Acute hemorrhagic cystitis: assessment in pediatric first aid

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Acute hemorrhagic cystitis (AHC) is one of the most common causes of gross hematuria in the pediatric population, especially in males (43%) rather than in females (9%), and more frequently in early childhood (1). However, macroscopic hematuria is the main clinical sign of urinary tract infection (UTI) in the emergency department and can be present in up to 26% of the cases. Therefore, it is essential to recognize this condition and be put in differential diagnosis with other causes of gross hematuria that, differently from AHC, do not have the same self-limiting and benign course.

Etiology

Up to 20-50% of AHC are consequences of infections sustained by Adenovirus types 11 and 21 (but types 14, 34, 35, 3, 7 can also affect urinary tract epithelium). Bacteria, fungi, and parasites are less common causes of hemorrhagic cystitis. In a smaller percentage of the cases, AHC may be determined even by Influenza A virus, Cytomegalovirus (CMV) and bacteria (such as *Escherichia Coli* and *Klebsiella pneumoniae*) (2, 3). The other bacteria isolated and causing hemorrhagic cystitis are *Staphylococcus saprophyticus, Proteus mirabilis* and *Klebsiella species. Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus,* are also associated with AHC. The urothelium in *Candida* infection is more frequently covered with pseudomembranes or pale plaques, while infections by parasites are rarer. The implant of *Schistosoma haematobium* in the mucosa predispose to the development of squamous cell carcinoma of the urinary bladder. Calcified cysts of *Echinococcus granulosus* infiltrate the bladder wall causing hematuria (4).

AHC can also be the consequence of exposure to radiation or alkylating drugs such as cyclophosphamide, busulfan, chlorambucil, ifosfamide. Moreover, in immunocompromised patients, the reactivation of latent Polyoma BK virus (less frequently, even JC virus) may play an essential role in AHC. For this reason, immunocompromised patients and, more specifically, the pediatric population undergoing bone marrow transplantation are more likely to suffer from AHC. In these cases, the resulting severe bleeding can be a life-threatening event and deserves specific treatment and opportune prevention (5). Nevertheless, it is important to remind how adenovirus infections

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are possible causes of glomerular hematuria in the context of IgA nephropathy (6).

Other uncommon causes of AHC are vasculitis, amyloidosis and genetic syndromes (mutation of ITGB4 gene for integrin β4 subunit in epidermolysis bullosa). However, it is necessary to remark that in an important percentage of the cases, it is impossible to determine a causal agent for AHC (7,8). From an omic science-based perspective, many basic and clinical investigators tried to decipher the pathophysiological factors underlying acute hemorrhagic cystitis in children; this led to the identification of an intricate and complex interplay of genetic and non-genetic (immunomediated, metabolic) factors which may cause acute hemorrhagic cystitis or predispose/ contribute to this condition (9, 10). This complex disease model covering different potential factors is commonly observed in the aetiology of several complex and not yet fully understood pediatric conditions. However, the advent of next-generation and other related technologies led to an increased understanding of the monogenic causes underlying many of these childhood diseases (11-16).

Several different genes and cellular mechanisms have thus been identified in recent years, and this highlighted the importance of omic sciences in defining the clinical spectrum and the therapies tailored to many disorders of infancy (17-20). Notably, genes that regulate response to environmental factors or influence metabolic substrate or sub-cellular events have been revealed to be causative for previously neglected disorders (21-29). In addition, our understanding of the processes associated with rare and/or multisystemic abnormalities will be pivotal for targeted treatments and the development of personalized pediatrics, according to several examples (30-36).

Acute hemorrhagic cystitis due to Escherichia coli

Escherichia coli (*E. coli*) is the most common organism causing urinary tract infection (UTIs) in infants (about 80-85% of cases). Among the different strains of *E.coli,* uropathogenic *E. coli (*UPEC*)* is a normal commensal of the human gut that colonizes the urinary tract from the ascension of focally derived microorganisms through the urethra. UPECs are opportunistic intracellular pathogens resistant to innate immune responses that invade the uroepithelium thanks to fimbriae (or pili). There are two types of fimbriae, type 1 pilus and type P pilus. Both types of pili consist of major pilus protein subunit (pilus stalk) and several minor subunit proteins representing the actual adhesins (37). These pili are involved in the initial attachment of UPEC to the urinary tract mucosa and biofilm formation. Other bacterial cell surface virulence factors include flagellum and capsular lipopolysaccharide (LPS). However, UPEC elaborates on other secreted virulence factors such as adhesins, toxins, enzymes that play different pathogenic roles during infection.

Hemolysins and siderophores are responsible for the colonization of urinary tract infection and persistence despite the host immune response. On the other hand, another virulence factor is activating the epithelium defence system after the adherence to the surface of the bladder. The LPS of *E. coli* activates Toll-like receptors (TLR); as a consequence should be the stimulation of inflammatory factors transcription, cytokine production, neutrophil recruitment and finally, exfoliation of infected bladder epithelial cells. These virulence factors of UPECs are associated with antimicrobial resistance (38).

Clinical features

AHC is characterized by sudden-onset gross hematuria in an otherwise healthy child; hematuria may appear at the end of the beginning of the voiding act, or less frequently, it can be present during the whole micturition; the color of urine is generally bright red and presence of blood clots is frequent. Hematuria is generally associated with or preceded by dysuria, frequency, urgency, tenesmus, oppressive suprapubic pain, enuresis, but it can rarely be the only clinical feature of AHC. Fever is uncommon, but it can be present in a small percentage of cases, together with other symptoms of adenovirus infection (ocular, gastrointestinal or respiratory). Possible complications may be anemia and clots that may obstruct the urine flow, but in

the otherwise healthy child, these occurrences are uncommon. Symptoms generally last 3-7 days (however, they regress within 2 weeks), and the course is self-limiting (39, 40).

Differential diagnosis in pediatric first aid

The evaluation should start in the pediatric emergency department from clinical condition (generally good in AHC), suggestive symptoms (as described before) and patient history. It is necessary to exclude traumas, drugs exposition, familial hematuria (e.g. Alport disease, associated with a history of neurosensorial dumbness). In addition, it is crucial to investigate abdominal or flank pain (that may indicate urolithiasis, joint stenosis or renal vein thrombosis), concomitant pathological conditions (transplantation of solid organs or bone marrow), current or previous upper respiratory tract infections (whose presence may indicate IgA nephropathy or acute postinfectious glomerulonephritis respectively), bloody diarrhea (prodrome of a hemolytic uremic syndrome), petechiae (Henock-Shonlein purpura or other vasculitides), or already known malformations (e.g. nutcracker syndrome, renal cysts).

It is important to exclude causes of the dark-reddish color of urine that may mimic gross hematuria, such as exposure to some foods or substances (e.g., beetroot, anthocyanins, rifampicin), inborn errors of metabolism (porphyria, alkaptonuria), myoglobinuria (rhabdomyolysis) and hemoglobinuria (hematological diseases that cause intravascular hemolysis). In addition, the characteristics of hematuria are important to exclude causes of glomerular hematuria (in which are present tea/cola-colored urines, instead of pink/bright red urines of no glomerular hematuria). Moreover, it should be evaluated for the presence of hypertension and peripheral edemas to exclude the causes of nephrotic syndrome.

Urine analysis should be performed to evaluate the presence of red blood cells (whose morphology reveals the origin of the hematuria, since erythrocytes are dysmorphic if the hematuria is glomerular), pyuria (possible sign of UTI), proteinuria, casts (signs of GN), electrolytes (hypercalciuria is associated to gross hematuria up to 20% of the cases), and urine culture should be set up for a correct and complete diagnostic evaluation. First-step blood analysis should be comprehensive of CBC, reticulocytes count, serum creatinine, urea, albumin, bilirubin, LDH, CPK, cholesterol, serum electrolytes, C3, C4, coagulation profile, RCP, ESR, ASOT. HMGB1 serum level may be altered (41, 42). Abdominal, renal and bladder the US should be performed to exclude the presence of calculi or tumor masses. Once other causes are excluded, diagnosis of AHC can be easily performed (43).

Therapy

There are no specific guidelines for the AHC treatment. The role of antibiotics remains unclear, even though viruses are the most common cause of AHC, there is the hypothetical increased risk of bacterial colonization due to the damage of bladder epithelium and the alterations of the regular mechanics of urination, especially in girls or in people who have risk factors in developing complicated UTI. It is possible to choose broad-spectrum antibiotics if the pathogen responsible for AHC has not yet been identified with certainty. AHC supported by viruses and fungi is eradicated by administering specific antivirals or antifungals. Instead, for alkylating drug-related AHC, this condition may be prevented by administering specific antidotes such as classical 2-mercaptoethanesulfonic acid (Mesna) (44). melatonin administration may be a beneficial treatment (45-49).

REFERENCES

1. Decker DB, Karam JA, Wilcox DT. Pediatric hemorrhagic cystitis. J Pediatr Urol. 2009 Aug;5(4):254-64.
2. Taktak A, Acar B, Gür G, et al. Cytomegalovirus-related hemorrhagic cystitis in an immunocompetent child. Ren Fail. 2014 Aug;36(7):1148-50.
3. Lynch JP 3rd, Fishbein M, Echavarria M. Adenovirus. Semin Respir Crit Care Med. 2011 Aug;32(4):494-511.
4. Chang CB, Chang CC. Emphysematous cystitis: a rare cause of gross hematuria. J Emerg Med. 2011 May;40(5):506-8.
5. Paduch DA. Viral lower urinary tract infections. Curr Urol Rep. 2007 Jul;8(4):324-35.

6. Allen CW, Alexander SI. Adenovirus associated haematuria. Arch Dis Child. 2005 Mar;90(3):305-6.
7. Gander R, Asensio M, Guillén G, Royo GF, Bolaños A, Pérez M, Diaz-De-Heredia C, Benitez M, López M. Hemorrhagic cystitis after hematopoietic stem cell transplantation: A challenge for the pediatric urologist. J Pediatr Urol. 2018 Oct;14(5):366-373.
8. Riachy E, Krauel L, Rich BS, McEvoy MP, Honeyman JN, Boulad F, Wolden SL, Herr HW, La Quaglia MP. Risk factors and predictors of severity score and complications of pediatric hemorrhagic cystitis. J Urol. 2014 Jan;191(1):186-92.
9. Cassão VD, Reis ST, Pimenta R, et al. Single nucleotide polymorphism analysis in interstitial cystitis/painful bladder syndrome. PLoS One. 2019;14(4):e0215201. Published 2019 Apr 11.
10. Liu JC, Chen YT, Hsieh YJ, et al. Association of urinary ketamine and APOA1 levels with bladder dysfunction in ketamine abusers revealed via proteomics and targeted metabolite analyses. Sci Rep. 2021;11(1):9583. Published 2021 May 5.
11. Miraglia Del Giudice M, Maiello N, Decimo F, et al. Airways allergic inflammation and L. reuterii treatment in asthmatic children. J Biol Regul Homeost Agents. 2012;26(1 Suppl):S35-S40.
12. Khan MU, Khalid H, Salpietro V, Weber KT. Idiopathic intracranial hypertension associated with either primary or secondary aldosteronism. Am J Med Sci. 2013;346(3):194-198.
13. Salpietro V, Chimenz R, Arrigo T, Ruggieri M. Pediatric idiopathic intracranial hypertension and extreme childhood obesity: a role for weight gain. J Pediatr. 2013;162(5):1084
14. Piard J, Umanah GKE, Harms FL, et al. A homozygous ATAD1 mutation impairs postsynaptic AMPA receptor trafficking and causes a lethal encephalopathy. Brain. 2018;141(3):651-661.
15. Salpietro V, Lin W, Delle Vedove A, et al. Homozygous mutations in VAMP1 cause a presynaptic congenital myasthenic syndrome. Ann Neurol. 2017;81(4):597-603.
16. Sheldon CA, Paley GL, Xiao R, et al. Pediatric Idiopathic Intracranial Hypertension: Age, Gender, and Anthropometric Features at Diagnosis in a Large, Retrospective, Multisite Cohort. Ophthalmology. 2016;123(11):2424-2431.
17. Salpietro V, Perez-Dueñas B, Nakashima K, et al. A homozygous loss-of-function mutation in PDE2A associated to early-onset hereditary chorea. Mov Disord. 2018;33(3):482-488.
18. Pedullà M, Miraglia Del Giudice M, Fierro V, et al. Atopy as a risk factor for thyroid autoimmunity in children. J Biol Regul Homeost Agents. 2012;26(1 Suppl):S9-S14.
19. Cuppari C, Manti S, Chirico V, et al. Sputum high mobility group box-1 in asthmatic children: a noninvasive sensitive biomarker reflecting disease status. Ann Allergy Asthma Immunol. 2015;115(2):103-107.
20. Lionetti E, Francavilla R, Castellazzi AM, et al. Probiotics and Helicobacter pylori infection in children. J Biol Regul Homeost Agents. 2012;26(1 Suppl):S69-S76.
21. Chirico V, Rigoli L, Lacquaniti A, et al. Endocrinopathies, metabolic disorders, and iron overload in major and intermedia thalassemia: serum ferritin as diagnostic and predictive marker associated with liver and cardiac T2* MRI assessment. Eur J Haematol. 2015;94(5):404-412.
22. Bell S, Rousseau J, Peng H, et al. Mutations in ACTL6B Cause Neurodevelopmental Deficits and Epilepsy and Lead to Loss of Dendrites in Human Neurons. Am J Hum Genet. 2019;104(5):815-834.
23. Ruggieri M, Polizzi A, Strano S, et al. Mixed vascular nevus syndrome: a report of four new cases and a literature review. Quant Imaging Med Surg. 2016;6(5):515-524.
24. Efthymiou S, Salpietro V, Malintan N, et al. Biallelic mutations in neurofascin cause neurodevelopmental impairment and peripheral demyelination. Brain. 2019;142(10):2948-2964
25. Salpietro V, Ruggieri M, Sancetta F, et al. New insights on the relationship between pseudotumor cerebri and secondary hyperaldosteronism in children. J Hypertens. 2012;30(3):629-630.
26. Salpietro V, Ruggieri M. Pseudotumor cerebri pathophysiology: the likely role of aldosterone. Headache. 2014;54(7):1229.
27. Niccolini F, Mencacci NE, Yousaf T, et al. PDE10A and ADCY5 mutations linked to molecular and microstructural basal ganglia pathology. Mov Disord. 2018;33(12):1961-1965
28. Giacobbe A, Granese R, Grasso R, et al. Association

between maternal serum high mobility group box 1 levels and pregnancy complicated by gestational diabetes mellitus. Nutr Metab Cardiovasc Dis. 2016;26(5):414-418.
29. Ruggieri M, Polizzi A, Schepis C, et al. Cutis tricolor: a literature review and report of five new cases. Quant Imaging Med Surg. 2016;6(5):525-534.
30. Chirico V, Lacquaniti A, Salpietro V, et al. High-mobility group box 1 (HMGB1) in childhood: from bench to bedside. Eur J Pediatr. 2014;173(9):1123-1136.
31. Chelban V, Wilson MP, Warman Chardon J, et al. PDXK mutations cause polyneuropathy responsive to pyridoxal 5'-phosphate supplementation. Ann Neurol. 2019;86(2):225-240.
32. Salpietro V, Efthymiou S, Manole A, et al. A loss-of-function homozygous mutation in DDX59 implicates a conserved DEAD-box RNA helicase in nervous system development and function. Hum Mutat. 2018;39(2):187-192.
33. Granata F, Morabito R, Mormina E, et al. 3T Double Inversion Recovery Magnetic Resonance Imaging: diagnostic advantages in the evaluation of cortical development anomalies. Eur J Radiol. 2016;85(5):906-914.
34. Chirico V, Cannavò S, Lacquaniti A, et al. Prolactin in obese children: a bridge between inflammation and metabolic-endocrine dysfunction. Clin Endocrinol (Oxf). 2013;79(4):537-544.
35. Salpietro V, Zollo M, Vandrovcova J, et al. The phenotypic and molecular spectrum of PEHO syndrome and PEHO-like disorders. Brain. 2017;140(8):e49.
36. Steel D, Salpietro V, Phadke R, et al. Whole exome sequencing reveals a MLL de novo mutation associated with mild developmental delay and without 'hairy elbows': expanding the phenotype of Wiedemann-Steiner syndrome. J Genet. 2015;94(4):755-758.
37. Shah C, Baral R, Bartaula B, Shrestha LB. Virulence factors of uropathogenic Escherichia coli (UPEC) and correlation with antimicrobial resistance. BMC Microbiol. 2019 Sep 2;19(1):204. doi: 10.1186/s12866-019-1587-3.
38. Loghman-Adham M, Tejero HT, London R. Acute hemorrhagic cystitis due to Escherichia coli. Child Nephrol Urol. 1988-1989;9(1-2):29-32. PMID: 3075151
39. Mufson MA, Belshe RB, Horrigan TJ, et al. Cause of acute hemorrhagic cystitis in children. Am J Dis Child. 1973Nov;126:605-9
40. deVries CR, Freiha FS. Hemorrhagic cystitis: a review. J Urol. 1990 Jan;143(1):1-9.
41. Stein E, Elbadawi LI, Kazmierczak J, et al. Babesiosis surveillance - Wis¬consin, 2001-2015. MMWR Morb Mortal Wkly Rep. 2017; 66(26): 687-691. Different concentration of human cord blood HMGB1 according to delivery and labour: A pilot study
42. D'Angelo, G., Marseglia, L., Granese, R., Reiter, R.J., Gitto, E. Cytokine, 2018, 108, pp. 53–56. High mobility group box 1 and markers of oxidative stress in human cord blood. D'Angelo, G., Granese, R., Marseglia, L., Corsello, G., Gitto, E. Pediatrics International, 2019, 61(3), pp. 264–270
43. Brown DD, Reidy KJ. Approach to the Child with Hematuria. Pediatr Clin North Am. 2019 Feb;66(1):15-30.
44. Mehta A, Williams V, Parajuli B. Child with Dysuria and/or Hematuria. Indian J Pediatr. 2017 Oct;84(10):792-79
45. D'Angelo G, Chimenz R, Reiter RJ, Gitto E. Use of Melatonin in Oxidative Stress Related Neonatal Diseases. Antioxidants (Basel). 2020;9(6):477. Published 2020 Jun 2. doi:10.3390/antiox9060477
46. Carloni S, Proietti F, Rocchi M, et al. Melatonin Pharmacokinetics Following Oral Administration in Preterm Neonates. Molecules. 2017;22(12):2115. Published 2017 Dec 1.
47. Marseglia L, Manti S, D'Angelo G, et al. Potential use of melatonin in procedural anxiety and pain in children undergoing blood withdrawal. J Biol Regul Homeost Agents. 2015;29(2):509-514.
48. Gitto E, Marseglia L, D'Angelo G, et al. Melatonin versus midazolam premedication in children undergoing surgery: A pilot study. J Paediatr Child Health. 2016;52(3):291-295.
49. Impellizzeri P, Vinci E, Gugliandolo MC, Cuzzocrea F, Larcan R, Russo T, Gravina MR, Arena S, D'Angelo G, Gitto E, Montalto AS, Alibrandi A, Marseglia L, Romeo C. Premedication with melatonin vs midazolam: efficacy on anxiety and compliance in paediatric surgical patients. Eur J Pediatr. 2017 Jul;176(7):947-953.