                                                 |
|----------------------------------|------------------------------------------|---------|----------------------|---------------|----------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Fitzgerald et al. (33) - #2      | Lithium withdrawal after lithium intoxication with AKI | M/61    | Chronic HTN          | 8 days after intoxication | SBP = 170      | Mental status altered Combined and symmetrical patterns                   | Discharged at day 25                                                     |
| Loens et al. (34)                | Lithium withdrawal after lithium intoxication with AKI | F/60    | Chronic HTN          | 3 days after intoxication | MAP > 130      | Somnolence, disorientation, dysarthria, cortical blindness, seizure Combined and symmetrical patterns, no restricted diffusion on ADC | ICU for 10 days, Full recovery after 22 days Regression of the edema with residual bi-occipital lesions at day 10 |
| Minhaj et al. (35)               | Dextroamphetamine and clonidine overdose | M/17 Ø  |                       | 9 h           | 182/111        | Headache, photophobia, confusion Combined pattern                        | Asymptomatic at 36 h and had no neurologic sequelae Not available          |
| Mann et al. (51)                 | Acetaminophen overdose with AKI at day 3 | F/21 Ø  |                       | 10 days       | 164/103        | Seizure Combined pattern Discharged at day 15 Asymptomatic at day 20       | Complete resolution at day 20                                             |
| Kinno et al. (49)                | Ephedrine overdose                       | M/28 Ø  |                       | 3 days        | Not available   | Paraplegia, agraphia Combined and symmetrical patterns                   | Not available Residual lesions in the parietal lobe at day 27             |
| Kawanabe et al. (36)             | Phenylpropanolamine misused as eye drops for 4 days | F/57 Ø  |                       | 3 days after the last dose | 186/106        | Headache, somnolence, seizure Atypical and symmetrical patterns, positive DWI, no restricted ADC Intraparenchymal left occipital hemorrhage | Discharge at day 34 Nearly complete resolution after 2 months          |
| Weidauer et al. (37) #1          | Digitoxin overdose                       | F/73    | Not available         | 3 days        | Normal          | Disorientation, vomiting, cortical blindness Parieto-occipital and symmetrical patterns, positive DWI | Slowly improvement of visual acuity over 4 months Not available        |
| Akinci et al. (15)               | Bismuth overdose with AKI at day 3 requiring HD | F/16 Ø  |                       | 15 days       | 110/70          | Confusion, somnolence, cortical blindness, ataxia, seizure Atypical and symmetrical patterns | Discharged 9 days after PRES Not available                               |
| Bazuaye-Ekwuyasi et al. (18)     | Cocaine HIV Chronic HTN ESRD             | F/41    | Not available         | Not available | 198/92          | Confusion, agitation Combined pattern Confusion and agitation slowly resolved at day 5 | Complete resolution at day 7                                           |
| Dasari et al. (19)               | Cocaine                                 | F/40    | Chronic HTN AKI on CKD| 4 days after heavy cocaine binging | 189/140        | Headache, somnolence, vomiting, photophobia Combined and symmetrical patterns, no restricted diffusion on DWI | Discharged after 2 days Not available                                   |
| Tantikititchaikul et al. (52)    | Amphetamine                             | M/45    | Not available         | Not available | SBP = 250       | Headache Atypical variant and no restricted Not available                 | Significant improvement of the lesions at day 3                        |
| Omer et al. (50)                 | Mephedrone                              | F/19    | Alcohol abuse         | 2 days        | SBP > 160       | Seizure Atypical and symmetrical patterns                                | No recurrence of seizure at day 10 Complete resolution at day 10        |

(Continued)
| References                  | Substance/context | Sex/age | Comorbidities                                                                 | Time to onset          | Blood pressure | Diagnosis                                                                 | Follow-up                                                                 |
|-----------------------------|-------------------|---------|--------------------------------------------------------------------------------|------------------------|----------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Castillo et al. (20)        | Kratom            | M/22    | Amphetamine, marijuana abuse                                                   | “Prior to admission”  | 180/105        | Headache, disorientation, photophobia, aphasia                           | Discharged after 5 days                                                  |
| Legriel et al. (21)         | Lysergic acid amide | M/39    | Alcohol abuse                                                                  | “Immediately”          | 185/130        | Confusion, hyperreflexia, visual hallucination, seizure                   | Discharged after 9 days in the ICU                                      |
| Delgado et al. (35)         | Snake bite (Bothrops asper) | M/18 Ø | 2 days                                                                        | <140/90                |                | Headache, respiratory distress, stuporous, seizure                       | Discharged asymptomatic                                                  |
| Varalaxmi et al. (42)       | Pit viper bite with AKI requiring HD at day 3 | M/45 Ø | 6 days                                                                        | 140/90                 |                | Headache, vision loss                                                    | Normal vision within 24 h                                                |
| Ibrahim et al. (39)         | Horned viper bite (Cerastes cerastes) | F/23 Ø | “Within a week”                                                               | 130/80                 |                | Stuporous, vision loss                                                   | Not available                                                            |
| Kaushik et al. (12)         | Indian krait bite (Bungarus caeruleus) | M/10 Ø | 15 days                                                                       | “HTN”                 |                | Visual loss, seizure                                                     | Persistence of vision loss 3 months later                                 |
| Marrone et al. (13)         | Scorpion sting (Tityus bahiensis) | M/13 Ø | 2 h                                                                            | 90/60                  |                | Vomiting, headache, visual disturbance, obtunulation, seizure            | Normal vision within 2 days                                             |
| Rebahi et al. (14)          | Scorpion sting (Androctonus mauretanicus) | F/3 Ø | 2 days                                                                         | 170/110, then cardiogenic shock |                | Vomiting, impaired consciousness, seizure                                | Asymptomatic at day 5                                                   |
| Loh et al. (40)             | Wasp stings complicated by AKI requiring HD | F/29 Ø | 1 month                                                                       | 190/104                |                | Loss of consciousness                                                   | Complete resolution at day 21                                             |
| Du et al. (48)              | Wasp stings       | F/66    | Not available                                                                  | 1 day                  | 135/85         | Headache, seizure                                                        | Not available                                                            |
| Chatterjee et al. (16)      | Licorice          | F/49 Ø | 4 months                                                                       | 230/130                |                | Headache, cortical blindness, hyperreflexia, seizure                     | Headache resolved at day 8                                               |
| Van Beers et al. (43)       | Licorice          | F/49 Ø | 2 weeks                                                                       | 219/100                |                | Headache, visual impairment                                              | Resolution of PRES, lobar hemorrhage after 3 months                     |
| Morgan et al. (44)          | Licorice          | F/65 Ø | 4 days after consumption                                                       | SBP > 220              |                | SBP > 220                                                                | Complete resolution at day 5                                              |

(Continued)
### Alcohol

In alcohol-induced PRES, three different situations have been described: chronic alcohol intoxication (29–32, 41), acute alcohol intoxication (22–25), and alcohol withdrawal (26–28). PRES in chronic alcohol abusers occurred in conjunction with other complications of alcoholism such as acute pancreatitis (26, 30, 41) and hepatic encephalopathy due to severe acute alcoholic hepatitis (32). PRES onset occurred at the same time as acute pancreatitis (26, 30) or 1 week later (41), whereas it occurred 3 weeks after acute alcoholic hepatitis onset (32). All but four patients were hypertensive. Patients were normotensive in acute alcoholic pancreatitis (26, 30) and acute alcoholic hepatitis (32). Headache was reported in only 17% of patients (2/12) (24, 32). In three patients, PRES was complicated by intracranial hemorrhage (30, 31) or brain infarction (28).

### Drug Overdose

Nine patients experienced PRES in a context of drug overdose, involving lithium (33, 34), dextroamphetamine (35), acetaminophen (51), ephedrine (49), phenylpropanolamine (36), digitoxin (37), and bismuth (15). The median time to PRES onset from the intoxication was 3 days, and two distinct situations were identified. PRES occurred during the acute phase of poisoning (35–37, 49) or at distance from intoxication (i.e., after stopping the causative drug) (15, 33, 34, 51). Three case reports indicated an association between lithium and PRES (33, 34). All these cases occurred after lithium discontinuation in patients with hypothyroidism, with chronic hypertension, and for whom intoxication was complicated by acute kidney injury (33, 34). Acute kidney injury occurred before the onset of neurological disturbances in five patients (56%) (15, 33, 34, 51). Angiography showed narrowing of the cerebral arteries in three cases (36, 37, 49). Infarction (49) and intraparenchymal hemorrhage (36) were also reported.

### Illicit Drug

We collected six reports of illicit drug–induced PRES, involving cocaine (18, 19), amphetamine (52), mephedrone (50), kratom (20), and lysergic acid amide (21). Acute high blood pressure was reported in all patients (18–21, 50, 52). Patients had several risk factors for PRES such as chronic hypertension (18, 19), chronic kidney disease (18, 19), alcohol abuse (21, 50), and HIV infection (18).

### Natural Toxin

In venom-induced PRES, snake bites [Cerastes cerastes (39), Bothrops asper (38), pit viper (42), Bungarus caeruleus (12)] were involved in four patients, scorpion stings in two patients [Tityus bahiensis (13), Androctonus mauretanicus (14)], and multiple wasp stings in two patients (40, 48). PRES was associated with mushroom (46) and licorice (16, 17, 43–45) in one and five patients, respectively. In 36% (5/14) of patients (12, 16, 17, 40, 43), the time from exposure start to PRES onset was more than 1 week. Patients required mechanical ventilation in 29% (4/14) of cases (14, 38, 46, 48); the duration of mechanical ventilation ranged from 2 (46) to 14 days (38). Acute kidney failure occurred in 36% (5/14) of patients (13, 40, 42, 44, 48), requiring resolution at day 24

| Substance/context | Time to onset | Blood pressure | Seizure | Comorbidities | Symptoms | Imaging | Outcomes | Follow-up |
|-------------------|--------------|----------------|---------|---------------|----------|---------|----------|-----------|
| Licorice F/56     | 210/80       | 144/102        | Headache, nausea, visual disturbance, seizure | Nonrefractive 1 month later | Combined and symmetrical patterns, positive DWI, no restricted ADC | Complete resolution at day 24 | Discharge at day 17 |
| Mushroom F/26     | 190/130      | 200/110        | Headache, visual disturbance, seizure | Complete resolution within 2 days | Combined and symmetrical patterns, positive DWI, no restricted ADC | Fully recovered within 2 days | Discharge at day 17 |
| Organophosphate M/32 | 12/100 | M/32 O | Headache, visual disturbance, seizure | Complete resolution within 2 days | Combined and symmetrical patterns, positive DWI, no restricted ADC | Complete resolution at day 24 | Discharge at day 17 |
hemodialysis in two cases (40, 42). Among the five patients with licorice-associated PRES, brain hemorrhage occurred in two patients (16, 43), one of which was associated with reversible cerebral vasoconstriction syndrome (16).

**Chemical Substance**

Phatake et al. (47) reported a patient complaining of headache and blurred vision 4 days after coma induced by consumption of organophosphorus compounds with suicidal intention. Brain MRI showed multifocal hyperintensities mainly in subcortical areas of parietal and occipital areas with increase ADC, suggesting PRES.

**DISCUSSION**

**Are Toxic PRES Different From Other Etiologies?**

As in other etiologies, poisoning-associated PRES are very polymorphic in terms of both exposure characteristics and patient comorbidities. Regardless of the substances involved, the median of 3 days for time to onset of PRES can dichotomize the presentation of this syndrome into two distinct situations. Indeed, PRES occurring after 3 days seems to be more related to a rebound effect of intoxication or to complications related to the management of the poisoning, whereas a shorter period would support a direct link between the causative agent and PRES.

**Clinical and Biological Findings**

Clinically, the prevalence of symptoms usually reported in PRES patients was consistent with the published literature (1). Indeed, acute high blood pressure, visual disturbance, and seizure were reported in 70, 55, and 50% of patients, respectively. Seizure is the most common symptom found in children (53), and all children had seizures (12–15). However, comorbidities such as chronic hypertension (17%, 7/42) and acute or chronic kidney failure (24%, 10/42) were less frequently reported than in patients with other PRES etiologies, where their estimated prevalence is about 50% (1). In the literature, the frequency of isolated CSF protein elevation without pleocytosis, as a biomarker of permeability disruption of the BBB, varies from 60% (54) to 75% (55). In this review, although few cases reported CSF analysis, only one case (1/10, 10%) (34) described elevated CSF protein.

**Radiological Features**

All reviewed patients presented cortical and/or subcortical T2/FLAIR hyperintensities or hypodensities on CT when MRI was not performed, which was consistent with the main findings of PRES (3, 4). These hyperintensities correspond to the brain edema caused by vascular dysregulation, leading to acute vasodilatation and classically vasogenic edema, with proven pathological/imaging correlation (56). While parieto-occipital involvement (12–14, 16–18, 20–34, 36–51) was predominant (39/42, 93%), as described in the literature (57), the isolated parieto-occipital was not the main pattern in this review, supplanted by the pattern combining various anatomical regions involved. Frontal (13, 17, 18, 20, 22, 24–26, 28, 31, 33, 38, 44, 46, 48, 49, 51), temporal lobe (18, 25, 26, 30, 32, 33, 47), and cerebellum (14, 15, 18–21, 30, 35, 41, 52) involvement occurred in 41% (17/42), 17% (7/42), and 24% of patients (10/42), respectively. In this review, the prevalence of frontal and temporal involvement is lower than previously described, where it can be seen in up to 75% of cases (3). Indeed, temporal involvement was rarely reported, even though MRI images seemed to show involvement in this region. This may partially explain the difference in prevalence, especially since the whole brain MRI was not available for neuroradiological analysis.

The atypical distribution involving the thalamus (18, 19, 21, 34), basal ganglia (18, 19, 46), midbrain (18, 19), and corpus callosum (39) was less commonly reported, as described in the literature. As with other PRES etiologies, atypical imaging appearances including hemorrhage, contrast enhancement, and restricted diffusion on MRI were reported in similar proportions (58). Intracranial hemorrhage occurred in 14% of cases included (6/42) (16, 20, 30, 31, 36, 43). Among these cases, minimal occipital intraparenchymal (20, 36), microbleeds in the cerebellum (30) and sylvian fissure (43), and subarachnoid hemorrhage (31) were reported. Regarding contrast enhancement (19, 20, 22, 23, 30, 31, 38, 52), only one case described gyriform enhancement (20). In this case of PRES induced by kratom, brain MRI showed multifocal areas of abnormal T2 FLAIR; restricted diffusion in the superior parietal lobes, both occipital lobes, and both cerebellar hemispheres; and minimal hemorrhage in the left superior parietal lobe consistent with atypical PRES (20). DWI positivity (20, 25, 26, 29, 30, 36, 37, 39, 47–49) due to advanced edema was higher (12/20, 60%) than previously described in other PRES etiologies. The occurrence of cytotoxic edema (19%, 4/21) was consistent with the literature (15–30%) (3). Areas of restricted diffusion can be reversible or, conversely, progress to frank infarction (58). For instance, Kinno et al. (49) reported a case of PRES with reversible cerebral vasocostriction syndrome due to ephedrine overdose. Initial brain MRI showed vasogenic edema in the left occipital and both parietal lobes with some hyperintense lesions on DWI with restricted diffusion on ADC maps, indicating the co-existence of cytotoxic edema. Follow-up MRI 1 month later showed residual partial hypertense areas in the superior parietal gyri bilaterally (49). Persistence of brain lesions on follow-up imaging (25, 49, 51) found in 12% of patients (3/25) is a proportion classically reported in various series of PRES.

Imaging analysis did not highlight a specific pattern for poisoning-associated PRES but reinforces the fact that PRES is neither only posterior nor always reversible.

**Are Toxic PRES Different According to the Causative Agents?**

**Similarities**

Neurological complications such as hemorrhage (16, 20, 30, 31, 36, 43), reversible cerebral vasocostriction syndrome (16, 49), and infarction (28, 49) occurred independently of toxic etiology, i.e., kratom (20), alcohol (28, 30, 31), drug overdose (36, 49), and licorice (16, 43).
Vasoconstriction and endothelial dysfunction

Most of the pharmacological and toxicological agents involved in this review are known to induce either or both vasoconstriction and endothelial dysfunction. High alcohol concentrations have been associated with dose-related vasoconstriction and impaired dilatation of cerebral vessels (22). In addition, chronic alcoholism and long-term lithium exposure increase reactive oxygen species and nitric oxide in brain endothelial cells. This oxidative stress can induce endothelial dysregulation, leading to the BBB breakdown (27, 34). Cocaine, amphetamines, lysergic acid amide, mephedrone, kratom, and phenylpropanolamine have sympathetic and/or serotonergic effects that cause vasoconstriction or vasculitis, leading to severe hypertension (36, 59).

In alcohol withdrawal, the hypothalamic–pituitary–adrenal system is stimulated, leading to increased levels of catecholamine and AVP, which can induce acute hypertension (27, 28). Similarly, the biologically active component of licorice, glycyrrhizic acid, inhibits 11 β-hydroxysteroid dehydrogenase, leading to hypervolemic hypertension (16). After snakebite envenomation and organophosphate severe poisoning, neurotoxins (14) and nicotinic stimulation (60), respectively, lead to autonomic dysregulation with massive release of catecholamines and angiotensin II. These effects, in combination with the presence of sympathetic denervated vasculature in the brain posterior area, may induce failure of the cerebral autoregulatory system (14). The increase in proinflammatory mediators, either exogenous, originating from the substance (e.g., venom itself), or endogenous (e.g., in acute alcoholic pancreatitis, induced by venom), can damage the BBB and is likely to cause the leakage of blood contents into the surrounding brain tissue (14, 30).

Cerebral hypoperfusion

In several reports, angiography showed multiple areas of narrowing of the intracranial arteries (16, 28, 36, 37, 49), especially in drug overdose (36, 37, 49) with sympathomimetic agents such as ephedrine (49) and phenylpropanolamine (36). Interestingly, in ephedrine overdose–induced PRES (49), although MRI revealed bilateral superior parietal lesions, single-photon emission computed tomography showed selective hypoperfusion in the left superior parietal region.

AVP axis hyperstimulation

A recent review highlighted that AVP overstimulation seems to be involved in PRES development and subsequent symptoms, in particular because of both its pathophysiologic mechanism in brain edema formation and its involvement in most PRES etiologies (5). AVP hypersecretion could be the trigger of PRES through a dysregulation of ionic/water transglial flux via astrocytic ion channel dysfunction and subsequent brain edema. In the periphery, AVP receptor stimulation could be responsible for symptoms usually reported in PRES such as hyponatremia, acute hypertension, and impaired renal function (5, 61). The use of cocaine, amphetamine (62), and lysergic acid diethylamide (63) and co-administration of alcohol with disulfiram (5) are known situations to stimulate AVP neurons. Thus, these agents could be directly responsible for the pharmacological cascade described above. In several cases, patients received multiple psychotropic drugs such as quetiapine (20, 33, 34), duloxetine (33), sertraline (33), amitriptyline (33), escitalopram (51), and valproate (51); it could be argued that these drugs, known to induce AVP release (64) and cerebrovascular effects, may serve as a contributing factor in the genesis of PRES.

In hepatic encephalopathy, in addition to dysregulation of cerebral blood flow and consequent cerebral vasodilation induced by hyperammonemia (32), ammonia reaching the astrocytes is detoxified in glutamine, and its overproduction promotes, through AVP stimulation, astrocytic swelling, resulting in brain edema (65). In contrast, acute alcohol intoxication (62) and licorice (66) inhibit AVP release, and lithium inhibits renal effects of AVP (5). In PRES associated with alcohol withdrawal (26–28), licorice (44), and lithium intoxication (33, 34), the onset of neurological symptoms ranged from 2 to 9 days after intoxication; this chronology of events may suggest a rebound phenomenon on the AVP axis (5).

Specific Characteristics

Visual hallucinations have only been reported in concomitant administration of disulfiram with alcohol (22) and in alcohol withdrawal (26, 27). Visual hallucinations may be a symptom of delirium tremens but also occur in patients with PRES (2). In natural toxin–and chemical substance–associated PRES, seizure was the most frequent symptom, accounting for 67% (10/15) of cases (12–14, 16, 17, 38, 45–48). Similarly, alertness disorders were at the forefront (92%, 11/12) in alcohol-associated PRES (22–32).

Multiple risk factors in substance abuse patients

In substance abuse–related PRES, patients had several risk factors for PRES such as chronic hypertension (18, 19), chronic kidney disease (18, 19), and HIV infection (18). In these cases, the different risk factors should act synergistically on the different pathophysiological pathways leading to PRES. For instance, cocaine has the ability to synergistically increase the pathologic processes induced by HIV infection (18) including endothelial dysfunction and disruption of the BBB integrity. Interestingly, single nucleotide polymorphisms in AVP gene and AVP V1a receptor have been associated with drug abuse disorders (67), suggesting a different probability of PRES occurrence in patients with substance abuse.

In patients with multiple risk factors of PRES or in the context of multiple drug intake (20), causality assessment is difficult. In addition, combined drug intoxication also exposes to a risk of drug cocktail effect. As with drug–drug interactions, illicit drug–drug interactions can occur both at the pharmacodynamic (i.e., interactions in which drugs influence each other's effects directly) and pharmacokinetic level (i.e., modification of drug absorption, distribution, metabolism, or excretion). In pharmacodynamic illicit drug–drug interactions, the neurotoxicity and/or endothelial toxicity of both the drug and illicit drug act synergistically, which can promote the occurrence of PRES. Legriel et al. (21) reported a case of lysergic acid amide–induced PRES in a depressed patient treated with clomipramine. The analysis of urinary catecholamines and
serotonin metabolites showed a massive sympathetic storm with high urinary serotonin levels, supporting the pharmacodynamic convergence of these two adrenergic and serotoninergic agents. Castillo et al. (20) reported a case of kratom-induced PRES in a patient on fluoxetine for depression with dextroamphetamine misuse. Kratom exerts α2-adrenoceptor agonistic effects and is known to induce high blood pressure, particularly when combined with other drugs (68). Mitragynine, the major indole-based alkaloid of kratom, is extensively metabolized by hepatic cytochrome P450 (CYP) isof orm 3A4 and 2D6 (69). Amphetamine metabolism primarily involves CYP2D6 (70). Fluoxetine and its main metabolite, norfluoxetine, are well-known inhibitors of CYP2D6 and CYP3A4, respectively (71). Taken together, a probable pharmacokinetic illicit drug–drug interaction occurred between mitragynine/dextroamphetamine and fluoxetine, causing overexposure in mitragynine and dextroamphetamine. This case of kratom/amphetamine interaction shares the pharmacological characteristics of PRES induced by clonidine, another α2-adrenoceptor agonist, and dextroamphetamine overdose described by Minhaj et al. (35).

Coagulopathy
Characteristics of PRES associated with snake bite included normal blood pressure (38, 39, 42), coagulopathy (12, 38, 39), and respiratory failure (12, 38). The mechanism of PRES associated with snake venom does not appear to be related to direct toxic effects of the venom within the central nervous system, because venom proteins do not cross the BBB. Instead, neurological manifestations are most often related to blockage of the neuromuscular transmission, causing paralysis, and abnormalities in the coagulation cascade, producing cerebrovascular events (38).

A Lack of Standardization in Reported Data on Poisoning-Induced PRES
The assessment of the methodological quality of the cases showed that the data reported are very heterogeneous, with a median overall score of 5/10 (IQR 3–6). In addition, none of the case reports met the domain selection criteria (Supplementary Table 1). An unclear selection approach leaves the reader with uncertainty as to whether this is the whole experience of the researchers or only the most serious case, and suggests possible selection bias. As the scientific literature on PRES is almost exclusively represented by case series and case reports, we propose a checklist with various items that should at least be reported in case reports of substance-induced PRES (Supplementary Table 4). Indeed, it seems essential to standardize the reporting of outcome so that studies collecting a large amount of data can be conducted.

CONCLUSIONS
PRES in a context of poisoning does not exhibit a specific imaging pattern. The predominance of various anatomical implications outside the parieto-occipital lobes in PRES, including toxic etiologies, is a key message for clinicians and radiologists. The prevalence of the neurological symptoms was also consistent with the published literature on other etiologies of PRES. In addition to toxic exposure, one-third of patients had at least one other risk factor of PRES. Chronic hypertension (17%) was less frequent than reported in other causes of PRES.

As in iatrogenic PRES, toxicology cases do not always have a temporally close relationship. PRES occurring after 3 days seems to be more related to a rebound effect of poisoning, to secondary brain damage, or to complications related to the management of the poisoning, whereas a shorter period would support a direct link between the causative agent and PRES. Poisoned patients may have a lower threshold for developing PRES. It may also be caused by the convergence of various pathophysiological processes (e.g., high blood pressure, endothelial dysfunction, AVP axis overstimulation) induced directly by the poison and/or indirectly by acting in concert with other factors such as drug–drug interaction or hypomagnesemia that ultimately causes the cerebrovascular cascade leading to PRES.

Although less described, PRES in a context of poisoning, which shares most of the clinical and radiological characteristics of other etiologies, is not to be ignored. The characterization of the pathophysiological mechanisms is essential to individualize management according to the presence of risk factors and/or specific features of PRES. Standardization of data reported in future case series of substance-induced PRES is required in order to better characterize and thus manage this syndrome.

DATA AVAILABILITY STATEMENT
Publicly available datasets were analyzed.

AUTHOR CONTRIBUTIONS
BL, CS, and SE conceived the idea. BL wrote the manuscript and performed the selection and summary of published literature on PRES in clinical toxicology. DB, CV-V, CS, and SE helped to design, write, and revise the paper. CC contributed in improving the article, notably enriching the analysis of neuroimaging data.

SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01420/full#supplementary-material

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59. Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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