นิพนธ์ต้นฉบับ

Reversal of elevated urinary N-acetyl-β-glucosaminidase in an asymptomtic, severe form of glomerulonephropathy with vasodilators.

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Buranasiri K, Saleekul P, Futrakul P, Thamaree S, Kingwatanakul P, Sensirivatana R, Watana D, Futrakul N, Panichpun S. Reversal of elevated urinary N-acetyl-β-glucosaminidase in an asymptomtic, severe form of glomerulonephropathy with vasodilators. Chula Med J 1993 Jan; 37(1): 21-27

Tubular enzymuria determined as urinary N-acetyl-β-glucosaminidase has been noted to be elevated in both mild and severe forms of NS. During remission, normal value of urinary NAG was observed in mild form of NS, whereas high values of NAG were still observed in one-third of the cases in the severe form of NS. Further reduction of urinary NAG could be achieved with therapeutic vasodilators in this latter group of patients-suggesting a hemodynamically mediated trigger being responsible for the tubular injury.

Key words: *Glomerulonephritis, Tubular enzymes, Vasodilators.*

Reprint request : Buranasiri K, Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.
Receiver for publication. October 14, 1992.

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ชนิษฐ บูรณศิริ, พรพิมล สาลีกุล, ประสิทธิ์ ฟูตระกูล, โสภิต ธรรมอารี, พรชัย กิ่งวัฒนากุล, รัชนี เซ็นศิริวัฒนา, เทวี วัฒนา, นริสา ฟูตระกูล, โสภณ พานิชพันธ์. การแก้ไขระดับเอ็น-อะเซ็ทติล-บีต้า-กลูโคสามินิเดส ที่สูงผิดปกติในปัสสาวะของผู้ป่วยไตอักเสบอย่างรุนแรงที่ไม่มีอาการ ด้วยยาออกฤทธิ์ขยายหลอดเลือด จุฬาลงกรณ์เวชสาร 2536 มกราคม; 37(1): 21-27

การศึกษาในผู้ป่วยไตอักเสบชนิดเนพโฟรสิส พบค่า N-acetyl-β-glucosaminidase สูงผิดปกติในปัสสาวะ ขณะที่กำลังมีไข่ขาวรั่วมาก ความผิดปกตินี้จะหายไปเองในผู้ป่วยเนพโฟรสิสที่ตอบสนองดีต่อยา Prednisolone แต่ในผู้ป่วยที่มีลักษณะโรครุนแรงและดื้อต่อยา เช่น พวก FSGS, MPGN หรือ DPGN ความผิดปกติของ N-acetyl-β-glucosaminidase อาจยังคงสูงอยู่ได้ในปัสสาวะในขณะที่ไม่มีอาการแสดงของโรค ความผิดปกติดังกล่าวสามารถแก้ไขได้โดยการใช้ยาที่ออกฤทธิ์ขยายหลอดเลือด คณะผู้วิจัยให้สมมติฐานว่า ความผิดปกติในการทำงานของเซลล์บุท่อไตน่าจะมีสาเหตุจากภาวะการไหลเวียนของเลือดในไตที่ผิดปกติ

Tubular dysfunctions such as renal tubular acidosis, tubular enzymuria, tubular transporting defect, impaired maximal tubular concentrating mechanism and acidification have been well substantiated in various glomerulonephrities particularly in those patients associated with severe form commonly destined for chronic renal insufficiency-namely focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN) and diffusely proliferative glomerulonephritis (DPGN).[1-18] In addition, tubulointerstitial fibrosis has recently been recognized as a pivotal risk factor of progressive process of glomerulotubulo-interstitial injury in this severe form of glomerulopathy.[19-24] The mechanism for such development of tubulor dysfunction and its relationship to the tubulo-interstitial fibrosis has still remained to be further elucidated. Nonetheless, the hemodynamically mediated glomerulo-tubular injury has been implicated in this progressively prone glomerulonephritis in which much reduction in peritubular capillary blood flow secondary to the increase in intrarenal resistance with particularly preponderant vasoconstriction at the efferent arteriole has been observed.[25-27]

The spatial interrelationship between tubular enzymuria and the altered intrarenal hemodynamics is needed to be established. If this will be the case, therefore, therapeutic implementation aiming to improve the abnormal intrarenal hemodynamics with vasodilators would provide some significant impact upon the status of tubular enzymuria and thus, such objective would form the basis of our present study.

Material and Method

Initial and subsequent urine samples from 59 nephrotic patients were subjected to N-acetyl-β-glucosaminidase (NAG) study according to the colorimetric method as described by Maruhn[28] and Werner[29] and the study in adult subjects was reported earlier in this journal.[30] Of these 59 nephrotics, 29 were classified clinically as mild form characterized by either therapeutic remission with prednisolone or histopathologically proven as minimal-change or mild mesangial proliferative GN., 30 were considered as a clinically severe subset with therapeutic resistant to the conventionally-treated with prednisolone and the histopathologic proven as FSGS, DPGN or MPGN.

Intrarenal hemodynamics had been assessed in some of these nephrotic patients and the detail of the study had been reported elsewhere.[18,25,32] The values of urinary NAG were subjected to the statistical analysis of variance using student Newman Keuls Test and using the Nonparametric Method by means of Wilcoxon Matched-pairs Signed-ranks test for the 9 nephrotics under therapeutic comparison,[31,32] the difference was significant statistically at the 0.05 level.

Therapeutic regimen

A combination of vasodilators consisting of dipyridamole 15 mg/kg/day, calcium channel blocker mainly nefedipine 1-3 mg/kg/day and angiotensin convertase inhibitor mainly enalapril 0.5-2 mg/kg/day was additionally prescribed to all of the 9 nephrotics who were clinically unresponsive to prednisolone therapy.

Results

Elevated levels of NAG were observed in both forms of NS during active proteinuria. Normalisation of urinary NAG value was documented in the mild form of NS during remission. In contrast in the severe form of NS during follow-up, partial reduction of urinary NAG was observed in 2/3 while in more than one-third it still remained highly elevated.(Table 1) However, further reduction of urinary NAG toward normal was substantiated following therapy with vasodilators. (Table 2)

Table 1. Summarised the study of urinary N-acetyl-β-glucosaminidase in mild and severe forms of nephrotic syndrome during both active proteinuria and remission.

Group	No. subjects	NAG unit/gm creatinine
severe NS (active)	n = 17	62.0 ± 56.3
severe NS (follow-up)	n = 30	10.0 ± 11.2
Mild NS (active)	n = 29	68.4 ± 69.9
Mild NS (remission)	n = 21	2.6 ± 3.0

* Statistical significance at $p < 0.05$

Table 2. Demonstrated the pre-and post-treatment values of urinary N-acetyl-β-glucosaminidase (NAG) in the 9 nephrotics with persistently elevated urinary NAG.

	NAG (unit/gm creatinine)
Pre-treatment	28.2* ± 16.5
Post-treatment	10.4 ± 8.1

* Statisticel sigmificance at $p < 0.05$

Discussion

Persistently elevated level of urinary NAG was demonstrated in one-third of the cases in severe form of NS of which rendered a supportive view that a certain degree of progressive process of renal tubular injury had still existed through the convalescent stage. Further supports to this view are the previous notions of abnormal expression of intercellular adhesion molecule-1 and aberrant expression of HLA-DQ and -DP autigens on proximal tubular epithelial cells in various form of glomerulonephritis associated with interstitial inflammation,[33-35] of tubular transport defect[18] and of persistent shortening of platelet half-life in nephrotic patients associated with severe form of glomerulonephritis during convalescence or asymptomatic, low-graded proteinuria.[36] The mechanism for such tubular dysfunction still remains to be further elucidated. Nontheless, the presence of marked reduction of peritubular capillary blood flow secondary to the high intrarenal resistance is quite an interesting observation in the severe form of NS associated with FSGS and MPGN.[25,37] Such reduction of peritubular capillary blood flow and the presence of tubular transporting defect and tubular enzymuria observed simultaneously in this NS may have a spatial relationship.

In relevant to this, renal perfusion in nephrotics is usually deficient in both quality and quantity. Of the former, abnormal blood rheology such as hypercoagulability,[38-41] hyperviscosity,[36] hyperlipidemia,[42-44] hyperaggregation of platelet[45-49] and less deformability of red blood cell due to increased glycosylation of hemoglobin and to lipid peroxidation of erythrocyte have been substantially documented in the NS.[50-51] Such defective blood rheology would predispose the endothelial cell of the renal microcirculation as well as the tubular epithelium to various injurious triggers known to be aggravated in the NS namely cytokines,[52,53] parathyroid hormone,[54] reactive oxygen methabolites,[55-57] platelet activating factor,[58] oxidized low density lipoprotein[59] and sensitized mononuclear cell,[33,34] macrophage[60] and platelet.[35-39] Consequence to the activation of endothelial cell, membrane phospholipid is perturbed, degraded, activated and transformed to the procoagulant state with subsequent releases of procoagulant protein namely large von Willebrand factor,[61] tissue factors, plasminogen activator inhibitor[62] and various proinflammatory mediators such as eicosanoids, leukotrienes, reactive oxygen metabolites and vasoconstricting mediators such as thromboxane A_2, endothelin and hydroxyeicosatetraenoic acid etc. All of these biopathologic factors would work in favor of the formation of local intravascular coagulation (LIVC) in the renal microcirculation and therefore, further deplete the peritubular capillary blood flow.

These preceding highly intricating agonists would injure the tubular cell as well as the endothelial cell of the microcirculation by increasing transmembrane calcium fluxes.[63,64] Increased intracellular cytosolic calcium would affect tubular cell functions as are reflected by the enhanced tubular enzymuria in this study and enhanced fractional excretion of solutes in another separate study. Further support that tubular cell injury may plausibly link to the impaired tubular blood flow is derived from the therapeutic observation. In this therapeutic view, improvement in tubular function is documented following the rising of renal blood flow in response to the usage of vasodilators.

Such preliminarily therapeutic benefit with vasodilators renders a suggestive view that hemodynamically mediated trigger may be central to the pathogenesis of tubular injury in this severe form of NS.

Summary

Tubular enzymuria determined as urinary N-acetyl-β-glucosaminidase has been noted to be elevated in both mild and severe forms of NS. During remission, normal value of urinary NAG was observed in mild form of NS, whereas high values of NAG were still observed in one-third of the cases in the severe form of NS. Further reduction of urinary NAG could be achieved with therapeutic vasodilators in this latter group of patients-suggesting a hemodynamically mediated trigger being responsible for the tubular injury.

Acknowledgement

The authors would express a great appreciation to Miss Venus Udomprasertkul for her valuable assistance in statistical analysis.

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