Decreased concentrating capacity in children with febrile urinary tract infection and normal 99mTc-dimercaptosuccinic acid scan: does medullonephritis exist?

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Background: **Although 99mTc-dimercaptosuccinic acid (DMSA) scan is considered the gold standard for the diagnosis of acute pyelonephritis (AP), sometimes it produces false results in children with clinical features of AP. There are no studies on the comparison of the sensitivity of DMSA and concentrating capacity test.**

Methods: **Eighty-five infants with AP of less than one year old were studied to evaluate whether they had real AP or not. Data were compared between infants with an abnormal (group A, *n*=64) and those with a normal DMSA scan (group B, *n*=21) respectively. A DDAVP test was performed for each infant.**

Results: **All the infants in both groups presented a high level of C-reactive protein and fever (≥38ºC). There were no differences in clinical and analytical variables except C-reactive protein level in the two groups. Both groups exhibited a low urinary osmolality (87.5% in the group A *vs.* 85.7% in the group B). The patients with normal DMSA and decreased concentrating capacity have some renal parenchymal damage and not only a lower urinary infection. Of the infants with an abnormal DMSA scan, 33.9% showed renal scars after 6-12 months. No infant with a normal DMSA scan showed scars. The biochemical variables in both groups of infants were not related to vesicoureteral reflux.**

Conclusion: **Infants with AP, normal DMSA scan and low concentrating capacity may be characterized by a localized infection in the medulla (medullonephritis) or by a false negative DMSA scan.**

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Introduction

Urinary tract infection (UTI) was considered until the 1930s as a primitive infection of the renal pelvis per se, with a secondary injury of the renal parenchyma.[1] In the thirties, it was proved "that the primary focus of infection is in the kidney itself",[2] which is why the disease was called acute pyelonephritis (AP).

Febrile UTI started to be successfully treated with the use of the first antibiotics and biochemical tests were specially designed to distinguish between lower UTI and AP. In addition to fever, these tests were performed in terms of the total number of neutrophils, erythrocyte sedimentation rate (ESR),[3,4] C-reactive protein (CRP) level,[4,5] maximum urinary osmolality[4,6-12] and the excretion of certain tubular proteins.[13,14]

With the appearance of isotopic techniques, 99mTc-dimercaptosuccinic acid (DMSA) scan has been accepted as the gold standard test for AP diagnosis,[15,16] and the evaluation of secondary renal scars (scar nephropathy). However, children with symptoms and biochemical markers of AP still present an unexpectedly normal DMSA scan. Garin et al[5] argue that these patients are

infants with cystitis who have been misdiagnosed as having AP because of the low sensitivity of laboratory tests. This is why they recommend DMSA renal scan as the test of choice to diagnose AP in children.[5] However, these researchers do not include maximum urinary osmolality in their practice, which we have analyzed thoroughly in this work.

Methods

Study subjects

An ambispective [retrospective (n=70) and prospective (n=15)] study was conducted in all infants younger than one year of age (44 males, 41 females) hospitalized in the Pediatric Department of the Nuestra Señora de Candelaria University Hospital with an episode of clinically suspected AP between January 2008 and December 2011. The criteria for inclusion in this study were as follows: 1) Infants who had at least two urinary tests for pyuria and bacteriuria and one positive urine culture with growth of only one bacterium and a concentration higher than 100 000 UFC/mL;[17,18] 2) Infants who had a fever higher than 38°C[17,19] and exhibited CRP levels higher than 20 mg/L;[17,20] 3) Infants who had a DMSA scan performed less than 10 days after admission; and 4) Infants who had underwent a concentrating capacity test after desmopressin (DDAVP) test performed less than 10 days after admission. Six infants without urine culture due to previous antibiotic treatments were also included because they were subjected to a DMSA scan and met the other criteria.

In addition, the ratios of ESR, albumine/creatinine, N-acetyl-beta-glucosaminidase (NAG)/creatinine, and calcium/creatinine were considered when available. These ratios were obtained from an isolated sample 48 hours after the decline of the fever. A voiding cystourethrography was performed for 76 children after the end of antibiotic treatment. Exclusion criteria included history of nephrourologic disease, prematurity, and genetic disease.

DDAVP test

A DDAVP test was performed 48 hours after the ending of parenteral saline administration. According to the standard protocol, 10 μg of intranasal DDAVP was administered at 9 hours. Three urine samples were then collected. When two samples were available, the test was discontinued eight hours later.[21,22] The highest osmolality value among the three measurements was taken as the test result. In order to reduce the risk of water intoxication, the liquid intake during the day of the test was restricted to half from 6 hours to18 hours.

Laboratory techniques

CRP, ESR, calcium and creatinine were measured by standard methods. Urine osmolality was measured by freezing point depression with an Osmo Station OM-6050 osmometer (Menarini Diagnostics, Florence, Italy). Albumin was measured by a nephelometric technique. NAG was determined by an enzymatic colorimetric method based on the hydrolysis of NAG-dichlorophenol sulfonephthalein (Boehringer Mannheim, Germany).

Normal values

The normal values used as a reference to the maximum urine osmolality were the standard values previously reported elsewhere.[23] Normal values published by other authors were used as ratios of albumin/creatinine and NAG/creatinine respectively.[24,25]

Statistical methods

The Kolmogorov-Smirnov test was used to study the distribution of the variables. When they fitted a normal distribution, data were presented with mean value and standard deviation. The other quantitative variables were expressed in terms of median and interquartile ranges. Bivariate techniques were used for the initial evaluation of contrasts. Thus, Student's t test or the Mann-Whitney U test was conducted to compare two quantitative variables. Fisher's exact test was used to compare the frequencies between the qualitative variables. A probability of less than 0.05 was considered statistically significant. All tests were performed using SPSS statistical software (SPSS v19.0, SPSS Inc., USA).

Results

The average age of infants at admission was 4±3.1 months (range: 0.5-12 months). Sixty-four of 85 infants showed an abnormal DMSA scan with hypocaptation areas at the cortical level (group A). The remaining 21 infants had a normal scan (group B). The most frequently cultured bacteria was *Escherichia coli* (n=73, 85.9%). Other bacteria were *Proteus* (n=2), *Klebsiella* (n=2), *Enterobacter* (n=1), and *Pseudomona* (n=1).

Clinical and biochemical parameters in both groups are shown in Table 1. Fifty-six of the 64 infants (87.5%) in the group A, and 18 of the 21 infants in the group B (85.7%) had a low maximum osmolality (not significant). Urine albumin excretion was high in 22 of 47 (46.8%) in the group A and in 36.8% in the group B, although the median of the albumin excretion values were twice as high in the group A. NAG was high in 64% infants in the group A and in 52.6 % in the group B, but the median NAG excretion was doubled in the group A.

During the follow up, 16 infants in the group A were

Table 1. Clinical and biochemical parameters in both groups of infants with abnormal DMSA scan and with normal DMSA scan

Variables	Abnormal DMSA scan	Normal DMSA scan	*P*
Age (mon)	3.0 (5.7) (*n*=64)	3.4 (3.7) (*n*=21)	ns
Temperature (ºC)	39.0 (1.0) (*n*=64)	39.0 (1.1) (*n*=21)	ns
Time with fever before going to the hospital (h)	21.0 (28.0) (*n*=64)	24.0 (54.0) (*n*=21)	ns
CRP (mg/dL)	12.7±7.9 (*n*=64)	7.5±3.8 (*n*=21)	0.004
ESR (mm/h)	60.3±31.5 (*n*=46)	73.8±36.9 (*n*=12)	ns
Maximum urine osmolality with desmopressin (mOsm/kg)	453.9±155.3 (*n*=64)	474.1±150.3 (*n*=21)	ns
Albumin/creatinine ratio (µg/µmol)	26.3 (41.6) (*n*=47)	11.6 (35.8) (*n*=19)	ns
NAG/creatinine ratio (U/g)	40.5 (72.7) (*n*=50)	19.7 (32.2) (*n*=19)	ns
Calcium/creatinine ratio (mg/mg)	0.29±0.23 (*n*=45)	0.27±0.24 (*n*=15)	ns

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate: NAG: N-acetyl-beta-glucosaminidase; ns: not significant; DMSA: 99mTcdimercaptosuccinic acid.

Table 2. Clinical and biochemical parameters in infants without VUR

Variables	Anomalous DMSA scan	Normal DMSA scan	*P*
Age (mon)	3.9 (6.3) (*n*=42)	3 (6) (*n*=14)	ns
Temperature (ºC)	39 (0.9) (*n*=42)	39 (1.1) (*n*=14)	ns
Time with fever before going to the hospital (h)	24 (40) (*n*=42)	36 (56.5) (*n*=14)	ns
CRP (mg/dL)	13.2±8.5 (*n*=42)	6.9±2.6 (*n*=14)	<0.001
ESR (mm/h)	61.7±27.9 (*n*=33)	81.7±34.3 (*n*=10)	ns
Maximum urine osmolality with desmopressin (mOsm/kg)	455.4±150.4 (*n*=42)	499.3±168.8 (*n*=14)	ns
Albumin/creatinine ratio (µg/µmol)	18.3 (54.5) (*n*=29)	9.7 (32.7) (*n*=12)	ns
NAG/creatinine ratio (U/g)	37.6 (71.1) (*n*=32)	21.8 (27.5) (*n*=12)	ns
Calcium/creatinine ratio (mg/mg)	0.28±0.24 (*n*=29)	0.29±0.28 (*n*=10)	ns

Children with VUR and those without any voiding cystourethrogram performed have been excluded. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate: NAG: N-acetyl-beta-glucosaminidase; ns: not significant; DMSA: 99mTcdimercaptosuccinic acid; VUR: vesico-ureteral-reflux.

Table 3. Clinical and biochemical parameters in patients with anomalous DMSA scan (group A) in relation to the presence of VUR or not (*n*=58)

Variables	VUR	Absence of VUR	*P*
Age (mon)	3.1 (3.5) (*n*=16)	3.9 (6.4) (*n*=42)	ns
Temperature (ºC)	39 (0.65) (*n*=16)	39 (0.9) (*n*=42)	ns
Time with fever before going to the hospital (h)	24.0 (36.0) (*n*=16)	24.0 (40.0) (*n*=42)	ns
CRP (mg/dL)	13.2±6.6 (*n*=14)	13.2±8.5 (*n*=42)	ns
ESR (mm/h)	63.3±40.0 (*n*=11)	61.8±27.9 (*n*=33)	ns
Maximum urine osmolality with desmopressin (mOsm/kg)	443.3±189.9 (*n*=16)	455.4±150.4 (*n*=42)	ns
Albumin/creatinine ratio (µg/µmol)	40.4 (37.0) (*n*=12)	18.3 (54.5) (*n*=29)	ns
NAG/creatinine ratio (U/g)	25.8 (79.4) (*n*=12)	37.6 (71.1) (*n*=32)	ns
Calcium/creatinine ratio (mg/mg)	0.28±0.19 (*n*=10)	0.28±0.24 (*n*=29)	ns

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate: NAG: N-acetyl-beta-glucosaminidase; ns: not significant; DMSA: 99mTcdimercaptosuccinic acid; VUR: vesico-ureteral-reflux; DMSA: 99mTcdimercaptosuccinic acid.

diagnosed with vesicoureteral reflux (VUR) (16/58, 27.6%). Only one infant in the group B had VUR (1/15, 6.7%). Eighteen of 53 (34.0%) infants in group A showed renal scarring on the second DMSA scan. None of the infants in group B had any residual renal scarring (0/15).

To detect whether VUR influences the results of the study, we excluded the data of infants with VUR and those without voiding cystourethrogram (Table 2). The results were similar to those described in Table 1. The statistical analysis was also repeated for infants with an abnormal DMSA scan (group A). Infants with VUR were compared with those without (Table 3).

Discussion

The infants in both groups exhibited a high CRP, fever (≥38ºC) and a positive urine culture, and most of the infants (87.5% in the group A *vs.* 85.7% in the group B) had a low concentrating capacity. There was no difference in maximum urinary osmolality between the two groups (Table 1). Since the concentrating capacity was closely related to the renal medulla, the infants with a low concentrating capacity showing either a normal or abnormal DMSA scan had damage of the renal parenchyma in addition to a lower UTI.

In the group B only three infants had a normal DMSA scan and a normal concentrating capacity. As they had a high CRP and fever, a lower UTI is not a likely case but cannot be ruled out. Garin et al[5] reported that 33% of infants under two years old, with clinical and biochemical lower UTI showed AP manifestations at DMSA scan; and 22% of the infants with AP had no manifestations at DMSA, and they were diagnosed with a lower UTI (maximum osmolality tests were not included).[5] Although DMSA has been considered the gold standard for AP confirmation,

discordant findings were already reported in the 1970s.[15,16]

Concerning the concentrating ability, it is well-known that it is impaired by AP in humans.[4,6-12] Furthermore, this defect has been demonstrated in experimental pyelonephritis several times.[26-29] The renal concentrating ability depends on a proper delivery of glomerular ultrafiltrate to the tubules, a hypertonic medullary interstitium, a structurally intact countercurrent medullary mechanism and a normal water permeability of the collecting tubules in response to vasopressin.[30] The concentrating capacity is then strongly dependent on the renal medulla.[31] The mechanism through which the concentrating ability in children with AP is affected remains unknown. Rodionova et al[32] found that the urinary excretion of AQP2 increases as a result of infection and returned to normal after treatment. This suggests that a defect proximal to the collecting duct may be responsible for polyuria in AP children. Increased urinary AQP2 levels suggest that a compensatory activation of AQP2 may occur in AP.

Maximum urinary osmolality was the most sensitive parameter for AP diagnosis in the present study. We observed that a high percentage of children with AP and abnormal DMSA scan (87.5%) had a decreased urinary osmolality. The sensitivity of CRP and ESR for the diagnosis of AP was 59% and 73%, respectively.[20] And procalcitonin is estimated to be 78%-83.3%.[33,34] Procalcitonin was considered, by some authors, the most reliable biological marker for the early prediction of renal parenchymal inflammation in children with a first episode of UTI,[34] but the maximum urinary osmolality was not included.

NAG is an enzyme from the cells of the renal proximal tubule that appears in the urine when there is a cellular aggression. Its utility in AP diagnosis is not clear. It is known that albumin excretion is a marker of glomerular dysfunction, which is reabsorbed in the proximal tubule, so that theoretically could also be a marker of tubular dysfunction. In the present study although net values were not statistically significant, patients with abnormal DMSA scan showed much higher urine albumin and NAG levels than those with normal DMSA scan. This might indicate a lesion at the cortex level in patients with an abnormal DMSA scan.

In the present study, *Escherichia coli* is the most frequently cultured bacteria in both groups as reported in other studies. However, the presence of bacteria with a variable capacity to join different glycolipid kidney receptors may be possible. The types of receptors may be different in each kidney structure. Thus, Virkola et al[35] described that receptors for type 1C fimbriae are present at the distal tubules and collecting ducts level in the kidney but not at the glomerular or proximal tubule level. In addition, it has been reported that medullary collecting tubule cells are the main site of bacterial adhesion and initiation of the inflammatory response, elicited by uropathogenic *Escherichia coli* (UPEC) in a mouse experimental model.[36] Moreover, Chassin et al[37] demonstrated that UPECs invading the kidney specifically bind to the apical surface of collecting duct cells, mainly to intercalated cells. Analysis of signaling pathways revealed that UPECs stimulated the expression of proinflammatory mediators in the medullary collecting ducts via TLR4-mediated, MyD88-dependent, TRIF-independent NF-kB and MAPK activated pathways.[37] Theoretically, if the infection is stopped when bacteria are at the medullary collecting duct level, its progression to the more proximal nephron level could be avoided.

In the present study, 6.7% of the patients with normal DMSA scan exhibited VUR, but 27.6% of the patients with abnormal DMSA scan showed VUR. This finding has been previously reported.[38] In the present study, the biochemical findings in both groups were not related to the absence or presence of VUR. Lee et al[39] compared the results of DMSA scan with those of multi-detector row computed tomography. They found that DMSA scan was effective in diagnosing AP in only 68% of children with AP.

In summary, the results of this study have two possible explanations. First, possibly there were infants with AP and false negative (normal) DMSA findings similar with Lee et al's study. Second, bacterial infection causing inflammation is mainly located in the renal medulla where DMSA is not absorbed. The etiological factors could be: 1) Parenchyma infection is caused by bacteria carrying fimbriae with an specific affinity to certain urothelial receptors in the renal medulla; and 2) The participation of defense mechanisms in the medullar collecting tubule cells, which are able to prevent the progression of infection to the proximal nephron level. This entity could be named medullonephritis.

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