Clinical Study

Hemolytic-uremic syndrome after Escherichia coli urinary tract infection: systematic review of the literature

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Abstract

Background Intestinal infections caused by a shigatoxin-positive Escherichia coli (mostly of the serogroups O26, O45, O103, O111, O121, O145 and especially O157) are a common cause of hemolytic-uremic syndrome. Forty years ago, hemolytic-uremic syndrome was first linked with an Escherichia coli urinary tract infection.

Methods We conducted a systematic review of the literature addressing the association between Escherichia coli urinary tract infection and hemolytic-uremic syndrome.

Results For the final analysis, we retained 23 original reports published since 1979. Five unselected pediatric case series addressed the possible occurrence of hemolytic-uremic syndrome after an Escherichia coli urinary tract infection among 266 cases and found the mentioned association in 8 (3.0%) cases. We also found 28 individual cases (17 female and 11 male subjects) of hemolytic-uremic syndrome preceded by an Escherichia coli urinary tract infection: 16 children aged from 2 days to 6.0 years and 12 adults aged from 22 to 75 years. Escherichia coli serotyping was performed in 16 cases. Testing for shigatoxin, performed in 17 cases, was positive in 13 cases. Testing for serotype O157, O103 and O145 was positive in 1, 1 and 2 cases, respectively. Serotyping for O26, O45, O111 and O121 was always negative.

Conclusions Hemolytic-uremic syndrome rarely occurs after an Escherichia coli urinary tract infection. It affects both children and adults and is mostly caused by a shigatoxin-positive germ.

Keywords Escherichia coli • Escherichia coli serotyping • Hemolytic-uremic syndrome • Shigatoxin • Urinary tract infection

Abbrevations None

Introduction

Hemolytic anemia with red blood cell fragmentation, thrombocytopenia and acute kidney injury characterize hemolytic-uremic syndromes [1]. The immense majority of childhood cases as well as many adulthood cases are precipitated by an infection [1]. Most cases are linked with an intestinal infection caused by a shigatoxin-positive Escherichia coli, mostly of the seven serogroups O26, O45, O103, O111, O121, O145 and especially O157 (often termed the "big seven group"), or, less frequently, a shigatoxin-positive Shigella dysenteriae [1, 2]. There is also a recognized association with an invasive pneumococcal disease [3].

Approximately 40 years ago, hemolytic-uremic syndrome was first linked with an Escherichia coli urinary tract infection [4]. Motivated by our experience [5, 6], we conducted a systematic review of the literature addressing the association between Escherichia coli urinary tract infection and hemolytic-uremic syndrome. The primary questions of this analysis were to document frequency, features and prognosis of hemolytic-uremic syndrome precipitated by Escherichia coli urinary tract infection. The characteristics of isolated Escherichia coli strains were also addressed.

Methods

Search strategy

Between April and June 2018, a search with no date limits of the Medical Subject Headings terms (h[a]emolytic-uremic syndrome OR thrombotic thrombocytopenic purpura OR h[a]emolysis) AND (urinary tract infection OR pyelonephritis OR prostatitis) AND (Escherichia coli OR E. coli OR Colibacillus) was conducted in the U.S. National Library of Medicine database. We also scanned the references of all included articles and our personal files for additional reports. We employed the principles underlying the U.K. Economic and Social Research Council guidance on the conduct of narrative synthesis and the "Preferred reporting items for systematic reviews and meta-analyses" statement [7].

Selection criteria

For the final analysis, we selected reports published as full-length articles or letters, which included original cases of hemolytic-uremic syndrome precipitated by an Escherichia coli urinary tract infection in subjects of both sexes without any age limit. Case series containing unselected patients with hemolytic-uremic syndrome addressing the possible occurrence of cases preceded by an Escherichia coli urinary tract infection were also included in the analysis. In some instances, authors of published reports were also asked to provide additional missing data. Reports published in languages other than Dutch, English, French, German, Italian, Portuguese,

or Spanish were excluded. Reports including patients previously exposed to drugs that have been implicated in causing hemolytic-uremic syndrome [8], patients with hemolytic-uremic syndrome immediately (≤7 days) preceded by diarrhea (with or without positive testing for shigatoxin in stool), by an invasive pneumococcal infection or by a non-Escherichia coli urinary tract infection were excluded. Cases of recurrent hemolytic-uremic syndrome and cases that were followed by an Escherichia coli urinary tract infection (usually secondary to the use of an indwelling bladder catheter) were also excluded. The possible occurrence of hemolytic-uremic syndrome in two or more first-degree relatives was also addressed. Strong emphasis was also put on the possible existence of an abnormal urinary tract. When more than one paper reported on the same patient or cohort, only the more comprehensive publication was retained.

Definitions - data extraction

The diagnosis of urinary tract infection and hemolytic-uremic syndrome were reviewed using the following recognized criteria.

Urinary tract infection was defined as Escherichia coli bacteriuria $\geq 10^4$ colony-forming units per milliliter from a sample collected by bladder catheterization or $\geq 10^5$ from a clean voided specimen. Information on results for the identification of Escherichia coli strains that produce shigatoxin or possess the serogroup O157, O26, O45, O103, O111, O121 and O145 was also collected.

Hemolytic-uremic syndrome was defined as (i) acute hemolytic anemia, (ii) microscopic evidence of red blood cell fragmentation in peripheral blood smear or elevation of lactate dehydrogenase, (iii) platelet count $\leq 150 \times 10^9$/L, and (iv) acute kidney injury. Kidney injury was categorized [9] as stage I, stage II and stage III.

Complete recovery was defined as normal blood pressure, circulating creatinine and urinalysis (without drugs).

Two authors independently extracted data on patients' characteristics, laboratory results, managements and outcomes. Disagreements were resolved by consensus.

Analysis

Results are given as frequency or as median and interquartile range (which includes half of the data points), as appropriate. The Fisher exact test was used to compare dichotomous variables and the Mann-Whitney–Wilcoxon rank-sum test to compare continuous variables. Statistical significance was assigned at $P<0.05$.

Results

Literature search results

The literature search process is summarized in Figure 1. For the final analysis, we retained 23 original reports [4-6,10-29] published since 1979 in English (N=19), French (N=2) or German (N=2). They had been reported from the following countries: France (N=6), Switzerland (N=6), The United States of America (N=3), Italy (N=2), Australia (N=1), Denmark (N=1), Republic of China (N=1), Spain (N=1), The Islamic Republic of Iran (N=1) and The Netherlands (N=1).

Five case series addressed the possible occurrence of hemolytic-uremic syndrome preceded by an Escherichia coli urinary tract infection among unselected pediatric hemolytic uremic syndrome patients [6, 11, 13, 25, 27]. Furthermore, the reports described 28 individually documented cases of hemolytic-uremic syndrome that were preceded by an Escherichia coli urinary tract infection [4-6, 10, 12, 14-24, 26, 28, 29].

Prevalence

The five above-mentioned case series included a total of 266 patients (146 girls and 120 boys 18 years or less of age) with hemolytic-uremic syndrome. The association with an Escherichia coli urinary tract infection was disclosed in 8 cases, resulting in a prevalence of 3.0%.

Presentation – course

The twenty-eight individual cases (17 female and 11 male subjects) of hemolytic-uremic syndrome preceded by an Escherichia coli urinary tract infection included 16 children aged from 2 days to 6.0 years and 12 adults aged from 22 to 75 years (Table 1). The case of a 75-year-old woman reported twice was considered only once [18, 19]. A blood culture was found to be positive for Escherichia coli in 8 out of 15 analyzed cases.

Testing for shigatoxin, performed in 17 cases, was negative in 4 and positive in the remaining 13 cases: both shigatoxin 1 and 2 (N=5), shigatoxin 1 (N=4), shigatoxin 2 (N=3), and unspecified (N=1). Escherichia coli serotyping was performed in 16 cases. The serogroup O157, O103 and O145 was positive in 1, 1 and 2 cases, respectively. Serotyping for O26, O45, O111 and O121 was always negative.

The acute kidney injury was severe (stage III) in approximately 60% of the cases. Acute renal replacement therapy was provided in 54% and plasma infusion (or exchange) in 29% of the cases. Chronic kidney disease developed in 25% and death in 3.6% of the cases. Finally, an abnormal urinary tract was found in 40% of cases, with vesicoureteral reflux being the most frequently observed abnormality.

The frequency of acute kidney injury, the use of renal replacement therapy and the tendency to develop a chronic kidney disease was similar in children

and adults. Plasma infusion (or exchange) was more frequently carried out in adult patients ($P<0.01$).

Discussion

This survey points out that hemolytic-uremic syndrome rarely may occur after Escherichia coli urinary tract infection. It is characterized as follows: a) it likely accounts for approximately 3% of pediatric cases of hemolytic-uremic syndrome; b) it affects both children 6 years or less of age and adults with a slight predilection for the female gender; c) it is often associated with an abnormal urinary tract, especially vesicoureteral reflux; d) it is mostly complicated by severe acute kidney injury; and e) it is frequently followed by a chronic kidney disease and is in rare instances fatal.

Hemolytic uremic-syndrome cases, which follow an intestinal infection, are caused by a shigatoxin-positive Escherichia coli [1, 2], mostly of the "big seven group" (O26, O45, O103, O111, O121, O145 and O157). The results of this analysis indicate that hemolytic-uremic syndrome linked to Escherichia coli urinary tract infection is also caused by shigatoxin-positive germs. On the contrary, no more than 25% of the cases are caused by the "big seven group".

Escherichia coli more commonly cause infections of urinary than of intestinal tract both in childhood and adulthood [30, 31]. Nonetheless, Escherichia coli urinary tract infections are an uncommon cause of hemolytic-uremic syndrome. This apparent discrepancy is related to the fact that Escherichia coli strains detected in patients affected by a urinary tract infection very rarely (≤1%) test positive for shigatoxin [32-34].

In hemolytic-uremic syndrome associated with either an intestinal or a urinary tract infection [1, 35], therapy is supportive, focusing on stabilizing the patient until natural disease resolution occurs and recovery begins. Most cases will be treated with careful fluid and electrolyte management, and medication for arterial hypertension. More severe cases may need renal replacement therapy. Despite a lack of evidence, plasma infusion or exchange is often used in cases with a nervous system involvement [1, 35]. Eculizumab, an antibody that blocks complement activation, has been successfully used in patients with complement-mediated hemolytic-uremic syndrome but its role in shigatoxin-positive cases is controversial [36].

Antimicrobials are not recommended for diarrhea-associated hemolytic-uremic syndrome [1, 35]. If hemolytic-uremic syndrome occurs after an Escherichia coli urinary tract infection, antimicrobials are indicated to prevent renal and systemic damage secondary to the infection. It is tempting to assume, however, that in this setting antimicrobials might induce

bacterial lysis and enhance toxin release, therefore negatively impacting on the course of hemolytic-uremic syndrome.

At least two limitations of this review should be acknowledged. First, it exclusively integrates data from single case reports or very small case series that were sometimes poorly documented. Second, recommended therapeutic strategies are extrapolated from management practices in diarrhea-associated hemolytic-uremic syndrome.

In conclusion, this analysis provides a substantial support for Escherichia coli urinary tract infections as a rare but established cause of hemolytic-uremic syndrome both in childhood and adulthood.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Figure 1 - Legend

Flowchart of the literature search process. The case of a patient reported on two occasions was counted only once [18, 19].