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A series of cases of rhabdomyolysis after ingestion of *Tricholoma equestre*

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Tricholoma equestre (hereinafter – *T. equestre*) is a common edible fungus that is considered to be toxic under certain conditions. Here, we report four cases of acute poisoning caused by *T. equestre*, including one lethal outcome in Lithuania between 2004 and 2013. In the severe case, fatigue, nausea without vomiting and muscle pain, profuse sweating without fever, and respiratory insufficiency occurred. Laboratory tests showed an elevation of creatine kinase (CK), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Although clinical findings and laboratory tests support evidence of rhabdomyolysis, no renal insufficiency was observed. Significance of *T. equestre* in cardiac changes is feasible but remains unclear.

Keywords: *Tricholoma equestre*, mushroom poisoning, rhabdomyolysis, creatine kinase

INTRODUCTION

We present four cases of rhabdomyolysis after ingestion of *Tricholoma equestre* (hereinafter *T. equestre*). Traditional Lithuanian cuisine regards this mushroom as edible and delicious. It is often served fried or boiled as a main course. The *T. equestre* species includes three ectomycorrhizal species: *Tricholoma flavovirens* (Pers.) S. Lundell, *Tricholoma auratum* (Paulet) Gillet, and *T. equestre* (L.) P. Kummer. All these species produce sporophores with intense yellow gills, but are difficult to distinguish during morphological analyses at both the macroscopic and microscopic levels. These species appear to be associated with various conifers, depending on the geographic origin (*Pinus pinaster* for *T. auratum, Pinus sylvestris* or *Abies alba* for *T. equestre* and *T. flavovirens*) (1). They grow in late autumn, when there are no other edible fungi. There are a few reports on poisoning by *T. equestre* worldwide. The first twelve cases were reported in France during the period of 1992 to 2001, including three lethal ones (2). Also there were two other cases in 2001 and one case of a child poisoning in 2003 in Poland (3, 4). The toxin of *T. equestre* and its mechanism are still unclear. Intoxication usually manifests via rhabdomyolysis. *T. equestre* toxicity has been confirmed by several studies with mice (2, 3, 5).

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Case report 1

A 56-year-old man was hospitalised after having been eating a litre of boiled *T. equestre* three times a day for six days. The exact weight of the consumed fungi is unclear. Three other people who ate smaller amounts of the same fungus had no symptoms. On the first day after the last ingestion, the patient became very weak, experienced nausea, and loss of appetite; he also had profuse sweating without fever and weakness in lower limbs (especially thighs). On the third day, he was admitted to a general practitioner but poisoning was not suspected. On the fifth day, the patient's

state of health deteriorated: fatigue and sweating increased, weakness of muscles worsened, and the patient was admitted to the Centre of Toxicology. Maximum levels of creatine kinase (CK) and aspartate aminotransferase (AST) reached 30571 IU/L and 1190 IU/L on day 5, respectively. Maximum value of alanine aminotransferase (ALT) was observed on day 10 (ALT – 457 IU/L) when symptoms had already been regressing. ECG (electrocardiogram) showed repolarization disturbances in lateral left ventricular wall, 5–15% prolonged QT, and left anterior fascicular block. The patient had primary hypertension for two years and had been using fosinopril before hospitalisation. Bilirubin, alkaline phosphatase, electrolytes, urea, creatinine, SPA (INR), and abdominal ultrasonography were normal; cardiac ultrasonography presented hypertrophy of the left ventricle due to hypertension, no ischemic changes. Severe erythrocyturia was found in the urine test – 250 erythrocytes per litre. The patient refused to undergo muscle biopsy. The treatment included fluids, correction of electrolytes, decreasing doses of diuretics, silymarin, betablockers, and hyperbaric oxygenation therapy. All biochemical tests and symptoms slowly disappeared during 14 days and he was discharged from the hospital without any sequels.

Case report 2

A 73-year-old man was hospitalised after having been eating a standard portion of *T. equestre* as a main dish once-twice a day for one month. The exact weight of *T. equestre* is unknown. On the second day after the last consumption, the patient became weak and reported excessive sweating without fever. Weakness and pain in legs appeared whereas diuresis reduced. Although the patient's wife and daughter had also consumed the fungus, they had no symptoms. The amount of mushrooms that the wife and the daughter consumed was smaller than that of the patient's. On the fourth day the patient's condition deteriorated and he was transferred to the Centre of Toxicology. The maximum observed values of CK, AST and ALT were reached on the day of admission: CK – 8011 IU/L, AST – 408 IU/L, ALT – 154 IU/L. The urea value was slightly elevated – 17.4 mmol/l. The urine test showed severe erythrocyturia – 250 erythrocytes per litre. Other laboratory tests including creatinine, troponin I, alkaline phosphatase, total bilirubin, SPA (INR), and full blood count values were in the normal range. Electrocardiogram (ECG) showed atrial fibrillation, diffused repolarisation disturbances in the anterior wall of myocardium, QT prolongation. The patient had chronic atrial fibrillation but had not been taking any medication. No clinical symptoms specific to an acute heart damage were observed. The patient was treated with fluids, diuretics, amiodarone, digoxin, anticoagulants, and silymarin. Within a few days of treatment, CK values decreased two times, and hepatic enzymes – four times. All the symptoms and biochemical abnormalities disappeared within ten days of hospitalisation.

Case report 3

A 55-year-old woman was hospitalised at the Centre of Toxicology after having been eating half a litre of *T. equestre* once a day for one week. On the second day after the last ingestion she started to feel tired; nausea and discomfort in the chest area occurred. She had no other diseases and did not use any medications or drugs. Despite being treated by a general practitioner, her health deteriorated and weakness of muscles progressed. No profuse sweating was observed. On day 5, she was hospitalised at the Centre of Toxicology. Full blood count, electrolytes, urea, creatinine, coagulation values were in the normal range. The total bilirubin reached 19.4 mmol/L, and the abdominal ultrasonography was without pathological changes. Within a few days of treatment, her symptoms fully regressed, despite the fact that on day 10 her CK value was 5363 IU/L. AST (454 IU/L) and ALT (244 IU/L) maximum concentrations were reached at the beginning of hospitalisation and decreased within a few days. Urine test was not performed on the admission day. ECG was carried out on the eighth day after *T. equestre* ingestion. The results revealed 15% prolonged QT and ischemical changes in lateral, inferior, and interseptal myocardium walls; however, no acute cardiac failure symptoms were observed. There was no progress in ischemic changes in ECG and no disturbances of electrolytes or renal failure. The patient was treated with fluids and hepatoprotectors. On the eleventh day after the first symptoms and when her health condition stabilized, the patient was discharged from the hospital.

Case report 4

A 44-year-old man was hospitalised after having been eating a standard portion of *T. equestre* three times a day as a main dish for three days. On the first day after the last ingestion, myalgia, fatigue, muscle weakness, and profuse sweating without fever occurred. From the previous history of the patient it was known that he was an alcohol abuser. On day four he was admitted to the intensive care unit of the Centre of Toxicology. The laboratory values on the admission day were as follows: CK 16590 IU/L, AST 1524 IU/L, and ALT 579 IU/L. Alkaline phosphatase (ALP) and troponin I test were normal, total bilirubin – 19 mmol/L. Slight leukocytosis was observed on the admission day – white blood cells reached 12.1×10^9/L, and erythrocyturia – 250 erythrocytes per litre. ECG presented 15% prolonged QT, subpericardial injury signs in lateral and inferior walls of myocardium, left anterior fascicular block. The patient's health condition worsened during the first few hours, with body temperature reaching 42 °C. Soon afterwards he lost consciousness. Two hours later, an acute respiratory insufficiency developed. His CK value reached 34600 IU/L, ALP increased to 534 IU/L, whereas AST and ALT values slightly decreased. On the sixth day after consumption of *T. equestre* the patient died from a heart attack. He was treated with fluids, diuretics, penicillin and gentamycin, thiamine, antipyretics, oxigenotherapy, and adrenalin for resuscitation. No other causes responsible for the signs such as trauma, viral, bacterial (such as septicemia), neurological and immune diseases, or exposure to medications were found. It was known that the patient had no other diseases and did not take any medications or drugs, except alcohol, prior to the poisoning.

DISCUSSION

In this report, we describe *T. equestre* poisonings that might be dangerous or even lethal to humans. All four cases support medical evidence regarding toxicity of *T. equestre*. Symptoms and laboratory tests were similar to those found in case reports of poisonings by *T. equestre* in Poland (2001–2010) (3, 4) and France (1992–2000) (2). In the severe case, poisoning manifested by fatigue, nausea without vomiting, profuse sweating without fever. No facial erythema or respiratory insufficiencies were observed in our cases (2). The relation between the picking time, place, and toxicity of *T. equestre* is not known. Laboratory tests suggested rhabdomyolysis, a condition when due to mechanic or toxic injury of muscles and large quantities of myoglobin releases it is bound to plasma globulin. When the binding capacity of the plasma protein is exceeded, it is filtered by the glomeruli and reaches the tubules. It may cause direct nephrotoxicity, tubular obstruction, vasoconstriction, and acute kidney injury (6). Rhabdomyolysis could also be a consequence of consumption of large quantities of other edible fungi, such as Boletus or Leccinum species, but our patients did not consume any other fungi (7). Although the fungus is widely known and eaten, just one or two cases of poisoning are registered in Lithuania per year. Most of poisonings are not identified because of delayed and unspecific clinical symptoms and high toxic dose that are reached only after repeated intake of large portions of fungi. In all cases, symptoms occurred after large consecutive meals (more than 500–1000 grams) of the fungi. Nieminen study suggests that a toxic dose of wild mushrooms for a human (according to the studies with mice) would be 830 g per day for 4 weeks, or 70 g per day if body surface area constant is applied for humans and mice (5). Powdered *T. equestre* at 1.33–2 g/kg per day for three days (2), or 9 g/kg per day for five days as well as 12 g/kg per day for 28 days of fresh *T. equestre* (5) induced a similar response in mice. Three other people in case 1, and patient's wife and daughter in case 2 also ate *T. equestre*, but they were not intoxicated because the total consumed dose was smaller than that of the patients'. It is also possible that personal sensitivity of muscles to *T. equestre* toxins could determine the dose that causes symptoms or death. In all cases, no pre-hospital cardiological pathology, or medications that could lead to these changes prior to hospitalisation were observed. No other possible causes of rhabdomyolysis, such as trauma, bacterial or viral infection, inflammatory myopathies, use of illicit drugs, such as cocaine, amphetamine, theophylline, phenothyzines, p-phenylenediamine, antihistamines, antilipidemic drugs, were found (2, 5). Biochemical findings showed a significant increase of CK, AST and ALT values, and the mortality rate reached around 25% which is

comparable to other studies (2, 8). Laboratory screening tests confirmed rhabdomyolysis. In all the cases, the maximum CK values were in the range of 5363 IU/L and 34600 IU/L; the maximum AST concentrations reached 454 IU/L to 1380 IU/L, and ALT values did not exceed 579 IU/L. Increased ALT, unchanged AST values in coagulation, and liver ultrasound showed that elevation of liver enzymes were probably due to musculoskeletal injury and not hepatotoxicity (9). However, Finnish studies with rodents showed that subchronic *T. equestre* consumption could cause myo-, cardio- and hepatotoxicity (5). In these cases liver biopsy had not been performed so hepatotoxicity could not be denied. Two patients complained of discomfort in the chest area. ECG abnormalities were considered as "ischemic", but troponine I values were normal, ECG showed a prolonged QT, although no medications that could induce the prolongation were taken. These myocardial injuries due to rhabdomyolysis could mimic ischemical changes in myocardium. Myocarditis itself could cause flu-like symptoms such as fever, fatigue and myalgia similar to the symptoms of *T. equestre* poisoning. Myocardium injury often occurs only if there are additional factors such as influenza or other virus action (10). Factors that cause rhabdomyolysis could have a direct toxic action to myocardium so cardiac injury manifests in both mechanisms. Experimental and necroscopic studies have convincingly shown that free radicals produced in any organ of the body can induce myocardial damage. As muscle damage due to rhabdomyolysis occurs, release of constituents of necrotic muscle results in the accumulation of free radicals and tumor necrosis factor-α (TNF-α) in the serum which are responsible for systemic inflammatory reaction during rhabdomyolysis (11).

CONCLUSIONS

These case reports support previous observations that a repeated ingestion of large amounts of *T. equestre* could cause severe rhabdomyolysis. Ingestion of just one portion containing a substantial quantity of *T. equestre* is harmless. Although symptoms were unspecific, laboratory tests showed elevated CK, AST, ALT values due to muscle toxicity. No renal insufficiency despite rhabdomyolysis was observed. The toxic mechanism and toxic substances of *T. equestre* remain unclear.

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ŽALSVOJO BALTIKO (*TRICHOLOMA EQUESTRE*) SUKELTOS RABDOMIOLIZĖS KLINIKINIŲ ATVEJŲ APTARIMAS

Santrauka

Tricholoma equestre (toliau – *T. equestre*) – dažnai sutinkamas valgomasis grybas. Tam tikrais atvejais jis laikomas nuodingu. Aptariami keturi apsinuodijimų *T. equestre* atvejai 2004–2013 m., įskaitant mirtiną atvejį. Sunkūs apsinuodijimai pasireiškia nuovargiu, pykinimu be vėmimo, raumenų skausmais, profuziniu prakaitavimu be karščiavimo ir kvėpavimo nepakankamumu. Laboratoriniuose tyrimuose stebima padidėjusi kreatinkinazė (CK), aspartataminotransferazė (AST), alaninaminotransferazė (ALT). Nors klinikiniais ir laboratoriniais tyrimais nustatyta rabdomiolizės diagnozė, inkstų funkcijos nepakankamumo pastebėta nebuvo. Taip pat galimas *T. equestre* sukeliamas kardiotoksiškumas, tačiau eiga nėra aiški.

Raktažodžiai: *Tricholoma equestre*, apsinuodijimas grybais, rabdomiolizė, kreatinkinazė