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## Urinary N-Acetyl-β-D-Glucosaminidase Excretion in Asphyctic Newborns-Does it Predict the Development of Acute Renal Failure?

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**Abstract:** Urinary N-acetyl-β-D-glucosaminidase (NAG) levels of twenty healthy full-term newborns and of seventeen full-term newborns with perinatal asphyxia were evaluated within the first 48 hours of life. Urinary NAG levels and NAG indices (urinary NAG/urinary creatinine ratio) were significantly higher in newborns with perinatal asphyxia than control group ( $p<0.001$ ). Four patients who developed an acute renal failure (ARF) had higher urinary NAG levels; but this

increase was not found to be significant comparing to the NAG enzymuria in 13 other asphyctic newborns with normal renal functions. It is concluded that NAG enzymuria is an early sensitive indicator of proximal renal tubular damage and perinatal asphyxia but it does not predict the further deterioration in renal functions and the development of ARF.

**Key Words:** perinatal asphyxia, urine, kidney, N-acetyl-b-D-glucosaminidase

### Introduction

Perinatal asphyxia is the major cause of acute renal failure (ARF) in neonates. The renal proximal tubules have a high metabolic activity and are extremely sensitive to hypoxia (1,2). Renal function deteriorates in a spectrum from mild tubular dysfunction to acute tubular necrosis depending on the severity of hypoxic insult. It is essential to evaluate renal function at an early stage to stabilize fluid and electrolyte balance which is of great importance to infants with hypoxic-ischemic encephalopathy (3). Yet, it is not quite easy to evaluate neonatal renal function accurately. First of all, 7% of healthy neonates may urinate as late as the second day of life and non-oliguric ARF is not uncommon during neonatal period. Secondly, serum BUN and creatinine levels determined during the first 24 hours of life reflect the maternal levels not those of the neonate and also increased levels of serum bilirubin and pyruvic acid in sick neonates may cause deviation in colorimetric assessment of serum creatinine level. Lastly, fractional sodium excretion (FeNa) which is an important parameter to differentiate prerenal and renal ARF should be cautiously interpreted in pretermes, and in neonates receiving diuretics, aminophylline and intravenous fluid with high sodium content (2-4).

Renal proximal tubular cells are rich in N-acetyl-β-D glucosaminidase (NAG) which is one of lysosomal

glucosidases. It has been shown that an injury to proximal tubular cells for whatever reason causes high urinary concentrations of this enzyme (enzymuria) (5).

We planned a study in neonates surviving perinatal asphyxia by measuring urinary excretion of NAG. The aim of this study was to determine the deleterious effect to proximal tubular cells and whether enzymuria correlates with perinatal asphyxia.

### Patients and Method

Seventeen full-term infants (10 males, 7 females) born at 38-41 weeks of gestational age admitted to the Neonatal Intensive Care Unit of Ege University Medical School, Department of Pediatrics were included in this study. The criterion for perinatal asphyxia was one or more of the following –5 minute Apgar score, lower than 5- intrauterine severe bradycardia-deterioration of biophysical profile-need of delivery room cardiopulmonary resuscitation –postnatal documented metabolic acidosis ( $pH<7.25$ ) and meconium staining –elevated lactate dehydrogenase, brain-myocardium isoenzyme of creatine phosphokinase (CPK-MB) which are considered markers for perinatal asphyxia (6,7).

Premature infants were excluded since nephrogenesis is not completed before 35th week of gestation. Gestational age was determined on the basis of last

menstrual date and postnatally by Dubowitz scoring scale (8). Urine samples were collected in sterile bags within the first 48 hours of life, before the initiation of aminoglycoside treatment and were stored at -20°C.

Renal function tests consisted of monitoring hourly urine excretion, urine osmolarity, assessment of serum urea and creatinine levels glomerular filtration rate ( $GFR=0.45 \times \text{Body length(cm)} / \text{serum creatinine}$ ), urinary NAG excretion (U/L), NAG index (urinary NAG(U/dl) / urinary creatinine (mg/dl)) and assessment of FeNa in infants who developed ARF. Oliguria (urine flow less than 1ml/kg/hour for at least 48 hours), serum creatinine level higher than 1.5 mg/dl and FeNa greater than 3.5% were the criteria to establish a diagnosis of renal paranchymal ARF (9,10).

The study group was divided into two; group I consisting of those with perinatal asphyxia without ARF, group II consisting of those with prinatal asphyxia and ARF. Twenty healthy full-term infants without perinatal asphyxia and predisposition to tubulopathy comprised the control group.

Serum and urinary cratinine and sodium were determined by autoanalyzer (Falcor-Menarini), and by electrolyte analyzer (Spotlyte-Menarini) respectively. Urinary NAG level was determined by colorimetric method utilizing 3-cresolsulphaphytaleinyl-N-acetyl-β-D-glucosaminide as substrate to measure the level 3-cresolsulphaphytalein sodium photometrically (Eppendorf photometer) at 580 nm (Boehringer-NAG, Cat. No: 875406) (11).

Data were analysed using the Statistical Package programe (Epistate). Significance was tested using Wilcoxon rank sum test and analysis of variance, differences between groups were tested using the least significant difference test at the 1% level.

**Results**

Clinical features of the study and control groups were summarised on Table I. Study and control groups were similar with regard to gestational age, birth weight and mode of delivery.

Renal type ARF developed in 4 (23.5%) infants in the study group at 2.8±0.5 days of life. None of them needed peritoneal dialysis and all carried out medical treatment.

Table 1. Clinical data of infants studied on days 1-2.

	Asphyxiated infants	Control infants	p Value
n	17	20	
Gestational age(weeks)	38.8 (38-40)	39.2 (38-41)	NS*
Birth weight (g)	3400 (2600-3800)	3540 (2750-3950)	NS
Mode of delivery:			
Spontaneous (n)	7	9	NS
Caesarian section (n)	10	11	NS
Apgar score:			
At 1 minute	2.6 (0-6)	8.1 (7-10)	<0.01
At 5 minutes	4.6 (2-7)	9.4 (8-10)	<0.01

\* Non significant

Seizures were observed in 7 infants with hypoxic-ischemic encephalopathy (HIE) in of whom ARF developed. Five (29.4%) infants presented with irritability, depression of neonatal reflexes and feeding intolerance in 2 of whom ARF developed. Two infants one with and one without ARF died at days 2 and 5 postnatally.

Biochemical data of the infants in the study group is summarised on Table 2. Mean serum creatinine level in group II was significantly higher than that in group I in accordance with significantly lower GFR and hourly urine flow in group II (p<0.01) Mean urinary NAG excretion of 17 infants with asphyxia was 27.75 ±23.2 U/L (range 5.1-74.8) which was significantly higher than that of the control group (1.61±0.22 U/L (range 0.2-2.1)) (p<0.0001). NAG index, too, was significantly higher in the study group (0.089 ± 0.062 U/mg creatinine (range 0.01-0.2) vs 0.0061 ±0.021 U/mg creatinine (range 0.001-0.0089); p<0.0001)(Table 2).

Urinary NAG excretion was 24.98 ±20.13 U/L (range 5.1-74.8) in group I (without ARF) and 28.25 ±29.31 U/L (range 6.3-70.6)in group I (with ARF) which were statistically similar (p>0.05). NAG index (0.081±0.058 U/mg creatinine (range 0.01-0.19) in group I and 0.112 ±0.071 U/mg creatinine (range 0.041-0.2) in group II) was also statistically similar between the study groups (p>0.05) (Table 2).

**Discussion**

Measurement of several tubular markers (retinol-binding protein, β2-microglobulin, myoglobinuria etc.)

	Control infants	Asphyxiated infants	
	(n=20)	Group I (n=13)	Group II (n=4)
Serum creatinine Concentration (mg/dl)	0.62 (0.4-0.9)	0.78 (0.5-1.1)	2.35(1.7-4.3)
Glomerular filtration rate (ml/min/1.73 M <sup>2</sup> )	5.28(24.5-57.35)	31.34(2.45-46.8)	9.21(13.12-5.33)
Fractional sodium Excretion (%)	Not measured	Not measured	31(12-69)
Urine output (ml/kg/hour)	Not measured	2.1 (1.5-2.7)	0.6 (0.3-0.8)
Urinary NAG excretion (U/L)	1.61 (0.2-2.1)	24.98 (5.1-74.8)	28.25 (6.3-70.6)
NAG indeks (U/mg creatinine)	0.0061 (0.001-0.0089)	0.081 (0.01-0.19)	0.112 (0.041-0.2)

Table 2. Results of biochemical tests in the study group and control

NAG: N-acetyl-β-D-glucosaminidase

were found useful in diagnosis and follow-up of renal failure. We aimed to explore the potential value of NAG enzymuria to predict ARF that perinatal asphyxia may cause.

Being a lysosomal enzyme, NAG, which is present in several viscera other than kidney, is not filtered across the glomerular membrane because of its high molecular weight (130000-140000 daltons) (5). Since it is more abundant in tubular cells compared to lower urinary tract, increase in urinary excretion of NAG reflects renal tubular damage. NAG originating from other viscera is cleared from the circulation by the liver. Urinary NAG excretion is a good indicator of neonatal renal tubular function for the following reasons: Firstly, urinary NAG is completely of renal origin even if glomerular permeability increases. Secondly, urine does not include the inhibitors and activators of this enzyme. Thirdly there is no difference in the urinary levels between preterm (34-37 weeks) and full-term infants, and lastly urinary NAG excretion does not decrease with aging during the neonatal period (5, 12, 13).

NAG enzymuria has been extensively used in evaluation of neonatal renal tubular function. Sheu et al (14) investigated the effect of unconjugated hyperbilirubinemia on renal tubuli and Watanabe et al (15) explored aminoglycoside nephrotoxicity by measuring urinary NAG excretion.

Oxygen consumption of renal proximal tubular cells is very high because of a great variety of functions and subsequent high metabolic activity; that is why tubular cells are very sensitive to both chronic and es-

pecially to acute hypoxia (1). Acute perinatal asphyxia which may present with a wide spectrum of clinical findings from simple meconium staining of the amniotic fluid to multiorgan failure is the major cause of renal tubular injury in neonates.

When proximal tubular cells which are rich in lysosomal due to their high metabolic rate are injured, lysosomal NAG diffuses directly to the filtered urine (12).

Mannarino et al measured amniotic NAG activity in fetuses with chronic hypoxia and intravertine growth retardation which was increased due to fetal tubular injury (16). Csathy et al on the other hand showed tubular injury in polycythemic neonates and premature infants with respiratory distress syndrome by measuring increased urinary NAG excretion (17). Watanabe et al were the first group to show increased NAG enzymuria in term infants with acute perinatal asphyxia (18). Adamovich et al showed that NAG excretion decreased by day 7 in term and preterm infants with perinatal asphyxia when treated with thyroxine which improved renal functions (19). Chen et al showed increased NAG enzymuria in meconium stained infants despite absence of neurologic symptoms and interpreted this increase as an indicator of mild perinatal asphyxia (20). NAG enzymuria was significantly increased in infants with perinatal asphyxia in our study group, be it associated with neurologic symptoms or not. NAG enzymuria is a good indicator of proximal tubular injury even in mild perinatal asphyxia.

Roberts et al showed that NAG enzymuria increased by 18 fold in term and preterm infants sur-

living perinatal asphyxia with ARF. This increase was 12 fold in those without ARF but they concluded that even if NAG enzymuria is a specific indicator of tubular injury, it is not of great importance in either early diagnosis of ARF or prediction of ARF development in perinatal asphyxia. They also showed that urinary excretion of retinol-binding protein and myoglobin was much more specific in early diagnosis of ARF compared to NAG enzymuria (21). In concert with Roberts' findings, we also failed to show a statistically significant increase in NAG enzymuria in infants with perinatal asphyxia who subsequently developed ARF compared to those without ARF.

However NAG enzymuria of those with ARF was somewhat higher than that of the group without ARF. We also conclude that the level of NAG enzymuria is not of great importance in predicting ARF development after hypoxic insult at an early stage. However, NAG enzymuria is considered to be a very sensitive indicator of renal tubular damage even if decrease in GFR as an indicator of ARF is not observed.

In conclusion we recommend that NAG may be used as a marker of perinatal asphyxia and tubular damage, since it is a good indicator of proximal tubular cell injury and readily measured in spot urine.

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