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CASE REPORTS

Liver failure secondary to poisoning by a homemade product made of star and green anise in a 4-month-old infant

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ABSTRACT

Intoxications in pediatric age represent a frequent cause of visit to the hospital emergency unit. Herb-made products can be toxic for the infant. The neurotoxic properties of the star anise *(Illicium verum)* have been widely described, although it is a classic product used to treat the infantile colic. Hepatic failure due to the consumption of anise herb elaborated infusions is presented as an exceptional finding in our environment. A case of a 4-month-old infant with hypertransaminasemia, severe coagulopathy, non ketotic hypoglycemia, moderated metabolic acidosis and neurologic symptoms such as seizures and nistagmus is described. After discarding infectious, metabolic and autoimmune etiology and through a meticulous anamnesis, the family referred having administered in the last two months a daily star anise and green anise *(Pimpinella anisum)* infusion to the patient. It is important to emphasize the serious risk of administering homemade herb infusions to infants.

Key words: Aniseed. Star anise. Hepatotoxicity by herbs. Neurotoxicity. Natural and herbal products.

INTRODUCTION

For several years there has been a significant increase in the use of natural remedies and the consumption of botanical products with the false perception that they necessarily induce a health benefit. Intoxications are a frequent cause for emergency consultation in childhood (1). Some natural products have been associated with severe poisoning, emphasizing on the star anise or "Chinese star anise" (*Illicium verum*), which is known for its use as a homemade remedy for the infantile colic, widely spread in our culture (2-4). The anethole, main compound of the star and green anise, is responsible for the odour and flavour and it can induce adverse neurological effects. Multiple neurological symptom cases associated to the use of star anise were communicated by the Spanish national net of hospitals. These facts brought about its withdrawal from the market between October of 2001 and May of 2002, and the strengthening of the product sale control measures (5). The Food and Drug Administration (FDA) also emitted a security warning after registering 40 cases of star anise poisoning in the USA, 15 of them in children (6). However, despite the recommendations and pharmacological control measures, intoxication cases still arise, favoured by the easy acquisition of the product in herb stores and the low awareness of toxicity among the population (7). A case of an infant with acute liver failure and neurological symptoms after the continuous intake of star and green anise infusion is described.

CASE REPORT

A 4-month-old male infant with hypotonia and respiratory distress was admitted at a local hospital. During his admission he was reported to have fever, watery stools, symptomatic hypoglycemia with myoclonic movements of extremities that lasted less than 30 seconds and nystagmus, metabolic acidosis, hyperlactacidemia and severe coagulopathy with gastrointestinal bleeding. He showed progressive hemodynamic deterioration until shock and needed administration of intravenous fluid therapy and dopamine as well as cefotaxime and clindamycin after showing increased procalcitonin (59.1 ng/ml). Due to the suspicion of septic shock with gastrointestinal etiology, the patient was transferred to our hospital and he was admitted to the Pediatric Intensive Care Unit.

Past medical history showed late preterm birth (34 weeks). His nutrition included infant formula feeding with appropriate weight gain and his parents reported frequent

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crying episodes that were considered as colics. A natural product that contained *Argentum nitricum D5*, *Chamomilla D1, China D3* and *Cuprum aceticum D4* was given to the infant. Chamomile infusions that were acquired in pharmacy and occasionally paracetamol in appropriate doses were also given to him. Physical examination demonstrated pale skin, vascular access site bleeding and capillaritis, abdominal bloating, hepatomegaly (3 cm below the right costal margin), irritability, hyperexcitability, and mild horizontal nystagmus.

Acute liver failure with hypertransaminasemia (aspartate aminotransferase [AST] 812 U/l, alanine aminotransferase [ALT] 1002 U/l) and serious coagulation disorder (prothrombin activity 22%, activated partial thromboplastin time [aPTT] 59 seconds, factor V Leiden activity 34%, platelets 86.000/µl) were found, therefore K vitamin and plasma were administered to him. Hypoglycemia (27 mg/dl) with negative ketonemia and moderate metabolic acidosis (pH 7.25, bicarbonate 13 mmol/l, base excess -12,7 mmol/l) were reported, so the patient needed a high amount of intravenous glucose (14 mg/kg/min) and bicarbonate. Total and conjugated bilirubin, ammonia and albumin levels were normal. An increased temperature in the first 72 hours was shown, as well as elevated C-reactive protein (56 mg/l) and procalcitonin (88 ng/ml), so the antibiotics were replaced. He was administered piperacillin/tazobactam due to probable enteric infectious disease, and infectious diseases diagnostic tests were also ordered. An abdominal ultrasound exam showed ascites and increasing intestinal motility without liver disorders.

Due to severe acute liver failure secondary to possible decompensated metabolic disease, metabolic tests were ordered and he was administered N-acetyl cysteine and NTBC (2-[2-nitro-4-trifluoromethyl benzoyl]-1-3-cyclohexanedione), as well as low tyrosine diet because of diagnostic suspicion of tyrosinemia.

A neurologic, hemodynamic, infectious and hepatic progressive improvement was found. Laboratory tests showed prothrombin activity 82%, AST 148 U/l and ALT 684 U/l sixty hours after his admission. Infectious diagnostic tests were negative, including hepatotropic (A, B and C) and influenza viruses (A, B), TORCH serologies, cerebrospinal fluid (CSF) cytochemical test and viruses detection by polymerase chain reaction, and cultures (blood, CSF, urine, stools). Autoimmune liver laboratory tests were also negative. Metabolic tests showed mild elevated excretion of homovanillic acid, vanillylmandelic acid and 4-hydroxyphenylpyruvic acid and mild hypoaminoacidemia. Tandem mass spectrometry, alpha-fetoprotein in blood and succinyl acetone levels in urine were normal.

Parents were comprehensively asked and they referred that the infant had been administered an infusion made of two chamomile tea spoons, a star shaped grain of star anise (*Illicium verum*) and two grains of green anise (*Pimpinella anisum*) in 500 ml of water. In the last two months the infant had been drinking 250 ml per day. The Toxicological Information Centre was contacted and it recommended to prove a possible contamination with *Illicium anisatum*, a toxic substance that could explain the symptomatology, through a simple method: to mix a portion of star anise with 3 ml of alcohol at 96 degrees, to boil, to filter and to add 5 drops of water to the liquid. The absence of turbidity was a sign of contamination with *Illicium anisatum*. Later on the patient was totally recovered and laboratory abnormalities were normalized.

DISCUSSION

The situation involving liver failure and neurological findings with rapid normalization and negative metabolic and infectious diagnostic tests suggested the toxic origin. Through a focused anamnesis we could document the existence of moderate and continuous star and green anise consumption. The consumption of these products based on its carminative effect has been prevalent in our environment in the last years. No relation was found between the rest of botanical products administered to the patient and hepatic or neurological toxicity. The toxicity of star anise has been described in many countries, characterized by gastrointestinal and neurological symptoms (3) such as seizures, abnormal limbs movements (tremor, hypertonia, spasms) and ocular movements (nystagmus) (2-4). In most severe cases, status epilepticus and apparent life-threatening episodes with central cyanosis and tetany (8,9) in association with gastrointestinal symptoms such as vomiting were communicated. Although reports of mild liver failure secondary to the use of green anise can be found in the literature, no previous reports associating star anise and severe hepatotoxicity could be found, even if both of them are similar in the essential oils (10-12).

Star anise is obtained from a tree of the *Magnoliaceae* family, whose fruits are red-brownish star shaped with six-eight follicles that are 2 cm wide. The fruits are arranged radially and each of them contains an ovoid seed of 10 mm diameter. Its wide diffusion as a homemade remedy to treat gastrointestinal discomfort occurs because of the properties attributed to this plant: antioxidant, antimicrobial, analgesic, antispasmodic, expectorant or sedative. Among the active ingredients of this plant, there are some components capable of producing hepatotoxicity *in vitro*, such as the anethole (11,12) (which is also found in a smaller quantity in green anise) and neurotoxicity, as in the case of anethole and anisatins (13,14). The latest ones are known as the most lethal toxins in the vegetal world because of their non-competitive antagonist activity against the gamma-aminobutyric acid A receptor (GABA). They are found in the form of veranisatins A, B and C as a minor component of *Illicium verum*. However, most poisonings related to the consumption of star anise seem to be secondary to contamination or adulteration with a highly toxic fruit which has similar macroscopic characteristics

and it is known as "Japanese star anise" or *Illicium anisatum*. This contamination probably occurred in our case (3,4). This plant has no medical effects, yet it has a high content in veranisatins (13).

Poisoning by star anise herbs should be considered in infants, probably related to the contamination with *Illicium anisatum* and not to the continuous intake of *Illicium verum*. The presence of green anise increases the risk of toxicity. Factors that may contribute to this toxicity are: the toxic properties themselves, a lack of proper identification of the product and its components, a selection of the wrong part of the plant, improper storage, contamination of plants by harmful chemical products, adulteration of the product and absence or wrong labelling (15).

It is important to perform a comprehensive anamnesis to research the possibility of intoxication in children with neurological and/or liver failure, once infectious, metabolic and autoimmune etiologies are discarded, and star anise poisoning should be considered in the differential diagnosis. The role of the pediatrician should not be reduced to a right feeding planning, but advice about drinking should also be provided to ensure a proper guidance. Nowadays homemade herb infusions should not be admitted as appropriate for infants.

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