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Case report

Fatal self administration of tramadol and propofol: A case report

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ABSTRACT

We describe a case of unintentional intoxication due to tramadol and propofol self administration, occurred in a middle aged man, healthcare provider, deceased despite advanced medical assistance an hour later the onset of severe and increasing dyspnea. Toxicological analysis performed with gas chromatography-mass spectrometry in blood sample, evidenced a lethal tramadol concentration and therapeutic level of Propofol. Quantitative determination was also performed in other specimens such as bile, tissues (liver, spleen, kidney) and pubic hair, to assess chronic exposure. Toxicological results and autopsy findings, supported by clinical and hematochemical data, suggested a myocardial damage, associated with respiratory failure.

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1. Introduction

We report the decease of a health care professional, due to a double intoxication. We performed toxicological analysis on different autoptic samples showing the presence of Propofol and Tramadol. This match is seldom described in the international literature examined.

Propofol is an intravenous anesthetic agent, few data on its toxic and lethal ranges are reported. In scientific papers concentrations associated with death were within or below the therapeutic interval. Tramadol is a synthetic opioid commonly used in acute and chronic pain. Severe side effects and toxicity are widely described in literature.

In this work we describe the autoptical findings and toxicological investigation performed on several biological samples, including nontraditional specimens such as pubic hair.

1.1. Propofol

Propofol (2,6-diisopropylphenol, Diprivan®) (Fig. 1) is an intravenous anesthetic also administered to treat tension headache, status epilepticus and refractory migraine.

It is a water-insoluble emulsion containing egg lecithin, soybean oil and glycerol, characterized by its unique milk-like color. Some formulations contain preservatives as EDTA (edetate disodium) or sodium metabisulfite, to prevent bacterial or mycotic growth that could lead to sepsis and postoperative infections.[1]

After injection, blood concentration rapidly declines, due to distribution of the drug in high perfused tissue (initial $t½$ 7–8 min, redistribution $t½$ 30–70 min, elimination $t½$ up 23 h).[1] Steady state volume of distribution range is 171–349 L, elimination is 209–1008 L, and it's >95% plasma-protein bound.[2]

It is mainly metabolized in liver to inactive catabolites, by two pathways: direct glucuronide conjugation or p-hydroxylation with subsequent glucuronidation (or sulphatation). These are excreted in urine, therefore only small amounts of propofol could be found unchanged in urine.[1] Propofol enhances the

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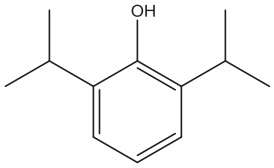

Fig. 1. Structural formula of propofol.

GABA A receptor activity, and inhibits the NMDA glutamate receptor.

The majority of abusers are medical providers, due to an easiest access to propofol.

Bell et al. inquired its incidence of abuse on 167 healthcare professionals, revealing that propofol was the fourth most frequently abused drug.[3]

Addiction could be generated by pleasant experiences reported in case of assumption, such as euphoria, disinhibition, illusion and relaxing.[4] Psychological dependence is supported by evidence of strong craving, frequent relapse, and continue use despite adverse effects.[4,5]

In propofol administration, several negative outcomes are described, such as: hypotension, apnea, airways obstruction, lung edema, oxygen desaturation and pancreatitis; the rate of these side effects is increased in case of intoxication. The main adverse reaction described in literature is Propofol- Related Infusion Syndrome (PRIS), reported for the first time in 1992, in pediatric patients hospitalized in intensive care unit, who developed metabolic acidosis, bradyarrhythmias and progressive myocardial failure after receiving prolonged propofol infusion.[6] Roberts et al. evaluated that PRIS's incidence in a heterogenous population of critically ill adults after administration of propofol for more than 24 h slightly exceeds 1%.[7]

1.2. Tramadol

Tramadol (Fig. 2) is a centrally acting analgesic for moderate to severe pain and it is not currently scheduled as a controlled substance.

Tramadol can be administered orally, subcutaneously, intravenously or rectally. It is almost completely absorbed after oral administration: therapeutic dose is 50 mg orally, 50–100 mg by injection, and 100 mg rectally. Total daily amount should not exceed 400 mg.[8]

In adults daily quantity higher than 500 mg may cause agitation, hypertension, tachycardia and seizures. Overdose of 800 mg may lead to coma, respiratory depression, and fatal hepatic failure.[9]

Therapeutic blood concentration ranges between 0.1 and 1 mg/L, toxic level from 1 mg/L, and lethal concentration is usually considered to be higher than 2.0 mg/L.[10] Tramadol is extensively metabolized in liver by phase I (mainly O- and N–demethylation) and phase II reactions (mainly conjugation of O- and N-demethylated compounds).

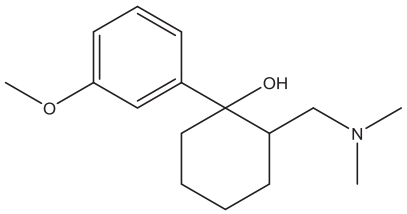

Fig. 2. Structural formula of tramadol.

O-monodesmethyltramadol (ODT) is an active metabolite with greater analgesic activity than the parent drug.[2]

Tramadol is eliminated in urine (90%) and feces (10%): about 29% of an oral dose is excreted unchanged, 71% as metabolite.[9]

Tramadol links with moderate affinity to μ opioid receptor, and weaker for the delta and kappa receptors. It also acts as serotonin and noradrenaline reuptake inhibitor.

The most common side effects reported in literature are nausea, vomiting, hypertension, tachycardia, central nervous system depression, respiratory depression, agitation, and seizures. Furthermore electrocardiographic changes are described, including QRS prolongation, not specific ST segment alterations, T-wave changes, first-degree atrioventricular block, atrial fibrillation, prolonged corrected QT intervals, and ventricular dysrhythmias.[11]

2. Case report

2.1. Anamnestic data

A middle aged health care professional was admitted to the emergency room with increasing dyspnea and cyanosis. On arrival, respiratory rate was 25/min, ECG showed atrial fibrillation (heart rate 100–110 bpm), blood pressure was 100/60 mmHg. Analysis performed on arterial blood revealed extreme acidosis. Troponin T (0.15 μg/L) and myoglobin (81 ng/mL) elevation suggested cardiac damage. Physicians administered sodium bicarbonate, epinephrine and atropine.

Despite advanced life support, patient deceased an hour later. Empty vials of drugs, needles and syringes for intravenous infusion were found in his bag. The decedent denied any history of addiction or drug abuse. Suicide notes were not found, neither previous suicides attempts or psychiatric treatment in the anamnestic data.

2.2. Autopsy results

Autopsy was performed in our Department. The deceased was an Italian male, 186 cm in height and 75 kg in weight. External examination revealed needle puncture marks on neck, forearms and lower limbs.

The internal examination showed the presence of lung edema whit a small distal vessels pulmonary thrombosis. A small liver congestion was observed. There was no preexisting disease causing the death. Samples were collected for toxicological analysis. No urine was found in the bladder.

3. Toxicological analysis

3.1. Samples

Heart blood (20 ml), bile (4 ml), as well as liver, kidney and spleen tissues (10–12 g each) were collected during autopsy and stored at −20 °C. In addition 80 mg of pubic hair were taken.

3.2. Chemical and reagents

Reference standards for tramadol and propofol were purchased from Cerilliant® (Round Rock, TX). Ethyl-acetate from Carlo Erba® (Milan, Italy) - β-glucuronidase type *Helix pomatia* HP-2 from Sigma–Aldrich® (Milan-Italy) - BSTFA and TMCS were purchased from Sigma–Aldrich® (Milan-Italy). Ultrapure distilled and deionized water was homemade (Millipore® Helix 70).

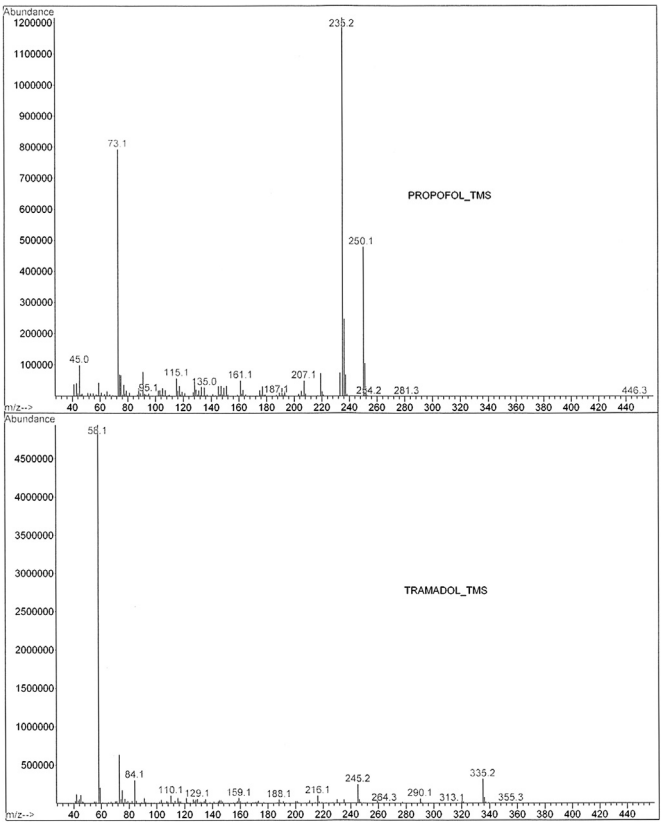

Fig. 3. Electron ionization mass spectra of propofol TMS and tramadol TMS.

3.3. Instrumentation and conditions

GC analysis was carried out on a gas chromatography instrument AgHP 7028A GC coupled with an Agilent MSD 5975. The capillary column used was an HP-5MS (17 m × 0.25 mm I.D coated with a 0.25 μm film). The GC conditions were as follows: the column temperature was programmed from 80 °C to 290 °C with an increase of 15 °C/min; the injection port and the transfer line temperature was 280 °C; helium was used as carrier gas with flow rate of 1 ml/min; the split injection mode had a ratio of 15:1. The mass analyzer operated by electron impact (−70 eV) in selected ion monitoring mode (SIM). Quantitative analysis was carried out recording ions *m/z* 207–235(249)–250(267) for propofol and *m/z* 58–245(249)–335(339) for tramadol (Fig. 3). The underlined ions were used for quantitative analysis.

Standard calibration curves were obtained by fortification of bovine blood (4 levels) with appropriate pure standards in range of concentration from 100 to 2000 ng/ml.

The r2 values of the calibration curves were over than 0.999 (Fig. 4).

The limit of detection (LOD) was 50 ng/ml for propofol and 30 ng/ml for tramadol with a signal-to- noise (S/N) ratio of 3 but the method was not optimized to obtain the lowest LOD, because the concentration values in biological samples analyzed were above 500 ng/ml.

3.4. Extraction procedure

Blood and bile were extracted according to the following procedures: to 1 ml of each sample was added 1 ml of deionized water, 400 ng of propofol d17 and 800 ng of tramadol C13-d3 as internal

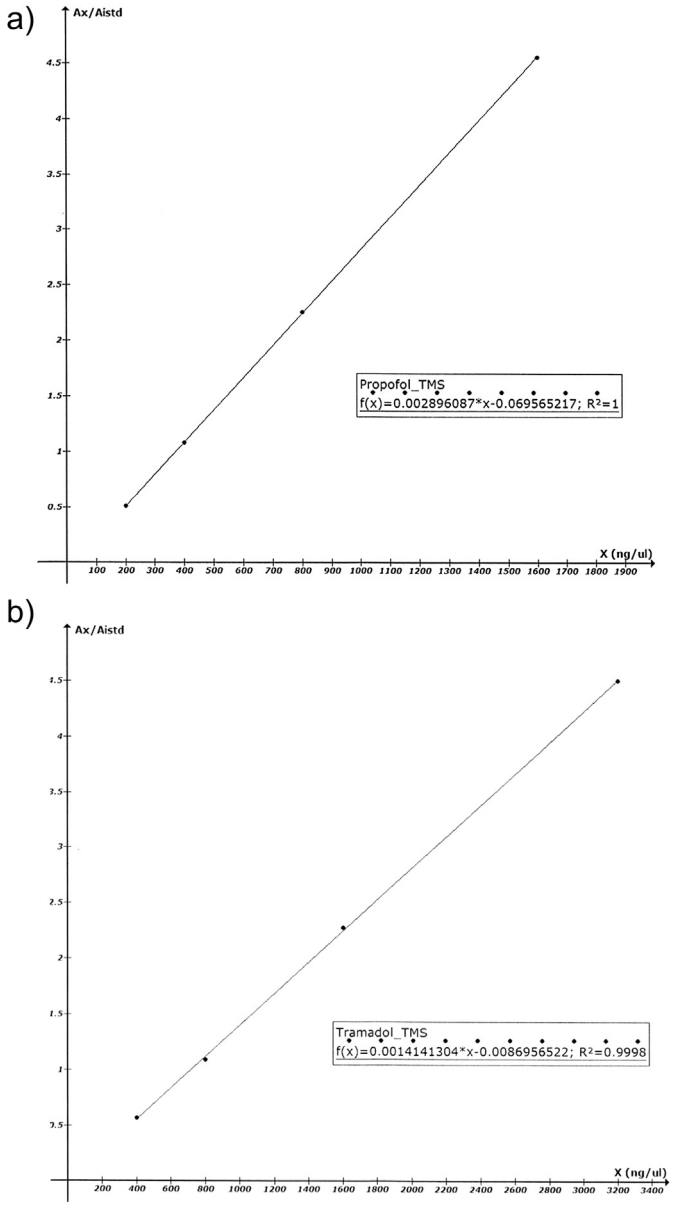

Fig. 4. a) Calibration curve of propofol TMS. b) Calibration curve of tramadol TMS.

standards. Bile sample was incubated with 50 μl of β-glucuronidase (Type HP-2 from *Helix Pomatia*®) adding 50 μl of acetate buffer (pH 5 1 M) for 3 h at 55 °C; after deconjugation it was cooled at room temperature.

Both bile and blood sample were extracted at pH 8–8.5[12] adding 50 mg of solid HCO_3^-/CO3 buffer and 4 ml of ethyl acetate, for 20 min on a rotating plate stirrer.

After centrifugation (at 4000 rpm for 3 min) the organic layer was evaporated to dryness under a gentle stream of nitrogen. The residue was derivatized with 50 μl of BSTFA+1% TMCS for 30 min at 70 °C. Liver, kidney and spleen tissues (3 g) were homogenized with 15 ml of deionized water using a blender (Waring® rotary blades) and sonicated for 15 min in a water bath. Aliquots (1–3 ml) of homogenized samples were deconjugated and processed as reported above.

Acid hydrolysis performed with 50 μl − HCl 6 N at 55 °C for 3 h was not suitable for tramadol quantification as we assessed a loss of

Table 1
Toxicological findings.

Samples	Propofol-TMS	Tramadol-TMS
Heart blood (μg/ml)	0.20	5.3
Bile (μg/ml)	0.71	15
Kidney (μg/g)	2.3	7.5
Liver (μg/g)	15.6	8.3
Spleen (μg/g)	0.74	7
Pubic hair (ng/mg)	0.42	608

substance. Bile and tissues were therefore processed using enzymatic hydrolysis that allowed both propofol (partially conjugated) and tramadol (present in an unconjugated form) extraction.

The pubic hair sample was washed twice in dichloromethane for few minutes to remove external contaminations. The sample was then dried at 40 °C and finely cut with scissors: 80 mg were spiked with 400 ng of propofol d17 and 800 ng of tramadol C13-d3 as internal standards and incubated in 2 ml of methanol for 12 h at 40 °C. After cooling, the hair sample was filtered and the methanolic phase was taken to dryness and extracted as reported above.

4. Discussion and results

The toxicological findings, are represented in the table below (Table 1).

The amounts of tramadol and propofol in all specimens suggested sequestration in kidney, liver and spleen according to the volume of distribution. Concentrations detected in liver and pubic hair in addition with anamnestic and circumstantial data, such as the finding of multiple needles and syringes, endorse the hypothesis of a chronic assumption. The absence of suicidal notes and the patient's attempt to alert the rescues didn't suggest suicidal intent.

Blood propofol concentration was 0.20 μg/ml (Fig. 5): this result is in accordance with other propofol-related deaths reported in literature,[1,13] in which decease resulted from respiratory failure in the absence of medical assistance after self administration of therapeutic dose.

In the case we describe, the patient was conscious and alert at the hospital admission and deceased an hour later, despite receiving ventilatory support with ventimask and endotracheal intubation. For this reason we can't really attribute the decease to a propofol intoxication even recognizing that it may have contributed in determining respiratory failure.

Tramadol concentration found in our blood sample was: 5.3 μg/ml (Fig. 5) a value higher than lethal range reported in literature.[10] Furthermore qualitative analysis performed in blood, bile and tissues highlighted the presence of O-desmethyl tramadol (ODT), tramadol's main metabolite (Fig. 6). Previous studies evidenced that repeated tramadol injections, as in case of chronic assumption, may increase its potential toxicity, by retention of catabolites, mainly ODT, which has greater affinity for μ-opioid receptor than the parental drug.

Clinical, hematochemical and toxicological findings suggest myocardial damage due to unintentional intoxication of tramadol, this hypothesis is supported by other cases of refractory shock described in literature, requiring an extracorporeal life support in a 33-year-old man with blood tramadol concentration of 23.9 mg/L, and concomitant consumption of hydroxyzine, gabapentin, and clonazepam. In this case no other drugs, with potential cardiac toxicity were detected.[14] Cole et al. described myocardial damage

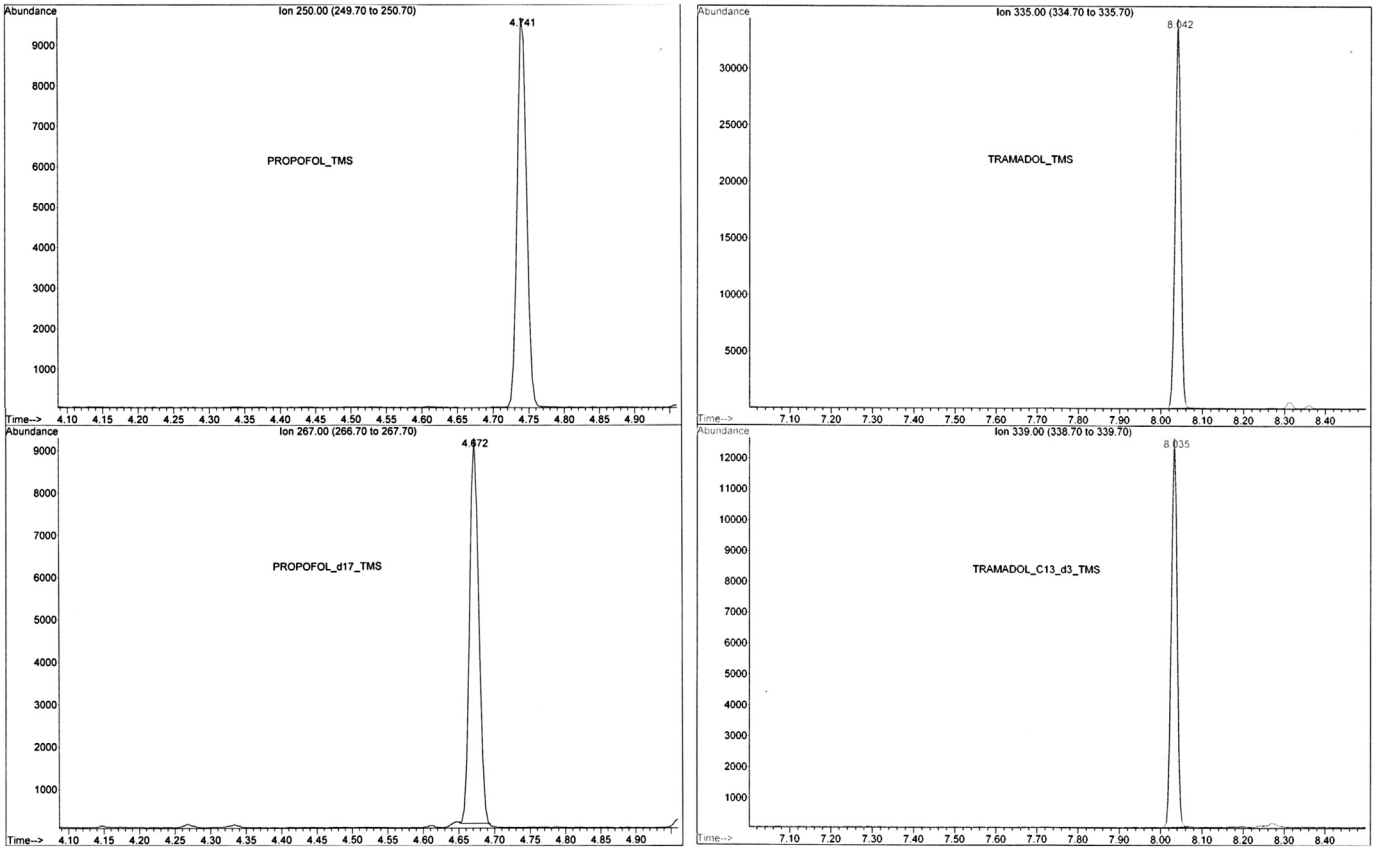

Fig. 5. Heart blood quantitative analysis of propofol TMS and tramadol TMS, in SIM mode.

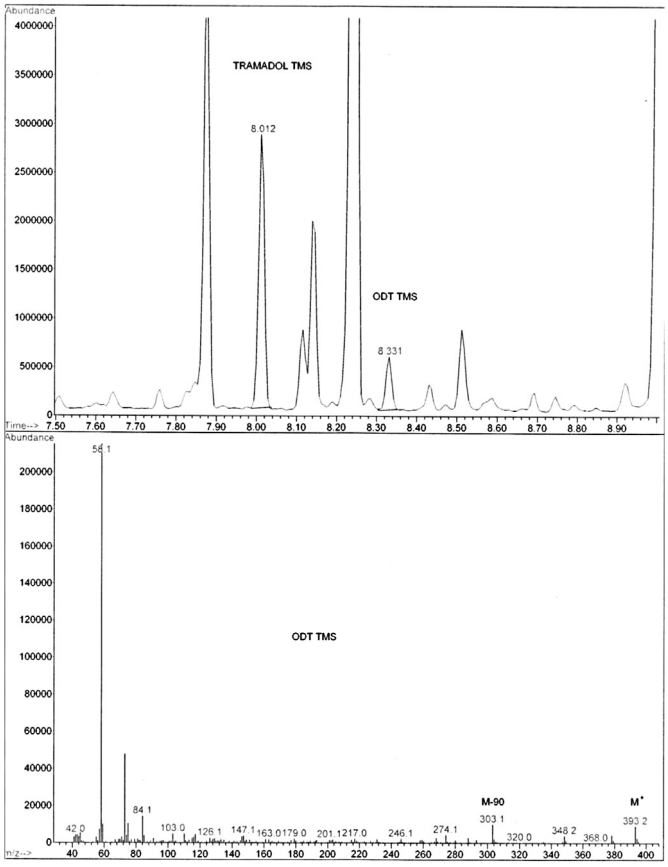

Fig. 6. Heart blood qualitative analysis of tramadolTMS and O-desmethyl Tramadol2TMS, in full scan mode.

leading to a Brugada ecg pattern associated with a rise of troponin I (0.13 ng/mL).[15] Tramadol cardiotoxicity has been moreover linked with ultrarapid CYP2D6 metabolism resulting in refractory cardiac arrest.[16] It has been also associated with serotonin syndrome leading to acute right heart dysfunction.[17] The cause of death was therefore finally attributed to a cardio circulatory arrest in a patient with acute respiratory failure.

5. Conclusion

Danger in propofol self-administration is primarily due to the absence of medical assistance. Its abuse potential may be consequent to the short length of effect (not more than 5–10 min)[13] and to the absence of withdrawal symptoms, that can lead to repeated injection procedures. Addiction is rare and more frequently reported in health care professionals, because of the higher opportunity to access controlled substances,[18] and as skills are required to administer this kind of drug intravenously. Tramadol is considered to be relatively safe when compared with other opioids, but, as we described, it could be life-threatening, therefore prescriptions should be carefully controlled in order to minimize the incidence of drug dependence and fatal complications in case of high dosage administration. In fact our results, suggest a death from cardio circulatory refractory arrest in a patient with acute respiratory failure. Several drugs, commonly used in medical practice, cannot be detected by immunological screening panels. Extensive toxicological analysis is recommended especially in absence of circumstantial and anamnestic data.

Ethical approval

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Conflict of interest

All authors have made a significant contribution to the findings in the paper. There are no financial or commercial interest. The work has not been published or submitted simultaneously to any other journal.

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