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Acute kidney injury following naphthalene poisoning in children

Lesión renal aguda después de la intoxicación por naftalina en niños

Dear Editor:

Acute poisoning in children is a frequent cause of admission to emergency units and can lead to death and acute kidney injury (AKI). The incidence of poisoning in children varies from 0.33% to 7.6%.[1] Naphthalene poisoning can lead to a severe clinical Picture.[2] AKI due to naphthalene poisoning is very uncommonly reported in the literature, especially if it requires renal replacement therapy. Acute intravascular hemolysis may be the major mechanism of AKI in naphthalene poisoning.[3,4] In this study, we described a rare case of AKI following naphthalene poisoning in a pediatric patient successfully treated.

Table 1 – Laboratory findings on admission and during the follow-up of the patient.

Parameters	Admission	9 h	24 h	3rd Day	5th Day	10th Day	12th Day	13th Day	Discharge
Potassium	4.09	4.04	4.53	4.23	3.33	5.39	6.93	5.63	3.83
Sodium	135	136	130	137	139	137	135	136	134
Urea	45	62	55	80	51	67	79	65	69
Creatinine	0.7	1.4	1.4	2.1	1.9	2.2	2.6	1.7	1.2
eGFR	51	25.5	0	0	0	16.2	21	32.4	30
AST	75	1281	738	64	**	**	**	**	23
ALT	22	687	569	139	**	**	**	**	10
DB	0.23	**	2.87	1.31	0.33	**	**	**	**
IB	0.34	**	3.14	1.23	1.02	**	**	**	**
PT	12.1	12.2	13.8	11.6	11.2	12	**	12.5	**
aPTT	26.7	25.9	32	27.5	23.8	31.3	**	31.7	**
D-LDH	**	3205	**	972	**	**	**	**	**
Hemoglobin	13	11.1	10.1	8.5	7.8	7.4	8.1	9.5	10.1
Leukocytes	12,420	7940	8020	15,820	11,170	10,230	**	11,000	7530
Platelets	479,000	281,000	209,000	188,000	139,000	323,000	**	403,000	367,000
PH***	**	7.38	**	**	**	**	**	**	**
pCO2***	**	30.5	**	**	**	**	**	**	**
HCO3***	**	19.5	**	**	**	**	**	**	**

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; D-LDH: D-lactate dehydrogenase; CK: Creatine phosphokinase; PT: Prothrombin time; aPTT: partial time of thromboplastin; DB: direct bilirubin; IB: Indirect bilirubin; eGFR: estimated Glomerular Filtration Rate. ** Not available. ***Arterial Gasometry.
Reference values: Potassium (3.5–5.5 mmol/L); Sodium (135–145 mmol/L); Chloride (96–109 mmol/L); Glucose (74–106 mg/dL); Urea (13–43 mmol/L); Creatinine (0.6–1.1 mmol/L); AST (<32 mg/dL); ALT (< 31 mg/dL); DB (< 1 UI/L); DI (< 1 UI/L); PT (10–14 s); aPTT (22–28 s); D-LDH (230–460 UI/L); Albumin (>3.5 UI/L); Hemoglobin 11.3/15.2 g/dL); leukocytes (3600–10,000/mm³); platelets (150,000–450,000/mm³); PH (7.35–7.45); pCO2 (35/45 mmHg); pO2 (85–100 mmHg); HCO3 (22/26 mmol/L); BE (−4/+4).
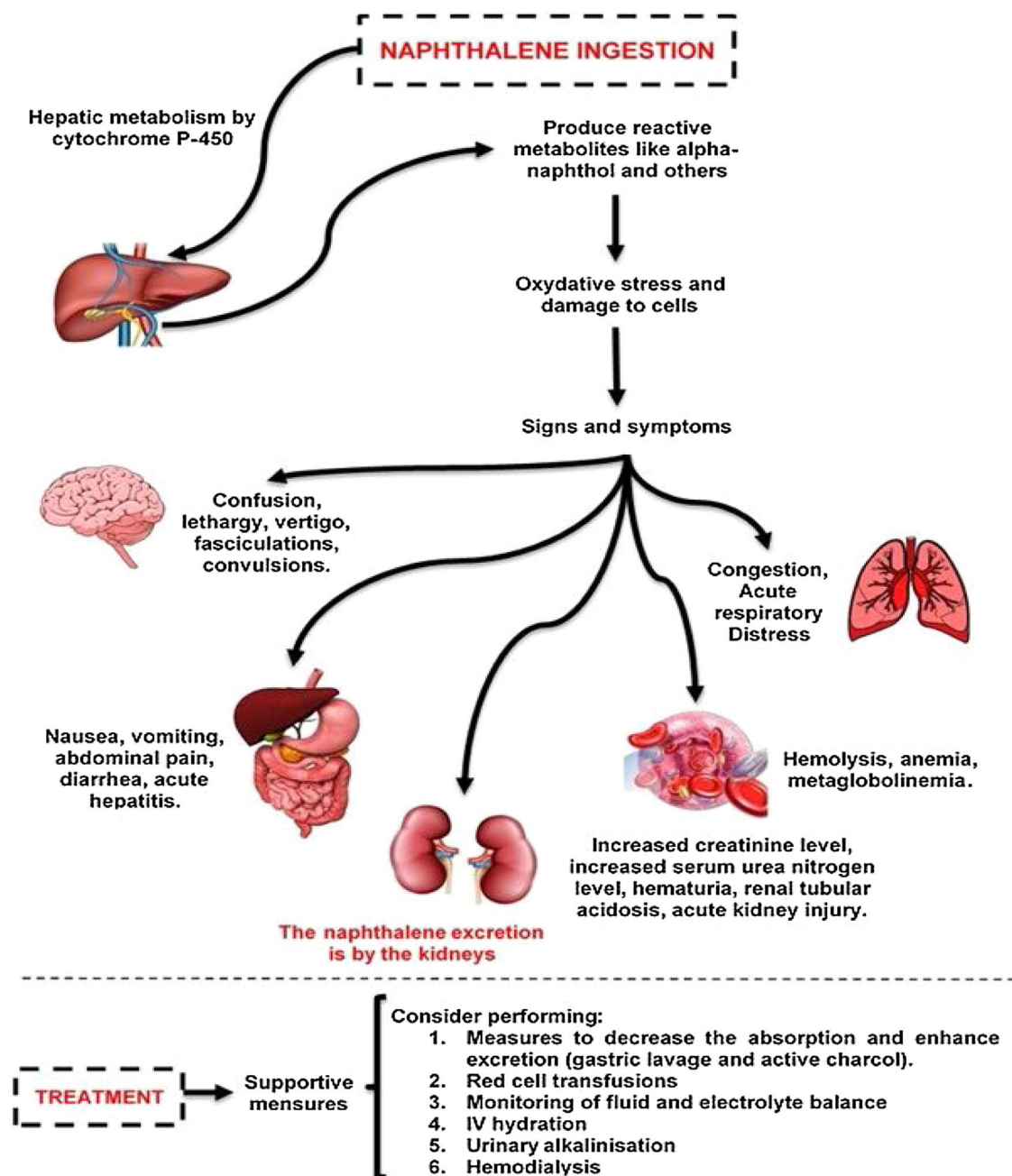
Fig. 1 – Physiopathology and systemic effects following human naphthalene exposure.
Naphthalene is metabolized in the liver and is oxidized to alpha-naphthol and other metabolites. The cytochrome P450 enzymes are capable of catalyzing these metabolic transformation reactions. Toxic manifestations are mainly due to production of oxygen free radicals leading to lipid peroxidation and deoxyribonucleic acid (DNA) damage, as well as produce oxidative stress. This poisoning could affect various body systems, such as the liver, skin, lungs, kidney, central and peripheral nervous system. The treatment in these cases are mainly supportive.

A 1-year-old girl was admitted to the emergency department after accidental consumption of naphthalene balls. The time elapsed until emergency admission was five hours from the ingestion. The patient presented with severe abdominal pain, emesis, serious general condition, and a decreased consciousness level.

In the emergency unit, gastric lavage and activated charcoal were administered. Moreover, she received primary medical care and vigorous intravenous hydration. Results of initial laboratory tests were in the normal range (Table 1), and initial estimated glomerular filtration rate (eGFR) was $51\,mL/min/1.73\,m^2$. Nine hours later, the patient had acute respiratory failure, requiring intubation and ventilatory support. The patient had a left hemorrhagic pleural effusion and severe and acute anemia. Transfusion therapy (1 unit of packed red blood cells) was required

and a thoracic surgeon performed chest drainage due to hemothorax.

Schistocytes on peripheral smear were demonstrated. Moreover, the increase in indirect bilirubin and D-LDH (D-lactate dehydrogenase) suggested an intravascular hemolysis in progress (Table 1). G6PD levels remained in the normal range. She developed laboratory worsening with abnormal renal markers, suggesting oliguric AKI in progress according to KDIGO's criteria (eGFR = 14 mL/min/1.73 m^2). The increase in markers in the liver test indicated acute liver damage.

Moreover, she developed signs of hypervolemia and the nephrologist's assistance was requested, who prescribed hemodialysis. Intravenous sodium bicarbonate was used to prevent renal tubular damage due to hemolysis. The patient had hypertension and medications were started. On the 5th day, she began to recover and was successfully extubated. The patient's urine output improved after eleven hemodialysis sessions, and after 20 days, she was discharged as clinically stable. However, she continued with high blood pressure and only partial recovery of her kidney functions was observed (eGFR = 30 mL/min/1.73 m^2).

Naphthalene poisoning is a relevant health issue due to the easy availability of this toxic agent, especially in low- and middle-income countries. Small doses of naphthalene in humans can affect various body systems – Fig. 1.[5] The patient reported here was a female child presenting with compromised serious general condition, emesis, and abdominal pain due to naphthalene poisoning within a period of 5 h from sucking a naphthalene ball. In this patient, the diagnosis of severe acute hepatitis was established from the clinical status, and the liver damage (observed in laboratory tests) should be attributed to naphthalene poisoning.[6]

Hemolysis is very often a consequence of naphthalene poisoning, and it can be worsened by G6PD deficiency. In this case, the diagnosis was suggested by schistocytes on peripheral smear, a high D-LDH level, and increased indirect bilirubin. In addition, G6PD deficiency was absent.

Naphthalene excretion occurs through the kidneys.[5] The major pathophysiologic mechanism of AKI is related to intravascular hemolysis and hemoglobinuria.[4] Despite the mild hemolytic anemia, the patient had severe AKI and required renal replacement therapy. This fact suggests other mechanisms for AKI development, such as direct nephrotoxicity and acute ischemic tubular necrosis.

There is no specific antidote for naphthalene toxicity and management guidelines are unclear.[7] Management is symptomatic with monitoring of fluid and electrolyte balance. Urinary alkalinization has been recommended in the case of hemoglobinuria to prevent it from being deposited in renal tubules.[4] The treatment in this case was mainly supportive with mechanical ventilation and blood pressure support with the use of inotropes. Nonetheless, gastric lavage and active charcoal were used to decrease absorption due to the severity of the case.

Hemodialysis is established as an important tool in some life-threatening poisoning cases.[8] Hemodialysis was utilized in this case due to the worsening of renal function, oliguria, hyperkalemia, metabolic acidosis, and hypervolemia. Hemodialysis added to the clinical measures promoted the clinical improvement.

Prognosis of naphthalene poisoning is multifactorial.[9] In the case reported, the patient had a remarkable improvement and was discharged on the 20th day. However, she continued to show elevated blood pressure.

Accurate examination of the AKI and CKD relationship has important clinical and public health implications. Complex and imperfect processes could follow AKI, subsequently limiting the repair of damaged cells and the return of their normal functioning. This mechanism appears to be one of the responsible factors for the elevated blood pressure and partial recovery of her kidney functions after AKI.[10]

Acute ingestion of naphthalene is an uncommon cause of poisoning in pediatric patients. Clinicians should be aware of the potential complications in that scenario, such as AKI, and the necessity of early identification, specific management, and follow up of these patients.

Authors' contributions

KNM, BLC and SMBM contributed to the case data collection. JHHGLP contributed to the draft of the article and the creation of tables and figure. GBSJ, EFD, and PLMMA critically revised the article and approved the version to be published. All authors have read and approved the manuscript.

BIBLIOGRAFÍA

1. Arachchige G, Prasadi M, Mohamed F, Senarathna L, Cairns R, Hangidi P, et al. Paediatric poisoning in rural Sri Lanka: an epidemiological study. BMC Public Health. 2018;18:1–8.
2. Kapoor R, Satish PS. Acute intravascular hemolysis and methemoglobinemia following naphthalene ball poisoning. Indian J Hematol Blood Transfus. 2014;30:317–9.
3. Kundra TS, Bhutani V, Gupta R, Kaur P. Naphthalene poisoning following ingestion of mothballs: a case report. J Clin Diagn Res. 2015;128:8–9.
4. Ekambaram S, Km CK, Mahalingam V. Acute kidney injury: a rare complication of mothball (naphthalene) poisoning. Saudi J Kidney Dis Transpl. 2017;28:1412–5.
5. Dubey D, Sharma VD, Pass SE, Sawhney A, Stüve O. Para-dichlorobenzene toxicity – a review of potential neurotoxic manifestations. Ther Adv Neurol Disord. 2014;7:177–87.
6. Liu J, Drane W, Liu X, Wu T. Examination of the relationships between environmental exposures to volatile organic compounds and biochemical liver tests: application of canonical correlation analysis. Environ Res. 2010;109:423–39.
7. Volney G, Tatusov M, Yen AC, Karamyan N. Naphthalene toxicity: methemoglobinemia and acute intravascular hemolysis. Cureus. 2018;10:6–11.
8. Goodman JW, Goldfarb DS. The role of continuous renal replacement therapy in the treatment of poisoning. Semin Dial. 2006;19:402–7.
9. Uthuman AAA, Jayasinghe CS, Fernando AHN. Acute intravascular hemolysis due to naphthalene toxicity: a case report. J Med Case Rep. 2019;13:4–6.
10. Chou Y, Huang T, Chu T. ScienceDirect Novel insights into acute kidney injury e chronic kidney disease continuum and the role of renin e angiotensin system. J Formos Med Assoc. 2017;116:652–9.

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Neumonía por SARS-CoV-2 y *Aspergillus* en trasplante renal: ¿más frecuente de lo que pensamos?

SARS-CoV-2 and *Aspergillus* pneumonia in kidney transplantation: More frequent than we think?

Sr. Director:

La aspergilosis pulmonar invasiva puede complicar algunas infecciones víricas, como la gripe, y comienza a evidenciarse como factor de mal pronóstico en pacientes coinfectados con neumonía por SARS-CoV-2.

Comentamos el caso de un varón de 67 años, con enfermedad renal crónica secundaria a glomerulonefritis focal y segmentaria, en hemodiálisis. En junio de 2020 recibe trasplante renal, realizándose inducción con basiliximab y tratamiento con tacrolimus, micofenolato y esteroides. Además asocia profilaxis con cotrimoxazol y valganciclovir.

Treinta días postrasplante se diagnostica por SARS-CoV-2. Se reduce la dosis de inmunosupresores y se inician azitromicina e hidroxicloroquina. El día +14 ingresa por fiebre e insuficiencia respiratoria. En la radiografía de tórax presenta infiltrados bilaterales y en la analítica presenta creatinina 1,5 mg/dL, PCR 72 mg/L, Hb 10,6 g/dL, linfocitos 340/ μL, dímero D 1,021 ng/mL e interleucina-6 31,9 pg/L. Al ingreso se suspende micofenolato y se inicia tratamiento con dexametosona + remdesevir + ceftriaxona + heparina profiláctica. Por criterios de gravedad se administra tocilizumab al tercer día de ingreso y se suspende tacrólimus el quinto día por mala evolución y por niveles supraterapéuticos.

El día +7 ingresa en la UCI por deterioro del nivel de consciencia e insuficiencia respiratoria que precisa ventilación mecánica. Se amplía cobertura con meropenem, amikacina, linezolid y voriconazol, manteniendo valganciclovir y soltrim profilácticos. Además de la persistencia de PCR positiva para SARS-CoV-2, en el broncoaspirado de rutina se halló *Aspergillus fumigatus* y el galactomanano en suero fue de 4,5. Dada la persistencia de niveles elevados de tacrolimus se sustituye voriconazol por isavuconazol intravenoso. Tras 13 días de ingreso el paciente presenta mala evolución con hemorragia cerebral masiva y fallece ese mismo día.

El Registro COVID-19 de la Sociedad Española de Nefrología (SEN) en noviembre 2020 reporta 2.474 pacientes en tratamiento sustitutivo renal, de los cuales un 37% son trasplantados renales[1]. Esta población es considerada de mayor riesgo debido a su estado de inmunosupresión y al contacto frecuente con centros sanitarios[2].

Los pacientes gravemente enfermos de COVID-19 presentan concentraciones más elevadas de citocinas proinflamatorias (IL-1, IL-2, IL-6 y factor de necrosis tumoral alfa) y antiinflamatorias (IL-4 e IL-10), con menor expresión de interferón-gamma y tienen un número más bajo de células CD4 y CD8[3]. Por ello, el riesgo de padecer coinfecciones fúngicas es mayor[4]. De hecho, se ha descrito una incidencia de aspergilosis invasiva de hasta un 0,65% dentro del primer año en trasplantados renales, con una tasa de mortalidad de hasta un 39% en las primeras 12 semanas[5].

A pesar del alto número de casos reportados de COVID-19, su asociación con aspergilosis invasiva ha sido poco descrita. El grupo europeo EORTC/MSG concluye que el diagnóstico de aspergilosis pulmonar asociada con la COVID-19 (APAC) constituye un reto, ya que las características radiológicas de la lesión invasiva fúngica se superponen a las alteraciones ya existentes por la neumonía viral por SARS-CoV-2[6,7]. Además, el elevado riesgo de generación de aerosoles limita en pacientes con COVID-19 la obtención de muestras respiratorias (broncoaspirado o lavado bronquioalveolar), por lo que el diagnóstico en muchas ocasiones se basa en el antígeno galactomanano en suero, considerado positivo un índice > 0,7[8].

El número de especies de *Aspergillus* spp. es muy numeroso, pero *Aspergillus fumigatus complex* es el agente etiológico más frecuente. El tratamiento de elección es el voriconazol. En nuestro caso se cambió a isavuconazol debido a la imposibilidad de la vía oral, su menor influencia en la actividad del