

RENAL DYSFUNCTION DETECTED BY BETA-2 MICROGLOBULIN URIA IN SICK NEONATES

K.P. Mehta, U.S. Ali, L. Shankar, D. Tirthani and M. Ambadekar

From the Nephrology Division and Research Department, Bai Jerbai Wadia Hospital for Children and Research Center, Parel, Bombay 400 012.

Reprint requests: Dr. Kumud P. Mehta, Nephrology Division, Bai Jerbai Wadia Hospital for Children, Parel, Bombay 400 012.

*Manuscript received: Oct 31, 1995; Initial review completed: March 25, 1996;
Revision accepted: August 28, 1996.*

Objective: To assess renal involvement in sick neonates referred to Neonatal Intensive Care Unit (NICU) using standard renal parameters and urinary beta₂ microglobulin (B₂M) excretion. **Design:** Descriptive study. **Setting:** Level II NICU and Nephrology Division of Pediatric Tertiary hospital. **Subjects:** Forty six term sick neonates transferred for neonatal care and forty healthy term neonates who served as normal controls for urinary B₂M excretion. **Methods:** Standard tests including estimation of BUN, serum creatinine, blood pH, serum bicarbonate, serum and urinary electrolytes, urine output, and urinalysis. Urinary B₂M levels were estimated from urine collected on day 1 (D₁) and day 3 (D₃) in all and 18 neonates were tested on day 7 (D₇) by radio-immunoassay method. **Results:** Statistically significant elevation of mean values of urinary B₂M were noted when sick neonates were compared with normal controls irrespective of primary disease, indicating tubular dysfunction (41/46=90%), whilst only 7 of these (17%) had abnormalities indicating renal involvement when judged by standard tests. Very high levels of urinary B₂M were noted with birth asphyxia (n=9), sepsis (n=8) and renal disease (n=7). Transient elevation of urinary B₂M was noted in meconium aspiration syndrome (n=4). Ten surgical cases with non renal congenital malformations showed high urinary B₂M and 12/18 tested on D₇ had persistently high urinary B₂M due to multiple factors. **Conclusions:** Elevated urinary B₂M in 90% sick neonates with apparently normal renal parameters in majority (34/41) indicates subclinical proximal tubular dysfunction especially in neonates with asphyxia, sepsis and congenital malformations. Persistent elevation of urinary B₂M appear to be a sensitive diagnostic indicator for defining a group of neonates with subtle renal tubular dysfunction, the clinical relevance of which on long term basis is a subject for future study.

Key words: Renal dysfunction, Tubular involvement, Neonates, Urinary B₂M microglobulin.

PERINATAL stresses such as hypoxia, sepsis, hemorrhage lead to underperfusion of the kidney and proximal tubules are extremely vulnerable to hypoxic injury. The spectrum of renal damage ranges from oliguric or nonoliguric renal failure to renal tubular dysfunction which can be detected by traditional tests or low molecular weight proteinuria such as beta₂

microglobulinuria(1-7). B₂M is a small polypeptide with a molecular weight of 11,800 daltons which occurs in all body fluids, is filtered freely by glomeruli and is reabsorbed almost completely (99.9%) by proximal tubules in health. Increased excretion of urinary B₂M is a sensitive indicator of renal tubular dysfunction. This study was designed to assess renal functions by

traditional methods and by estimation of urinary B₂M excretion in full term sick neonates admitted to Neonatal Intensive Care Unit (NICU) to detect renal dysfunction.

Subjects and Methods

Forty six sick full term neonates (gestational age between 37-40 weeks and birth weight 2.6-3.4 kg) born outside and referred to NICU were the subject of this study. Forty healthy term neonates served as control for urinary B₂M levels.

Protocol

Clinical assessment on admission included vital parameters, evidence of dehydration, shock, hypothermia, circulatory insufficiency and perusal of clinical data along with investigations done prior to referral to NICU.

Investigations done on admission included standard renal parameters such as monitoring of urine output to establish oliguria, estimation of BUN, serum creatinine, serum and urinary electrolytes, blood pH and serum bicarbonate levels, complete blood count, urinalysis and urine culture. Blood cultures and appropriate imaging study were performed whenever required.

Urinary B₂M estimation: Within 12 hours of admission (or delivery in healthy term neonates) a urine sample was collected using urinary bags on day 1 and day 3 in 46 sick and 40 healthy term neonates; 18/46 sick neonates were retested for urinary B₂M on day 7. Within half hour of collection of urine, urine pH was adjusted between 7-8 by adding 0.1 N NaOH and then stored at -80°C. Urinary B₂M was estimated by double antibody competitive radioimmunoassay technique using the kits supplied by Pharmacia, Uppsala, Sweden. Appropriate administration of oxygen, fluid and electrolytes, antibiotics and surgical intervention was planned in the management of the sick

babies. Statistical analysis was done by unpaired Student's *t* test and Mann Whitney test.

Results

The primary conditions requiring admission to NICU in the 46 sick neonates are summarized in *Table I*. Statistically significant ($p < 0.001$) elevation of mean values of urinary B₂M (mg/L) was observed in sick neonate when compared with controls, irrespective of the underlying condition (Normal D₁-1.58 ± 0.30; D₃-1.27 ± 0.28 and sick neonates D₁-12.1 ± 9.7; D₃-10.2 ± 11). There was concordance between day 1 and day 3 values in majority of cases. Forty one out of 46 (90%) had significantly high urinary B₂M and 5 cases had values less than 2 SD (1 case each of vomiting, imperforate anus, diaphragmatic hernia, intestinal perforation and abscess).

Out of 41 cases with elevated urinary B₂M, signifying proximal tubular dysfunction, only 7(17%) showed evidence of renal disease by standard clinical and laboratory investigations (*Table II*). Thus 34 cases had subtle subclinical renal dysfunction evidenced only by B₂ microglobulinuria. Very

TABLE I—Reasons for Admissions to NICU.

Medical (32)	Surgical (14)
Birth asphyxia (9)	Gastrointestinal anomalies (6)
Septicemia (8)	Neural tube defects (4)
Meconium aspiration (4)	Hydrocephalus (1)
Hyperbilirubinemia (4)	Obstructive uropathy (1)
Cardiorespiratory disorders (4)	Respiratory (1)
Renal problems (3)	Multiple anomalies (1)

Figures in parentheses indicate numbers of cases.

TABLE II—Renal Diseases Detected by Traditional Methods* (7/41-17%)

Age (days)	Primary disease	Renal problem	Urinary B ₂ M (mg/L)	
			D ₁	D ₇
1	Operated for tracheo-esophageal fistula + sepsis	Urinary infection, azotemia	26.7	12.8
5	—	Posterior urethral valves + urinary infection	3.3	—
5	Septicemia	Acute renal failure + urinary infection	4.95	0.15
1	Imperforate anus	Urinary infection	10.3	3.2
1	Meningomyelocele	Urinary infection	8.5	3.6
21	Septicemia	Azotemia	8.1	0.9
3	Asphyxia	Oliguria + hematuria	40	3.0

* Abnormal urinalysis, urine culture, BUN >20 mg/dl, serum creatinine >1 mg/dl, oliguria.

high mean values of urinary B₂M (mg/L) were observed in babies suffering from birth asphyxia (n=9; 18.7±11.8); sepsis (n=8; 15.4±13) and renal problems (n=7; 14.6±13.7). A transient elevation of urinary B₂M was noted in 4 cases of meconium aspiration with normal values on day 3 and in 2 cases of septicemia (Table II) denoting recovery. Significantly high urinary B₂M levels were noted in 10/13 cases of congenital malformations, 4 of whom had abnormal renal parameters (Table II). Elevated urinary B₂M values were noted in 12/18 babies retested on day 7; seven of these had congenital malformations (4 operated within 48 hours of admission for meningomyelocele-2, tracheo-esophageal fistula-1 and imperforate anus-1). Five babies suffering from severe asphyxia (n=2), sepsis (n=1), kernicterus (n=1) and congenital heart disease (n=1) had persistently elevated urinary B₂M on day 7 (Table III).

Of the 38 babies who received aminoglycosides, gentamicin or amikacin was given for 3-21 days in 35 babies while

both were used sequentially in 3 babies. Of these, 4 had values of urinary B₂M below 2 SD (2.5, 2.5, 2.3 and 1.0 mg/L). Two cases of septicemia with raised urinary B₂M and

TABLE III— Persistent High Urinary B₂M Levels on day 7 in 12/18 cases

Medical (5)	Surgical (14)
Severe birth asphyxia (12)	Meningomyelocele with urinary infection (1)
Severe sepsis (1)	Operated tracheo-esophageal fistula with sepsis (1)
Severe kernicterus (1)	Imperforate anus with urinary infection (1)
Congenital heart disease (1)	Hirschsprung's disease with sepsis (2) Encephalocele (1) Spinabifida + Hydrocephalus (1)

Figures in parentheses indicate number of cases.

abnormal renal parameters like azotemia and urinary infection were treated with aminoglycosides and recovered fully with normal values of urinary B₂M on day 7. Hence it seems that aminoglycosides did not play a major role leading to renal tubular dysfunction.

Discussion

Low molecular weight proteinuria is used to detect renal tubular dysfunction or injury in several diseases like perinatal problems, drug toxicity (aminoglycosides, ifosamide, cadmium), reflux nephropathy, diabetes mellitus and screening for congenital malformations(5-12). In our study we assessed all the sick neonates who were admitted to level 2 NICU for management of perinatal problems, and observed a very high frequency of elevated urinary B₂M in 90% of sick babies when compared with healthy normal term neonates. The renal involvement could be confirmed by traditional tests in only 7 (17%) of sick neonates whilst in the remaining 34 the standard tests did not reveal abnormalities but the urinary B₂M values were significantly high indicating subclinical renal tubular dysfunction. The possibility of poor transport facilities contributing to the subtle renal dysfunction cannot be ruled out as the sick

neonates were transported from maternity homes 5-20 km away from our hospital. The high levels of urinary B₂M in babies suffering from birth asphyxia, sepsis and renal diseases is similar to earlier observations(5,6,9). Urinary B₂M has proved useful in differentiating meconium aspiration syndrome from transient tachypnea of newborn and severe birth asphyxia, all 3 presenting with respiratory distress in newborn (*Table IV*). In our study also transient elevation of urinary B₂M was observed in 4 cases of MAS, whilst persistently elevated urinary B₂M was noted in 2 cases of birth asphyxia on day 7 as has been observed by others(5,6,7).

Multiple factors seem, to play a role in disturbing the tubular function in many sick babies like hypoxic ischemic insults, sepsis, urinary tract infection, drugs and operative procedures including anesthesia in 10 cases of congenital non renal malformations (4 operated). The nephrotoxicity due to aminoglycosides is well known. Serious toxicity leading to nonoliguric renal failure and Fanconi syndrome with high doses given for prolonged duration to subclinical and transient effects as evidenced by increased B₂ microglobulinuria are described(10-12). The frequency of amino glycoside nephrotoxicity is thought

TABLE IV—Comparison of Data on Urinary B₂M Excretion in Sick Neonates.

Author (Reference)	No. of sick babies	Gestational age	Diagnosis	% with elevated B ₂ M excretion
Tack <i>et al.</i> (5)	109	Preterm + term	Asphyxia + respiratory distress	40.7 (56% in asphyxia)
Cole <i>et al.</i> (6)	35	Full term	Meconium aspiration	49
Tsukahara <i>et al.</i> (7)	19	Preterm + full term	Meconium aspiration + transient tachypnea	Elevated in meconium aspiration
Present study	46	Full term	Asphyxia, sepsis, meconium aspiration and surgical cases	90

to be lower in neonates and infants(11,12). In our study, 38/46 subjects received aminoglycosides because of a common practice of using parenteral ampicillin and gentamicin/amikacin prophylactically in sick babies. However, its use cannot be blamed for elevated urinary B₂M because 4 babies who received 3-21 days of treatment had normal levels of urinary B₂M and raised urinary B₂M levels on day 1 are unlikely to occur with 1-2 injections of aminoglycoside therapy as seen in 17 sick babies admitted within 24 hours of birth. Persistently elevated values of urinary B₂M on day 7 seem to be due to severe perinatal medical problems in five cases and in seven subjects related to congenital malformations with urosepsis compounded by drugs and operative trauma (*Table III*).

To conclude, we report a high frequency of renal tubular dysfunction as evidenced by elevated urinary B₂M values in 41/46 (90%) sick newborns admitted to NICU. Highest values were found in babies suffering from birth asphyxia, sepsis or renal disease. Majority of babies did not exhibit overt renal abnormalities when standard tests were used, hence the renal dysfunction is subclinical and subtle. Persistently abnormal values on day 7 in 7 babies with congenital malformations could be due to multiple factors including operative procedures in the first few days. The role of aminoglycosides in renal dysfunction in our study is ambiguous. Estimation of urinary B₂ microglobulin before discharge is useful to define a group of newborns with subclinical renal dysfunction; the clinical relevance of subtle and subclinical renal dysfunction in sick neonates and its long term effects is a subject for future study.

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