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pL4. Hematuria

Definition: Is the presence of at least 5 red blood cells (RBCs) per microliter of urine and occurs with a prevalence of 0.5-2 % among school-aged children.

The presence of 10-50 RBCs/ μ L by a urinary dipstick may suggest underlying pathology, but significant hematuria is generally considered as >50 RBCs/ μ L.

False negative results can occur in the presence of formalin (used as a urine preservative) or high urinary ascorbic acid concentrations (vitamin C intake >2000 mg/day).
False-positive results seen in alkaline urine (pH > 8), or contamination with oxidizing agents such as hydrogen peroxide used to clean the perineum before obtaining a urinary specimen.

Causes of hematuria:

A. Factitious hematuria (red urine but without presence of RBS in the urine):
1. Non-pathologic (urate crystals in infants, ingested foods, drugs, dyes)
2. Pathologic (hemoglobinuria from hemolytic anemia, myoglobinuria from rhabdomyolysis)

B. Glomerular causes:
1. Immunologic injury (Glomerulonephritis (GN) e.g., poststreptococcal GN, IgA nephropathy, membranoproliferative GN, systemic diseases)
2. Structural disorder (Alport syndrome, thin basement membrane disease)
3. Toxin-mediated injury: hemolytic uremic syndrome (HUS)

C. Tubulointerstitial/ Parenchymal causes:
1. Inflammation (interstitial nephritis, pyelonephritis)
2. Vascular (sickle cell trait/disease)
3. Structural (cyst rupture, Wilms tumor, urinary tract obstruction, renal trauma)

D. Lower urinary tract causes:
1. Inflammation (cystitis, hemorrhagic cystitis, urethritis)
2. Injury (trauma, stone)
3. Hypercalciuria

****Drug causing red urine:** Chloroquine, Deferoxamine, Ibuprofen, Iron, Metronidazole, Nitrofurantoin, Phenothiazines, Rifampin, Salicylates, and Sulfasalazine.

Acute Poststreptococcal Glomerulonephritis (APSGN):

It is a postinfectious complication of Group A β-hemolytic streptococcal infections.
It is a classic example of the **acute nephritic syndrome** characterized by the sudden onset of gross hematuria, edema, hypertension, and renal insufficiency.
It is one of the most common glomerular causes of gross hematuria in children and is a major cause of morbidity in group A β-hemolytic streptococcal infections.

ETIOLOGY AND EPIDEMIOLOGY:

APSGN follows infection of the throat or skin by certain **"nephritogenic"** strains of group A β-hemolytic streptococci. 97% of cases occur in less-developed countries.
Poststreptococcal GN commonly follows streptococcal pharyngitis during cold-weather months and streptococcal skin infections or pyoderma during warm-weather months.
This disease is most commonly sporadic although endemic attacks has been reported.

CLINICAL MANIFESTATIONS:

APSGN is most common in children ages 5-12 yr and uncommon before the age of 3 yr.

1. The typical patient develops an acute nephritic syndrome (gross hematuria, edema, hypertension, and renal insufficiency) 1-2 wk after a streptococcal pharyngitis or 3-6 wk after a streptococcal pyoderma.
2. The severity of kidney involvement varies from asymptomatic microscopic hematuria with normal renal function to gross hematuria with acute renal failure. Patients have various degrees of edema, hypertension, and oliguria depending on the severity of renal involvement.
3. Hypertensive encephalopathy cause blurred vision, severe headaches, altered mental status, or new seizures.
4. Pulmonary edema and heart failure occur due to hypertension and hypervolemia causing respiratory distress, orthopnea, and cough.
5. Peripheral edema typically results from salt and water retention and is common.
6. Nephrotic syndrome develops in <5% of childhood cases.
7. Nonspecific symptoms such as malaise, lethargy, abdominal pain, or flank pain are common.
8. The acute phase generally resolves within 6-8 wk. The urinary protein excretion and hypertension usually normalize by 4-6 wk after onset, but microscopic hematuria can persist for 1-2 yr after the initial attack.

Investigations:

1. Urinalysis :RBCs, RBC casts, proteinuria, and polymorphonuclear leukocytes.
2. Mild normochromic anemia due to hemodilutic and low-grade hemolysis.
3. Serum C3 level is decreased in >90% of patients in the acute phase, and returns to normal after 6-8 wk
4. Serum C4 level is normal, or only mildly decreased.
5. Serum creatinine and BUN increased due to renal insufficiency.
6. Evidence of a recent streptococcal infection by the following:
   A. Positive throat culture in acute infection but it might represent the carrier state.
   B. Serological tests: Rising antibody titer to streptococcal antigen(s) confirms diagnosis of acute streptococcal infection and these are:

i. Antistreptolysin O (ASO) titer is commonly elevated after a pharyngeal infection but rarely increases after streptococcal skin infections.
ii. Antideoxyribonuclease B level is The best single antibody titer to document skin streptococcal infection (pyoderma).
iii. Positive streptozyme screen (which measures multiple antibodies to different streptococcal antigens)

Serologic evidence for streptococcal infections is more sensitive than the history of recent infections and positive bacterial cultures for diagnosis of APSGN.

7. Brain MRI indicated in patients with suspected HT encephalopathy.
8. Chest x-ray for patients with signs of heart failure or respiratory distress.
9. Renal biopsy: indicated in:
    a. Presence of acute renal failure.
    b. Presence of nephrotic syndrome.
    c. Absence of evidence of streptococcal infection (-Ve throat culture and serological tests).
    d. Normal complement levels at onset.
    e. Persistent hematuria and proteinuria, decreased renal function, and/or a low C3 level for more than 2 mo after onset.

CLINICAL DIAGNOSIS: APSGN is Consider in the presence of:

1. Acute nephritic syndrome (gross hematuria, edema, hypertension, and renal insufficiency).
2. Evidence of recent streptococcal infection by culture or serological tests.
3. Low serum C3 level.

COMPLICATIONS: Acute complications result from:

A. Complication of hypertension : hypertensive encephalopathy which is reversible with appropriate management, but severe prolonged hypertension can lead to intracranial bleeding.
B. Complications of acute renal failure: heart failure, hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, seizures, and uremia.

PREVENTION:

1. Early systemic antibiotic therapy for streptococcal throat and skin Infections, to eradicate the infection but it does not eliminate the risk of GN.
2. Family members of patients with acute GN, especially young children, should be cultured for group A β-hemolytic streptococci and treated if positive.

TREATMENT:

1. Treatment of acute renal insufficiency and hypertension.
2. 10 day course of systemic antibiotic therapy with penicillin is recommended to limit the spread of the nephritogenic streptococci, but antibiotic therapy does not affect the natural history of APSGN.

PROGNOSIS:

1. Complete recovery occurs in >95% of children with APSGN.
2. Recurrences are extremely rare.

3. Mortality in the acute stage can be avoided by appropriate management of acute renal failure, cardiac failure, and hypertension.
4. Acute phase may be severe and leads to glomerulosclerosis and chronic renal disease in <2% of affected children.

HEMOLYTIC UREMIC SYNDROME (HUS)

HUS is characterized by the triad of **microangiopathic hemolytic anemia, thrombocytopenia,** and **renal injury** and is an important cause of acute kidney injury in children.
HUS is more common in pre-school and school age children but it can occur in adolescents and adults.

ETIOLOGY:

HUS can be classified according to its etiology in to two categories:
A. Typical or Diarrhea-associated HUS: It's the most common type of HUS. It is associated with a prodromal diarrheal illness (**often bloody**) then followed by clinical manifestations of HUS.
This diarrhea is commonly caused by verotoxin (VT)-producing *Escherichia coli* (most commonly ***E. coli* O157:H7**) but it could be caused by other *E. coli* strains as well as other bacteria such as *Shigella* VT which causes bloody diarrhea and HUS in 5-15% of affected children.

B. Atypical (non-diarrheal) HUS: Is HUS presenting without a preceding diarrhea. It may occur at any age. The clinical course is usually more severe than that of diarrhea-associated HUS. Atypical HUS can be secondary to the following:

1. Infection e. g *Streptococcus pneumoniae* and HIV infections
2. genetic and acquired defects in complement system.
3. Drugs e.g. cyclosporine and contraceptive pills.
4. Systemic diseases e.g. malignant HT, SLE, malignancy, bone marrow or organ transplantations and pregnancy.

PATHOGENESIS:

Microvascular injury with endothelial cell damage is characteristic of all forms of HUS.
In the diarrhea-associated HUS, enteropathic organisms produce either Shiga toxin or Shiga-like verotoxin which are directly cause endothelial cell damage.
Capillary and arteriolar endothelial cell damage in the kidney leads to localized thrombosis, particularly in glomeruli, causing a direct decrease in glomerular filtration.
Progressive platelet aggregation in the areas of microvascular injury results in consumptive thrombocytopenia.
Microangiopathic hemolytic anemia results from mechanical damage to red blood cells as they pass through the damaged and thrombotic microvasculature.

CLINICAL MANIFESTATIONS:

1. Typical diarrhea-associated HUS preceded by gastroenteritis with fever, vomiting, abdominal pain, and diarrhea (often bloody).
2. After 5-7 days of onset of gastroenteritis, patient develop sudden onset of pallor, irritability, weakness, and lethargy due to microangiopathic hemolytic anemia.
3. Oliguria can be present in early stages but may be masked by ongoing diarrhea.
4. Dehydration is often present; however some children have volume overload due to oliguria.
5. Hypertension may be due to volume overload and/or renal injury.
6. Central nervous system (CNS) involvement, including seizures, occurs in up to 25% of cases due to focal ischemia secondary to microvascular CNS thrombosis.
7. Other manifestations: pancreatitis, cardiac dysfunction, and colonic perforation.

INVESTIGATIONS:

I. EVIDENCE OF MICROANGIOPATHIC HEMOLYTIC ANEMIA:

1. CBC shows Anemia and Thrombocytopenia
2. Peripheral blood smear shows schistocytes, helmet cells, and burr cells
3. Increased indirect bilirubin
4. Increased reticulocyte count

II. EVIDENCE OF RENAL INJURY:

1. Increased serum creatinine
2. Presence of hematuria, proteinuria, pyuria, and casts on urinalysis

III. OTHER POTENTIAL FINDINGS:

1. Leukocytosis
2. Positive stool culture for *E. coli* O157:H7 but it might be negative at time of presentation of HUS.
3. Positive stool test for shiga-toxin
4. Elevated amylase and lipase enzymes due to pancreatitis.
5. Negative Coombs test

TREATMENT:

1. supportive therapy includes fluid replacement, control of hypertension, and treatme complications of renal insufficiency, including dialysis if indicated.
2. RBC transfusions in severe anemia.
3. Platelet transfusions should be avoided because they may add to the thrombotic microangiopathy and are indicated only in active hemorrhage.
4. Antibiotics and antidiarrheal agents may increase the risk of developing HUS.

PROGNOSIS: Most children (>95%) with diarrhea-associated HUS survive the acute phase and recover normal renal function, although some may have evidence of long-term morbidity.

Poor prognosis associated with non-diarrheal and familial HUS.