Marchelek-Myśliwiec Małgorzata, Wilk Aleksandra, Turoń-Skrzypińska Agnieszka, Nowosiad-Magda Monika, Dutkiewicz Grażyna, Dołęgowska Barbara, Stępniewska Joanna, Ciechanowski Kazimierz, Wiszniewska Barbara. Acute kidney injury related to wild mushrooms intoxication. Journal of Education, Health and Sport. 2020;10(1):42-46. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2020.10.01.005
https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2020.10.01.005
https://zenodo.org/record/3611248

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

Received: 20.12.2019. Revised: 25.12.2019. Accepted: 17.01.2020.

Acute kidney injury related to wild mushrooms intoxication

Running title: Mushroom intoxication related acute kidney injury

Małgorzata Marchelek-Myśliwiec[1], Aleksandra Wilk[2], Agnieszka Turoń-Skrzypińska[3], Monika Nowosiad-Magda[3], Grażyna Dutkiewicz[1], Barbara Dołęgowska[4], Joanna Stępniewska[1], Kazimierz Ciechanowski[1], Barbara Wiszniewska[2]

1. Clinic of Nephrology, Transplantology and Internal Medicine, Pomeranian Medical University, Szczecin, Poland
2. Department of Histology and Embryology, Pomeranian Medical University, Szczecin, Poland
3. Department of Medical Rehabilitation and Clinical Rehabilitation, Pomeranian Medical University in Szczecin, Poland
4. Department of Microbiology, Immunology and Laboratory Medicine, Pomeranian Medical University, Szczecin, Poland

Corresponding author:
Małgorzata Marchelek-Myśliwiec
Clinic of Nephrology, Transplantology and Internal Medicine
Pomeranian Medical University in Szczecin
Powstancow Wielkopolskich Str 72
70-111 Szczecin, Poland
phone nr: 0048607490780; fax nr: 048914661196; e-mail: malgorzata.marchelek@gmail.com

Abstract:
The problem of mushroom intoxication has been brought up more often in both scientific journals and media, particularly in autumn – the period when mushroom hunting is most intense. Mushroom intoxication is mainly perceived as being associated with acute hepatic insufficiency. However, apart from strong hepatotoxic effects, some mushroom species are characterized by effects that lead to renal damage, sometimes irreversible in character. This article relates to the toxic mushroom species considered to be nephrotoxic and discusses different mechanisms and symptoms of kidney injury as well as methods of treatment.

Keywords: Wild mushroom intoxication, Nephrotoxicity, Kidney insufficiency, Orellanine nephrotoxicity, Amatoxin nephrotoxicity, Paxillus syndrome

Article:
In recent years, the problem of mushroom intoxication has been brought up more often in both scientific journals and media, particularly in autumn – the period when mushroom hunting is most intense. According to the National Institute of Hygiene of Poland there is a downward trend in the incidence of mushroom intoxication, resulting mainly from a higher public awareness. A disturbing fact is an increased interest in hallucinogenic effects of mushroom among young people [1]. Mushroom intoxication is mainly perceived as being associated with acute hepatic insufficiency. However, apart from strong hepatotoxic effects, some mushroom species are characterized by effects that lead to renal damage, sometimes irreversible in character. This article relates to the toxic mushroom species considered to be nephrotoxic.
The subject of toxic properties of species of the *Fungi* kingdom was studied in 1950s by Stanislaw Grzymała who isolated orellanine – a hit-stable substance responsible for renal damage [2]. He also presented case reports on orellanine intoxication. In 1957 Grzymała reported the first incidence of acute intoxication after ingestion of *Cortinarius orellanus* in Bydgoszcz in Poland. About 100 inhabitants developed acute kidney failure after an ingestion of this mushroom. The mortality was over 10%.
Orellanine is an alkaloid that is insoluble in water. The substance is thermostable, i.e. it does not undergo degradation upon boiling or frying. Orellanine chemically resembles pyridine herbicides paraquat and diquat and deoxidizes in ultraviolet light to a non toxic metabolite – orelline [3, 4, 5]. Nephrotoxic activity of orellanine mostly occurs through selective damage to renal tubule cells, which leads to necrotic and degenerative lesions. However, the exact mechanism behind orellanine nephrotoxicity has not yet been explained [6]. Renal biopsy in affected patients reveals interstitial glomerular damage [4, 7, 8]. Orellanine causes severe non glomerular renal injury by an unknown mechanism [7, 9]. Clinically the patients presents anorexia, headache, nausea, vomiting, diarrhea, flank pain. The initial symptoms may be easily overlooked as the first symptoms begin 36 to 48 hours post ingestion [7, 10]. Serious toxicity does not occur for several days [11, 12]. The nephrotoxin causes an irreversible renal failure in severe cases (orellanus syndrome). Acute kidney injury (AKI) occurs only in 30-50% of cases [10, 12, 13]. Due to dilate presentation, a clinician must consider orellanine toxicity in any patient with an unexplained AKI. Damage to the kidneys can be confirmed by thin layer chromatography of renal biopsy specimens or by plasma assays for orellanine and orellin [14, 15, 16]. Due to an accumulative properties ingestion of small yet repeated doses of orellanine can lead to fibrosis and acute tubular necrosis.
An example of species containing orellanine is fool's webcap, *Cortinarius orellanus*, which may be fatal when ingested even in small quantities (~150g). Intoxication with *Cortinarius orellanus* is characterized by a relatively late onset of full symptoms which may develop as late as after several days. The only treatment that may be applied at the time of the onset of

symptoms is hemodialysis as a temporary support until an adequate renal function returns, and finally a renal transplant [17]. A successful case of living donor kidney transplantation to a patient with kidney insufficiency related to *Cortinarius orellanus* intoxication after 20 months haemodialysis treatment has been recently described [18]. The efficacy of the treatment with N-acetylcysteine and corticosteroids reported by Kilner [6] was not confirmed in another study [19].

Orellanine was recently also found in a mushroom *Cortinarius armilatus* with HPLC (high-performance liquid chromatography) and LC-MSMSL (liquid chromatography-tandem mass spectrometry) [20].

Another popular mushroom-related nephrotoxin is an amatoxin. The amatoxin containing species of mushrooms, which is the most common of its critical intoxication, is *Amanita phalloides* and it is responsible for over 90% of fatalities worldwide. The most notorious for intoxication incidence is death cap (*Amanita phalloides*), that similarly to the well-known destroying angel (*Amanita virosa*), contains hepatotoxic cyclopeptides which, when ingested, lead to fulminant hepatic failure and multiple organ dysfunction referred to as Phalloides syndrome. A particular danger with this intoxication lies in the fact that the symptoms may develop as late as after 24 hours when, in most cases, the liver has become completely insufficient. The genus *Amanita* includes also two other species, i.e. *Amanita smithiana* and *Amanita proxima*, which has been described as nephrotoxic in numerous reports [11, 21]. *A. smithiana* occurs mostly on the west US coast (California), while *A. proxima* grows in the Mediterranean Basin. Intoxications with *A. smithana* are due to its high similarity to edible species, particularly matsutake (*Tricholoma magnivelare*), which is much valued by culinary connoisseurs with price reaching USD 2000/kg. Other species of the genus were also subjected to toxicity tests. The toxin responsible for renal damage was detected also in *A. boudieri* (Portugal), *A. gracilior* (Portugal), *A. echinocephala* (Germany) [22]. Symptoms of intoxication with *Amanita* mushrooms include mainly gastrointestinal disorders with a quite early onset of about 6 hours. Most studies demonstrate increases in aminotransferase levels which may occur between the first and the fifth day after ingestion. Renal failure develops over 3-5 days in contrast to nephrotoxic orellanine containing ingestions. Chronic renal disease and stage V chronic renal failure occurs in as many as 51% of patients. Renal function recovery in *Amanita* intoxication is estimated at 100% [12].

Another species responsible for an acute renal damage is *Paxillus involutus*. It exerts nephrotoxic effect in an indirect mechanism. Ingestion of the mushroom leads to antigenic stimulation and secretion of IgG antibodies followed by development of immune complexes, which bind to the erythrocyte membranes and lead to a massive hemolysis, hemoglobinuria and renal damage. The symptoms are referred to as the Paxillus syndrome. Since the symptoms originate from the activity of immune complexes, plasmapheresis has been used successfully in the treatment of the syndrome [23].

Renal damage secondary to mushroom consumption may also be due to ingestion of yellow knight - *Tricholoma equestre*. Nephrotoxic properties of the mushroom entails the development of rhabdomyolysis – a process of myoglobin permeation from damaged muscles into the blood. This may lead to a necrosis of renal tubules. Main clinical symptoms include muscle weakness, fatigue, myalgia, erythema, nausea without vomiting. The symptoms develop within 24-72 hours. Deviations in laboratory investigations include significant elevation in creatine phosphokinase (CPK) levels [22]. In one of the reported cases, concentration of CPK following ingestion of *Tricholoma equestre* was 44767 U/L. Another report was a case of a patient who died due to respiratory failure caused by a strong intoxication with *Tricholoma equestre* despite an extensive treatment [24].

Poisoning with fungus Russula subnigricans is another cause of rhabdomyolysis, which can be classified as a late onset rhabdomyolysis. Such case, which led to rhabdomyolysis, acute kidney injury, renal failure, cardiac arrhythmias and patient's death was described in South Korea [25].

Studies of toxins contained in various mushroom species are ongoing and one may suspect that there is a considerable number of potentially life-threatening substances that have not been described to date. Mechanisms leading to renal damage caused by these mushrooms have not been fully elucidated and require a continued monitoring.

So far there is no specific treatment for mushroom poisoning and attempts of application of N-acetylcysteine and GKS were not successful [19].

Thus, one should exercise particular care when hunting for mushrooms and be sure to eat only the species that one is 100% certain are edible.

References

1. Marciniak B, Ferenc T, Kusowska J, Ciećwierz J, Kowalczyk E. Poisoning with selected mushrooms with neurotropic and hallucinogenic effect. Med Pr. 2010;5:583-595.
2. Grzymała S. Śmiertelne zatrucia rzekomo jadalnym gatunkiem grzyba III. Wyodrębnienie trującej substancji - orellaniny. Rocz Państw Zakł Hig. 1961;12:491-498.
3. Kilner RG, D'Souza RJ, Oliveira DB. Acute renal failure from intoxication by *Cortinarius orellanus*: recovery using anti-oxidant therapy and steroids. Nephrol Dial Transplant. 1999;14:2779-2780.
4. Prast H, Werner ER, Pfaller W, Moser M. Toxic properties of the mushroom C*ortinarius orellanus*. I. Arch toxicol. 1988;62:81-88.
5. Horn S, Horina JH, Krejs GJ, Holzer H, Ratschek. M. End-stage renal failure from mushroom poisoning with *Cortinarius orellanus*: report of four cases and review of the literature. Am J Kidney Dis. 1997;30:282-286.
6. Andary C, Rapior S, Delpech N, Huchard G. Laboratory confirmation of *Cortinarius* poisoning. Lancet. 1989;1(8631):213.
7. Short AI, Watling R, MacDonald MK, Robson JS. Poisoning by *Cortinarius speciosissimus*. Lancet. 1980;2:942-944.
8. Holmdahl J, Ahlmen J, Bergek S, Lundberg S, Persson S. Isolation and nephrotoxic studies of orellanine from the mushroom *Cortinarius speciosissimus*. Toxicon. 1987;25:195-199.
9. Raff E, Halloran PF, Kjellstrand CM. Renal failure after eating "magic" mushrooms. Can Med Assoc J. 1992;147:1339-1341.
10. Bouget J, Bousser J, Pats B. Acute renal failure following collective intoxication by *Cortinarius orellanus*. Intensive Care Med. 1990;16:506-510.
11. Leathem AM, Purssell RA, Chan VR. Renal failure caused by mushroom poisoning. J Toxicol Clin Toxic. 1997;1:67-75.
12. Warden CR, Benjamin DR. Acute renal failure associated with suspected *Amanita smithiana* mushroom ingestion: a case series. Acad Emerg Med. 1998;5:808-812.
13. Gerault A. Intoxication collective de type orellanien provoquee par *Cortinarius splendens*. R Hy. Bull Trimest Soc Mycol Fr. 1981;97:67-72.
14. Rapior S, Delpech N, Andary C,Huchard G. Intoxication by *Cortinarius orrelanus*: detection and assay of orellanine in biological fluids and renal biopsies. Mycopathologia. 1989;3:155-161.
15. Cantin D, Richard JM, Alary J. Chromatographic behaviour and determination of orellanine, a toxin from the mushroom *Cortinarius orellanus*. J Chromatogr. 1989;1:231-237.
16. Delpech N, Rapior S, Cozette AP. Outcome of acute renal failure caused by voluntary ingestion of *Cortinarius orellanus*. Presse med. 1990;3:122-124.

17. Diaz JH. Syndromic diagnosis and management of confirmed mushroom poisoning. Crit Care Med. 2005;33:427-436.
18. Nagaraya P, Thangarelu A, Nair H, Kumwenda M. Successful living related kidney transplantation for end-stage renal failure caused by orellanine syndrome. QMJ; 2015;5:413-415, https://dx.doi.org/10.1093/qjmed/hcs201.
19. Grebe SO, Langenbeck M, Schaper A, Berndt S, Aresmouk D, Herget-Rosenthal S. Antioxidant treatment and outcome of *Cortinarius orellanus* poisoning: a case series. Ren Fail. 2013;35:1436-1439, https://dx.doi.org/10.3109/0886022X.2013.826110 .
20. Shao D, Tang S, Healy RA, Imerman PM, Schrunk DE, Rumbeiha WK. A novel orellanine containing mushroom Cortinarius armillatus. Toxicon. 2016;114:65-74, https://dx.doi.org/10.1016/j.toxicon.2016.02.010.
21. Leray H, Canaud B, Andary C, Klouche K, Béraud JJ, Mion C. Intoxications with *Amanita proxima* - a new case of acute renal failure. Nephrologie. 1994;15:197-199.
22. Bedry R, Baudrimont I, Deffieux G, Creppy EE, Pomies JP, Ragnaud JM et al. Wild mushroom intoxication as a cause of rhabdomyolysis. N Engl J Med. 2001;345:798-802. https://dx.doi.org/10.1056/NEJMoa010581
23. Winkelmann M, Stangel W, Schedel I, Grabensee B. Severe hemolysis caused by antibodies against the mushroom *Paxillus involutus* and its therapy by plasma exchange. Klin Wochenschr. 1986;64:935-938.
24. Sein Anand J, Chwaluk P, Sut M. Acute poisoning with *Tricholoma equestre*. Przegl Lek. 2009;66:339-340.
25. Cho J, Han J. A case of mushroom poisoning with Russula Subnigricans: developement of rabdomiolysis, acute kidney injury, cardiogenic shock and death. J Korean Med Sci. 2016; 31(7):1164-1167, https://dx.doi.org/10.3346/jkms.2016.31.7.1164.