

Neurotoxicity and PRES after severe citalopram intoxication in a 12-months-old baby

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Abstract

Citalopram intoxications can lead to Serotonin Syndrome (SS) development, characterized by altered mental status, seizures,

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autonomic instability, hyperthermia and extrapyramidal signs. We review the literature about pediatric acute citalopram intoxications, and we report a case of severe SS in an infant associated to Posterior Reversible Encephalopathy Syndrome (PRES) treated with cyproheptadine as an antidote. An adequate 12-month-old girl displayed a sudden global neurological regression with hypotonia, prolonged occipital seizures, right hemiparesis and a progressive wakefulness reduction associated with blindness. Plasmatic concentration of citalopram was equal to 3225 ng/mL (50-110 ng/mL). MRI revealed a transient bilateral caudate and putamen hyperintensity, associated to an occipital cortical and subcortical hyperintensity. She was treated with IV cyproheptadine with progressive benefit in few days. Only 4 children with citalopram intoxication are previously described with neurological involvement. Pediatric citalopram intoxication could cause SS leading to PRES, and cyproheptadine could be used with benefit.

Introduction

Citalopram is a Selective Serotonin Reuptake Inhibitors (SSRIs) used in adults to treat major depressive disorder, obsessive compulsive disorders, panic disorder, anxiety disorders, post-traumatic stress disorder.¹ The daily therapeutic dose of citalopram is 20-60 mg/day and it is used as off-label in pediatric patients.² The most common side effects include tiredness, confusion, dizziness, stomach pain, sweating, nausea, sinus tachycardia and tremor,³ but it can also cause Serotonin Syndrome (SS) characterized by altered mental status, anxiety, confusion, agitation, hallucinations, coma, seizures, autonomic instability and extrapyramidal signs. Among SSRIs, citalopram has a high rate of seizures in overdose and cardiac toxicity, most of all in doses higher than 400mg/day.^{4,5} Posterior Reversible Encephalopathy Syndrome (PRES) is described in adult patients with SSRI accidental ingestions.⁶⁻⁹ When SS occurs in adults, cyproheptadine is used as an antidote (12-32 mg/day).¹⁰ Within this context, we review the literature on pediatric citalopram intoxication and we describe the first case of pediatric SS with PRES after accidental ingestion of an unspecified dose of this drug treated with cyproheptadine.

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 2021, used in conjunction with the Explanation and Elaboration document and the PRISMA-S extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews.^{11,12} We performed a search using MEDLINE via the PubMed interface for original studies (Figure 1). References were identified from PubMed searches from 1990 to 2023. We combined

the terms “Citalopram” and “Intoxication” or “Ingestion” and/or “Pediatric”. Moreover, the reference lists of eligible articles were screened to identify any further relevant articles. We manually selected articles related to paediatric patients (≤ 18 years old). We excluded articles without patient clinical descriptions and/or with multiple intoxications. Finally, we limited our search to original studies published in the English and French languages.

Case Report

Here we describe a 12 months female child (10 Kg), with adequate psychomotor development, born from blood relatives parents (cousins) originating from Africa, with an uneventful birth. The baby was brought to our attention at the age of 12 months in the Emergency Department (ED) because of a first seizure without fever. The mother referred at home an episode lasting 4-5 minutes, characterized by ocular revulsion and four arms tonic-clonic movements with spontaneous resolution.

At the ED, the baby was afebrile and she presented a second similar paroxysmal episode. She was submitted to complete blood chemistry tests (blood gas analysis, electrolyte, carboxyhemoglobin dosage, ethanol and substance abuse), which resulted negative. Cardiological evaluation did not reveal any involvement: heart rate and pressure remained regular for the entire hospitalization. In that context, the mother appeared globally numb to clinicians. She referred to a personal recent history of psychogenic non-epileptic seizures, treated with Citalopram and Delorazepam (the child was not breastfed). Child hospitalization was required and she was submitted to sleep-awake EEG: negative (Figure 2A). The brain MRI was normal (Figure 3A). During the second hospitalization day, she displayed fever and three paroxysmal episodes with desaturation, loss of consciousness, leg hypertonia, and clonic movements of the left arm, treated with Midazolam IV and

Levetiracetam IV bolus with partial seizures control (Figure 2B). In the following days, the baby still displayed frequent occipital focal seizures (Figure 2C) and she started to display a global neurological regression, with hypotonia, less of head and trunk control, right hemiparesis and a progressive wakefulness reduction associated to visual impairment and progressive blindness. Phenobarbital infusion was started with seizures resolution, associated with ceftriaxone, acyclovir and dexamethasone in order to treat a possible infectious pathogenesis.

Lumbar puncture with immunological screening, link index and cultural exams was negative. Metabolic discharges (plasmatic amino acid, plasmatic acylcarnitines, urinary organic acid) were excluded. Epilepsy gene panels, and mitochondrial gene panels (Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-Like Episodes (MELAS), Maternally Inherited Diabetes mellitus and Deafness (MIDD)) were negative.

In the following days the baby presented an ulterior global worsening with persistent seizures, hypotonia, inconsolable crying and irritability. EEG displayed concomitant left occipital epileptic discharges (Figure 2D). Due to the progressive clinical deterioration, the baby was conducted to the intensive care unit where she remained persistently lethargic but autonomously breathing.

In the meanwhile, the mother was found persistently drowsy. Suspecting a voluntary child intoxication, it was hence required a baby plasmatic dosage of citalopram on the blood sample executed in the ED with confirmation of plasmatic concentration equal to 3225 ng/mL (therapeutic interval 50-110 ng/mL), 125 ng/mL after 4 days, 25ng/mL at day 8. We estimated an oral assumption equal to 450 mg (45 mg/kg). The baby was immediately separated from the mother, according to judicial authority indications. After these results (5th hospitalization day), we started therapy with cyproheptadine 6 mg/day (0,6 mg/kg/day) per nasogastric tube with progressive seizures resolution and consequent dosage reduction in 5 days. The baby displayed a progressive global improvement with

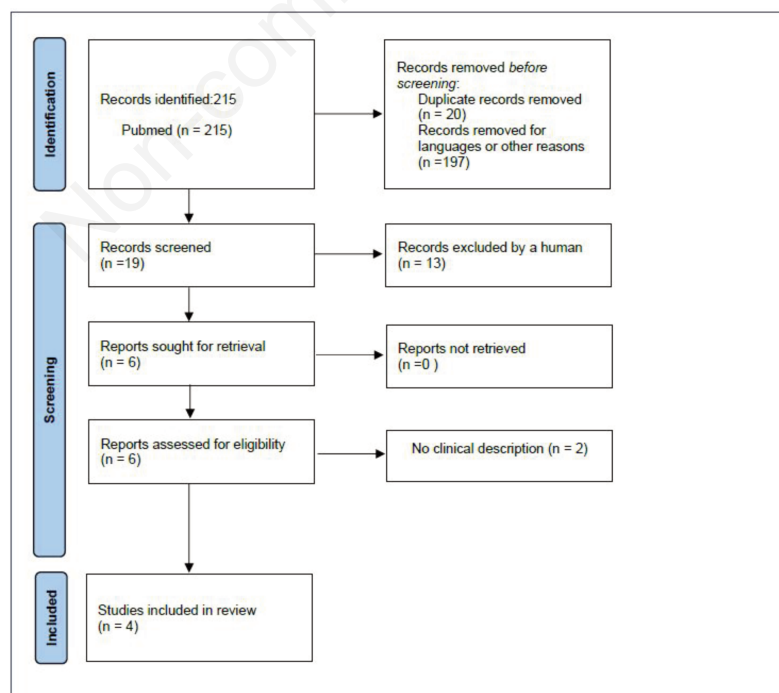


Figure 1. PRISMA 2020 flow diagram of study selection about citalopram intoxications in pediatric patients (0-18 y).

reduction of somnolence, staying seated alone capability recovery and right hemiparesis resolution. The ERG was negative. Visual evoked potentials and electroretinogram displayed a bilateral adequate latency, while a reduced amplitude was observed in the left eye. We opted for a slow reduction of the therapy because, after a rapid reduction attempt, she presented a new seizure (Figure 2F). Repeated EEGs displayed a progressive improvement (Figure 2G-H). Visual impairment and oculo-manual coordination had a slower but still partial resolution. A second brain MRI was executed after 18 days hospitalization (Figure 3B) revealing bilateral caudate and putamen hyperintensity, associated to an occipital cortical and subcortical hyperintensity, with PRES features. The baby was hence transferred to a pediatric rehabilitation center, where she showed a progressive clinical resolution with oculo-manual coordination skills recovery. Despite this, PEV FLASH highlights bilateral severe abnormalities of visual conduction. An MRI control after 2 months displayed a global hyperintensities reduction of both basal ganglia, and bilateral subcortical parieto-occipital white matter. A moderate cortical-subcortical thinning of the bilateral parieto-occipital regions was revealed with consequent ex-vacuo ventricular enlargement (Figure 3C).

Discussion

We reported the first pediatric case of PRES due to severe citalopram intoxication, treated with cyproheptadine. We

reviewed the previous pediatric literature and only 4 papers about 3 infants and an adolescent were clinically described (Table 1):¹³⁻¹⁶ two infants presenting seizures, requiring anti-seizures therapy and with ocular involvement: nystagmus, mydriasis and absence of visual tracking. No precise information about posology assumed was available and none of them displayed brain imaging involvement and/or had permanent sequelae. Analyzing literature, these pediatric patients presented acute reversible symptoms, not requiring Cyproheptadine.

On the contrary, in our patient, seizures occurred suddenly in our patient, and within a few days, she showed a progressive neurological impairment and a neuroradiological worsening, requiring antidote treatment with cyproheptadine.⁴ Her brain MRI displayed both a vasogenic and cytotoxic edema damage at the posterior cortical regions with consequent parieto-occipital neuronal loss and the transient involvement at the level of the basal ganglia, compatible with transient toxic damage due to overstimulation of serotonergic receptors.⁶⁻⁸ This edemigenous involvement typical of PRES had a sure causative role both in seizures, visual impairment occurrence and progressive neurological decay. We could only hypothesize that the progressive occurrence of symptoms could be due to variable protein binding, floating volume of distribution and rates of hepatic metabolism and excretion of drugs, typical of infants, that could alter citalopram pharmacodynamics and clinical evolution.¹³⁻¹⁷

In literature, no evidence of cyproheptadine use as antidote in case of pediatric intoxications and few evidences are available

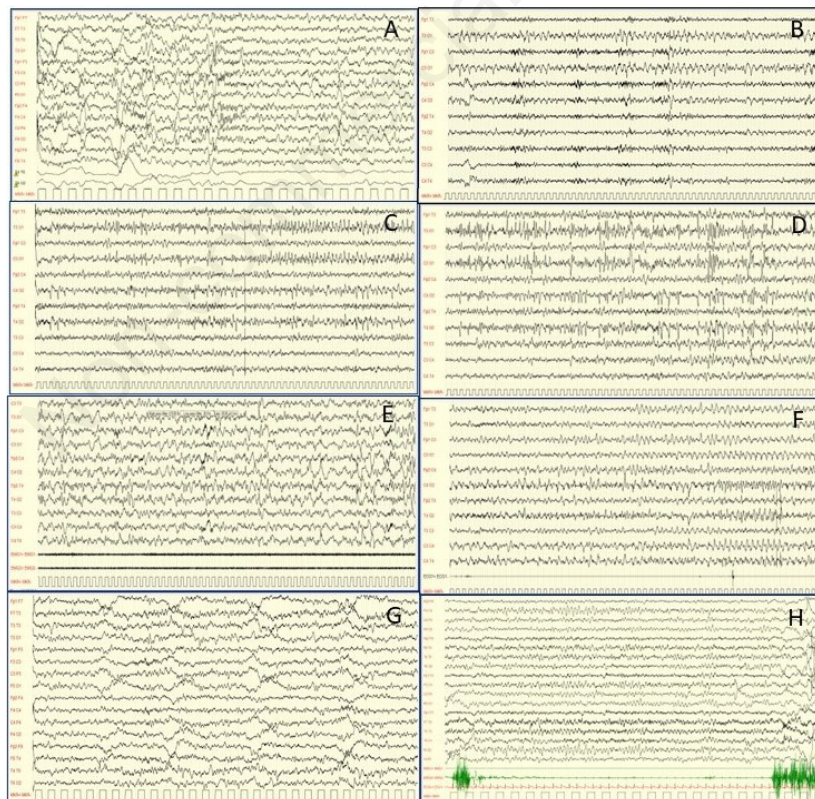


Figure 2. EEG evolution after acute citalopram intoxication. **A)** Sleep EEG; regular EEG without paroxysmal discharges observed. Artifacts on right temporal regions (admission); **B)** Left rhythmic theta activity on the left TO regions during sleep (2nd day hospitalization); **C)** Left Temporo-Occipital seizure (4th day Hospitalization); **D)** Secondary bilateralization of the left TO seizure (4th day Hospitalization); **E)** Sleep EEG after 2 hours of Cyproheptadine iv infusion (5th day Hospitalization); **F)** Right Temporo-occipital seizure after Cyproheptadine iv infusion dosage reduction (6th day Hospitalization); **G)** Sleep EEG without paroxysmal discharges (22nd day Hospitalization); **H)** awake EEG with persistent right slow occipital activity without paroxysmal discharges (60th day Hospitalization).

about anti-seizures therapy in SS. Cyproheptadine is an histamine-1 receptor antagonist, available only in oral form and it has increasing evidences as antidotal therapy in SS. As side effects it could cause hypotension (not observed in our patient) and sedation, that could have a secondary positive effect in seizures control: we observe a focal seizures resurgence during a rapid cyproheptadine reduction attempt. Antiseizures drugs such as valproic acid, lamotrigine, gabapentin, pregabalin, topiramate and carba-

mazepine, phenytoin and oxcarbazepine could have serotonergic properties and should be avoided in case of SS.¹⁸

In conclusion, pediatric citalopram intoxication could represent a severe neurological pediatric emergency with PRES features. Cyproheptadine could be a safe and effective antidote to minimize the side effects of citalopram intoxication. Further studies are required to understand the pharmacokinetics of this drug and the pathophysiology of this cortical and subcortical involvement.

Table 1. Literature review of pediatric patients with citalopram intoxication.

Paper	Pt N	Age	Sex	Dosage	Plasma dosage	SYMPTOMS		Imaging	Therapy	Outcome
						Neurological	Cardiological			
Masullo, 2006 ¹³	1	10 m	F	NA	1400 ng/ml (1 h), 583 ng/mL (6 h), 416 ng/mL (13 h), 296 ng/mL (23 h),	Horizontal nystagmus, 3 TC seizures	-	NA	MDZ + PHT + PB + 10 g AC (NG tube) + OTI + MDZ	NS
Janson, 2020 ¹	1	1 m	M	20 mg (6 mg/kg)	77 µg/L (2 h)- 23 µg/L (50 h)	Jitteriness, opisthotonos	↑SBP (110/38 mmHg)	CUS: normal	AC, sodium sulfate	↑muscle tone, GER (for w)
Weigl, 2020 ¹	1	14 y	F	800 mg (10.4 mg/kg)	633 ng/mL	Dizziness, drowsiness	NA	NA	AC	NS
Borkar, 2022 ¹	1	7 w	M	NA	NA	Seizures: intense cry, extension of both arms, clenching of the fists, facial redness, eye deviation to the left, nystagmus, mydriasis, absence of visual tracking. Neck, arms and legs hypertonic flexion	Intermittent tachycardia, hypertension	normal	MDZ (0.1 mg/kg)	At 2 year FU: mild speech delay

Legend: AC, activated charcoal, CUS, cranial ultrasound, FU, follow-up, GER, gastro-esophageal reflux, MDZ, midazolam, NA, non available, N, number, NS, no sequelae, OTI, orotracheal intubation, PB, phenobarbital, PHT, fosphenytoin, PT, patients; SBP, systolic blood pressure, TC, tonic-clonic.

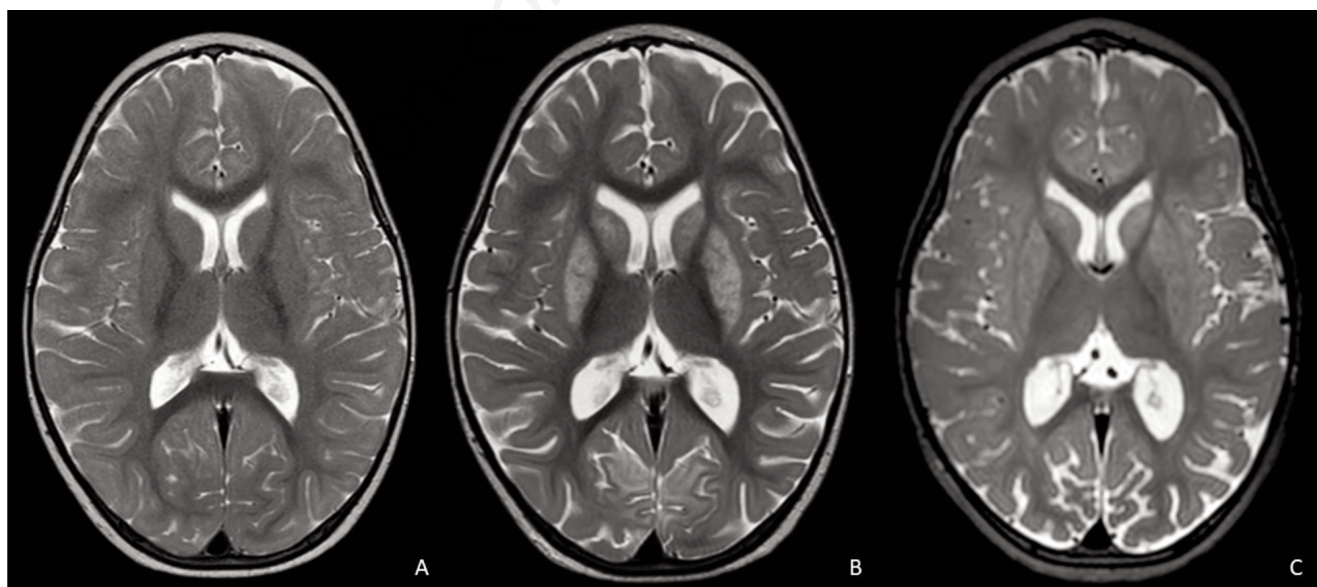


Figure 3. Brain MRI evolution after citalopram intoxication. **A)** normal second day brain MRI; **B)** bilateral caudate and putamen hyperintensity, associated to an occipital cortical and subcortical hyperintensity, similar to PRES at 18th day hospitalization; **C)** basal ganglia, and bilateral subcortical parieto-occipital white matter hyperintensities reduction without volumetric modifications. Moderate cortical-subcortical thinning of the parieto-occipital regions with ex-vacuo ventricular enlargement.

References

1. Javad Alaghband-Rad MH. A randomized controlled clinical trial of citalopram versus fluoxetine in children and adolescents with obsessive-compulsive disorder (OCD). *Eur Child Adolesc Psychiatry* 2009;183:131–5.
2. Cipriani A, Zhou X, Del Giovane C, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet* 2016;388:881–90.
3. Bezchlibnyk-Butler K, Aleksic I, Kennedy SH. Citalopram - A review of pharmacological and clinical effects. *J Psychiatry Neurosci* 2000;25:241–54.
4. Personne M, Sjöberg G, Persson H. Citalopram overdose - Review of cases treated in Swedish hospitals. *J Toxicol - Clin Toxicol* 1997;35:237–40.
5. Klein-Schwartz W, Benson BE, Lee SC, Litovitz T. Comparison of citalopram and other selective serotonin reuptake inhibitor ingestions in children. *Clin Toxicol* 2012;50:418–23.
6. Ducros A, Boukobza M, Porcher R, et al. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. *Brain* 2007;130:3091–101.
7. Prakash S, Rathore C, Kaushikkumar R. Posterior reversible encephalopathy syndrome in a patient with serotonin syndrome. *BMJ Case Rep* 2020;13:e236450.
8. Bhutada AS, Kodankandath TV. Delayed presentation of posterior reversible encephalopathy syndrome in the setting of serotonin-norepinephrine reuptake inhibitors. *Cureus* 2022;14:e22454.
9. Malik MT, Majeed MF, Zand R. Serotonin syndrome presenting as a posterior reversible encephalopathy syndrome. *Case Rep Neurol* 2020;12:63–8.
10. Tormoehlen LM, Rusyniak DE. Neuroleptic malignant syndrome and serotonin syndrome. 1st ed. Vol. 157, *Handbook of Clinical Neurology*. Elsevier B.V.; 2018. 663–675 p.
11. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
12. Rethlefsen ML, Kirtley S, Waffenschmidt S, et al. PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. *Syst Rev* 2021;10:39.
13. Masullo L, Miller M, Baker SD, et al. Clinical course and toxicokinetic data following isolated citalopram overdose in an infant. *Clin Toxicol* 2006;44:165–8.
14. Janson JA, Wasylewicz ATM, Eijkemans M, et al. Citalopram intoxication in four week old infant. *BMC Pediatr* 2020;20:1–5.
15. Weigl J, Vloet T, Egberts K, et al. Non-fatal intoxication with a high dose of citalopram in a suicidal 14-year-old girl. *Z Kinder Jugendpsychiatr Psychother* 2019;47:168–70.
16. Borkar D, Kiragub A W, Arensc A, Montaguec A J. A 7-week-old infant with serotonin syndrome. *North American Congress of Clinical Toxicology (NACCT) 2022*. *Clin Toxicol* 2022;60:1–162.
17. Schult RF, Morris AJ, Picard L, et al. Citalopram overdose and severe serotonin syndrome in an intermediate metabolizing patient. *Am J Emerg Med* 2019;37:1993.e5-1993.e6.
18. Prakash S, Rathore C, Rana K, Patel H. Antiepileptic drugs and serotonin syndrome - A systematic review of case series and case reports. *Seizure* 2021;91:117–31.