Acute lobar nephritis in children: Not so easy to recognize and manage

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Abstract

Acute lobar nephritis (ALN) is a localized non-liquefactive inflammatory renal bacterial infection, which typically involves one or more lobes. ALN is considered to be a midpoint in the spectrum of upper urinary tract infection, a spectrum ranging from uncomplicated pyelonephritis to intrarenal abscess. This condition may be difficult to recognize due to the lack of specific symptoms and laboratory findings. Therefore the disease is probably underdiagnosed. Computed tomography scanning represents the diagnostic gold standard for ALN, but magnetic resonance imagine could be considered in order to limit irradiation. The diagnosis is relevant since initial intravenous antibiotic therapy and overall length of treatment should not be shorter than 3 wk. We review the literature and analyze the ALN clinical presentation starting from four cases with the aim to give to the clinicians the elements to suspect and recognize the ALN in children.

Key words: Acute lobar nephritis; Children; Computed tomography; Magnetic resonance imagine; Upper urinary tract infection

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Core tip: Acute lobar nephritis (ALN) is a renal bacterial infection presenting difficult diagnosis due to the lack of specific symptoms and laboratory findings. Suspecting ALN in children with septic fever with or without clinical signs should be part of the diagnostic tool of clinicians. The diagnosis is relevant both to prefer intravenous antibiotic therapy and suggest an overall length of antibiotic treatment not shorter than 3 wk. We review the literature and analyze the ALN clinical presentation, with the aim to give to the clinician the elements to suspect, diagnose and accurately treat ALN in children.

INTRODUCTION
Acute lobar nephritis (ALN), also known as acute focal bacterial nephritis, is a localized non-liquefactive inflammatory renal bacterial infection, which typically involves one or more lobes[1,2]. It presents as an inflammatory mass without frank abscess formation[3]. ALN is considered to be a midpoint in the spectrum of upper urinary tract infection (UTI), a spectrum ranging from uncomplicated pyelonephritis to intrarenal abscesses[4]. According to some authors[5], this spectrum lacks a dynamic progressive nature and two patterns, based on computed tomography (CT) findings, are described: Simple ALN, which represents progression of acute pyelonephritis (APN), and complicated ALN, which may progress into renal abscess without or even with treatment[6]. The typical presentation of ALN shares some common clinical and laboratory features with both renal abscess and APN including septic fever, flank pain, sick appearance, nausea or vomiting, elevation of inflammatory markers, pyuria and bacteriuriain[1-7]. According to a recent study patients with ALN are febrile for longer after hospitalization and have more nausea/ vomiting symptoms than those with APN[8]. A timely diagnosis is relevant because under-diagnosis may result in late renal scarring, and/or evolution in renal abscess, which in turn may lead to hypertension or renal failure[9].

CASE REPORT
Case 1
A 4-year-old girl was admitted with a 2 d history of high fever and abdominal pain. Fever persisted despite oral amoxicillin-clavulanate treatment prescribed by her family physician.

The patient’s medical history was remarkable for an episode of APN 2 years before, successfully treated with oral antibiotics. At admission she was febrile and looked sick with an unremarkable physical examination. White blood cell count (WBC) was 24,600/mm3, C-reactive protein (CRP) 24.52 mg/dL (normal range 0-5 mg/dL) and erythrocyte sedimentation rate (ESR) 97 mm/h (normal range 0-20 mm/h). Urinalysis revealed leukocyturia (200 WBC/mm3 at standard optical microscopy) without bacteriuria. Urine cultures were repeatedly negative as was chest X-ray. Abdominal ultrasonography (US) showed a nonspecific diffuse increased echogenicity of the right kidney, which appeared smaller than the left; no focal masses were detected on both kidneys. A CT scan showed multiple lesions with irregular margins and variable size in the right kidney, which appeared hypodense after contrast medium administration (Figure 1). ALN was diagnosed and a three weeks intravenous antimicrobial therapy with ciprofloxacin and tobramycin was started with clinical improvement. Voiding cystourethrography (VCUG) and dimercaptosuccinic acid (DMSA) renal scintigraphy performed 6 mo later showed a reflux with associated renal scarring nephropathy.

Case 2
A 13-year-old boy was admitted after 3 episodes of high fever in the last 2 mo, without an obvious focus. During the first episode, the boy was confused and agitated; CT and magnetic resonance imagine (MRI) of the brain, cerebrospinal fluid (CSF) examination, electroencephalography (EEG), chest X-rays, urinalysis with standard optical microscopy, urine culture were normal; blood test showed increased CRP (10.8 mg/dL). Empirical therapy with acyclovir and ceftriaxone was started with clinical success, maintained for 5 d and switched to oral treatment for 5 more days. The boy was discharged with a diagnosis of suspected encephalitis. After 2 wk of wellness, the patient presented fever, vomiting and drowsiness. MRI of the brain was normal. Chest X-ray and echocardiogram were also normal. CRP was 13.9 mg/dL. Abdominal US was negative. Empirical treatment with ceftriaxone was started with rapid improvement. The boy was discharged after 5 d of intravenous therapy; at home he continued with 3 oral amoxicillin-clavulanate. Four days after the end of treatment, he was admitted for the third time with a high fever in the last 2 mo, without an obvious focus. CRP was 10.4 mg/dL. Urinalysis revealed leukocyturia (200 WBC/mm3), C-reactive protein (CRP) 24.52 mg/dL (normal range 0-5 mg/dL), and erythrocyte sedimentation rate (ESR) 97 mm/h (normal range 0-20 mm/h). Urinalysis revealed leukocyturia (200 WBC/mm3 at standard optical microscopy) without bacteriuria. Urine cultures were repeatedly negative as was chest X-ray. Abdominal ultrasonography (US) showed a nonspecific diffuse increased echogenicity of the right kidney, which appeared smaller than the left; no focal masses were detected on both kidneys. A CT scan showed multiple lesions with irregular margins and variable size in the right kidney, which appeared hypodense after contrast medium administration (Figure 1). ALN was diagnosed and a three weeks intravenous antimicrobial therapy with ciprofloxacin and tobramycin was started with clinical improvement. Voiding cystourethrography (VCUG) and dimercaptosuccinic acid (DMSA) renal scintigraphy performed 6 mo later showed a reflux with associated renal scarring nephropathy.

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Case 3
A 17-year-old girl was admitted with a 2 d history of high fever, chills and pain on the left flank. On physical examination, she looked sick; the abdomen was soft and painful in the left flank. WBC count was normal (8340/mm$^3$), while there was a marked increase of both CRP (25.33 mg/dL) and ESR (62 mm/h). Urinalysis revealed leukocyturia (50 WBC/mm$^3$ at standard optical microscopy) but no bacteriuria. Urine and blood cultures were repeatedly negative. Abdominal US (Figure 4) showed an increased volume of the left kidney with a small hyperechoic mass (1 cm diameter), consistent with ALN. Intravenous therapy with ceftriaxone and tobramycin was started; after 48 h the patient was still febrile and sick, therefore treatment was switched to intravenous ciprofloxacin, teicoplanin and cefotaxime. There was a slow and gradual clinical improvement and after 72 h, the fever disappeared. Intravenous antimicrobial therapy was maintained for three weeks.

Case 4
A 6-year-old girl presented with a 24 h history of high fever, vomiting and abdominal pain on the left iliac fossa without diarrhea. Physical examination was unremarkable except for an abdominal evoked pain in the left iliac fossa. WBC was 21.190/mm$^3$, CRP 34 mg/dL. Urinalysis with standard optical microscopy was negative and therefore urine cultures were not performed. Chest X-ray was normal. Abdominal US showed an increased volume of both kidneys; CT scan was then performed revealing multiple wedge-shaped cortical hypodense lesions in both kidneys, more represented in the left one (Figure 5). Intravenous therapy with ceftriaxone was started; after 48 h, the patient was still febrile and sick, so intravenous netilmicin was added with clinical improvement. The therapy was continued for 10 d, then switched to oral ciprofloxacin, for additional 2 wk.

DISCUSSION
When should ALN be suspected?
ALN may be difficult to recognize due to the frequent absence of specific signs and symptoms and the wide differential diagnosis (Table 1). Specific symptoms as flank pain or laboratory findings (positive urinalysis and bacteriuria) may be absent. Therefore the disease is probably underdiagnosed. Nevertheless, fever with septic features (sick appearance, malaise, chills, and nausea or vomiting), increased inflammatory indexes...
**Table 1 Clinical and laboratoristic acute lobar nephritis differential diagnosis**

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Differential diagnosis with other conditions such as abdominal abscess, infected intestinal duplication and nephrolithiasis need radiological evaluation. ALN: Acute lobar nephritis; APN: Acute pyelonephritis.

**How to confirm the ALN diagnostic suspect?**

Sonographically, ALN presents as focal hypoperfused lesions with poorly defined irregular margins disrupting cortico-medullary differentiation. Masses can be respectively hyper-, iso-, or hypo-echogenic depending on the temporal sequence of the lesions and resolution of the disease\[11,12\]. Renal pole swelling has also been reported\[11,13,14\]. Although renal US is an effective diagnostic method, there may be false positive and false negative results\[13,15\], and often a false negative US is frequently reported. A study\[16\] demonstrated that isolated severe nephromegaly (defined as renal length of greater than mean +3 SD for age) has a diagnostic sensitivity of 90%; the finding of a focal renal mass increases the sensitivity to 95% (compared with the gold standard CT), with a specificity of 86.4%. The diagnostic gold standard for ALN is CT scanning\[11,13,15,17\]. CT images of the involved areas are usually normal in non-enhanced scans but appear as wedge-shaped, poorly defined regions of decreased nephrogenic density after contrast medium administration\[11,12\]. With the aim to avoid radiation exposure, MRI should be strongly considered\[18\], in fact CT scan results in a small but not negligible increased lifetime risk for cancer\[19,20\]. Enhanced ultrasound in the near future could replace CT scan because of comparable sensitivity and specificity. Unfortunately second-generation contrast agents are off-label in children, even if there are no adverse events documented in literature\[21\]. Static scintigraphy with DMSA, the gold standard to identify renal involvement in UTI, has no application in the differential diagnosis of this condition showing only focal uptake defects with the means of a hypoactive area in the renal parenchyma. In the literature, positive urine culture rate has a wide variability; the bias probably depends on the ability of different centers to diagnose ALN, particularly when urinalysis and urine are negative. When positive, results are not different from other forms of UTI: The most represented urinary pathogen is *Escherichia coli* in 40%-75% of the cases, while other gram negative germs are less frequent; gram positive germs infection is unusual\[8,10,22\].

**Treatment**

Treatment is based on antibiotic therapy. Empiric approach, before antibiogram response when available, should be targeted at gram negative germs. Intravenous administration is recommended at least until 2 to 3 d after defervescence with a possible switch to oral treatment. A study suggested that a 3 wk antimicrobial therapy protocol should constitute the treatment of choice for all radiographically documented patients with ALN\[22\]. Surgical intervention is needed in the 25% of the cases where the lesion turns to renal abscess\[23\].

**Integrating literature evidence and daily clinical practice: The diagnostic clues**

These 4 cases presented with high fever, toxic appearance and abdominal pain. Only 1 case presented with flank pain, a specific UTI symptom not reliable before age of 6-8 years. Furthermore, as a confounding factor, urinalysis showed leukocyturia only in 2 cases, both with no bacteriuria at microscopy and negative urine cultures (one of these children started antibiotic treatment prior to admission). The other 2 patients presented negative microscopic and dip stick urinalysis. In case 4, urine cul-
Fever without sources—abdominal pain—poor general condition

Clinical evaluation and anamnesis are suggestive of recognizable illnesses? (see Table 1)

Yes Confirm diagnosis and start the specific treatment

No Not confirmed

Positive urinalysis?

Yes Urine culture and urinary tract infection therapy

No

Positive inflammatory indexes?

Yes Abdomen ultrasound suggestive of abdominal abscess, appendicitis, infected urachal cyst/intestinal duplication, nephrolithiasis, pelvic inflammatory disease or ALN?

No Consider viral causes and re-evaluation after 6-12 h or pancreatitis

Yes Confirm diagnosis and start the specific treatment

No

Abdomen ultrasound suggestive of abdominal abscess, appendicitis, infected urachal cyst/intestinal duplication, nephrolithiasis, pelvic inflammatory disease or ALN?

No Perform renal CT or MRI

Yes Suggestive of ALN?

No

Yes Confirm diagnosis and treatment

Figure 6 Diagnostic algorithm to suspect and then recognize acute lobar nephritis in children. ALN: Acute lobar nephritis; CT: Computed tomography; MRI: Magnetic resonance imagine.
that could be used to suspect and then recognize ALN in children (Figure 6).

COMMENTS

Background
Climicians often take on challenge with septic fever without clear clinical signs; the authors report four cases presenting with acute lobular nephritis (ALN), an underestimated condition, with the aim to give to the clinicians the instruments to suspect and diagnose ALN. A timely diagnosis is relevant because under-diagnosis may result in late renal scarring, and/or evolution in renal abscesses, which in turn may lead to hypertension or renal failure.

Research frontiers
Important areas of research could be the evaluation of the sensitivity and specificity of both magnetic resonance and intravenously enhanced ultrasound in diagnosing ALN with the aim to avoid computed tomography and then to spare radiations.

Innovations and breakthroughs
In literature there is lack of data about ALN in childhood. The authors report four cases of pediatric ALN, rising diagnostic and therapeutic issues.

Applications
All children with septic fever with or without abdominal pain should raise in the clinicians the suspect of deep bacterial infection. For a correct diagnosis it is essential both performing urinalysis before antibiotic therapy and abdominal imaging.

Terminology
Enhanced ultrasound is a free radiation imaging technique consisting in instillation of microbubble in bladder or vein emphasizing structures. Unfortunately, its use in children is still off-label.

Peer-review
This is a series of 4 cases with acute lobular nephritis in children discussing the clinical presentation, radiological features, treatment and management issues.

REFERENCES
28. Allen JW, Song J, Velcek FT. Acute presentation of infected urachal


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