Eur J Pediatr (1993) 152 [Suppl 1]: S60–S62

European Journal of
Pediatrics

Renal complications in glycogen storage disease type I

W. C. C. Reitsma-Bierens

Department of Paediatrics, University Hospital, 59 Oostersingel, NL-9713 EZ Groningen, The Netherlands

Abstract. Deficiency of the enzyme glucose-6-phosphatase is the biochemical defect in glycogen storage disease type I (GSD I). Normally this enzyme is present in the liver, intestine and kidneys. The lack of the enzyme in the kidney makes it obvious that glycogen storage will not be restricted to the liver but that also the kidneys will be involved, possibly resulting in renal damage. Glycogen storage in the kidney is most outspoken present in the proximal tubular cells. In case of insufficient metabolic control, a Fanconi-like syndrome can develop, disappearing with improved therapy. Although renal disease has not been considered a problem in GSD I, recent findings indicate that especially in adult patients chronic renal disease is a common complication. In the past gout nephropathy and renal stones were the complications mentioned. Recently it appears that in a considerable number of patients after a period of 'silent' hyperfiltration, renal damage develops with proteinuria, hypertension and renal dysfunction later on. In biopsies of such patients focal glomerulosclerosis is found.

Key words: Glycogen storage disease type I – Chronic renal insufficiency – Glomerulosclerosis – Hyperfiltration – Proteinuria

Introduction

Glycogen storage disease type I (GSD I) is caused by the deficiency of the enzyme glucose-6-phosphatase. As this enzyme normally is present in the liver, gastro-intestinal tract and in the kidneys it is obvious that in cases of deficiency, glycogen storage might be expected not only in the liver but also in the kidneys, probably giving rise to renal damage or dysfunction. The original pathological description of the disease by von Gierke [5] is titled 'hepatonephromegalia glycogenika'. He emphasized the enormous enlargement of the liver and the kidneys, both organs were overloaded with glycogen. Afterwards the kidneys have not drawn much attention of investigators and clinicians and for many years renal complications have not been considered as an important problem.

Abbreviations: GBM = glomerular basement membrane; GSD I = glycogen storage disease type I

Renal findings in GSD I

In the literature publications of renal findings in GSD I are rather scarce and include: renal enlargement, gout nephropathy, renal stones, nephrocalcinosis, Fanconi-like syndrome, hyperfiltration and chronic renal disease leading to renal insufficiency.

Enlargement of the kidneys

This is a common finding in GSD I and is ascribed to the accumulation of glycogen. Being easily demonstrable by ultrasound, increase in kidney size in some cases can contribute to the differential diagnosis between various types of hepatomegalic glycogenosis, for example types I and III [7].

Gout nephropathy and renal stones

Hyperuricaemia in GSD I is explained by a combination of increased synthesis of purine and a competative inhibition of renal tubular excretion of urate by lactate [7]. Longstanding hyperuricaemia can lead to uric acid nephrolithiasis, and chronic interstitial nephritis (gout nephropathy). Intraluminal uric acid cristallization occurs especially in acid urine. For that reason besides sufficient diuresis, therapy with alkali contributes to the prevention of nephrolithiasis. Gout nephropathy is the result of deposition of sodium urate monohydrate crystals in the medullary interstitial tissue leading to secondary inflammation and giant cell reaction; ultimately resulting in interstitial fibrosis [6]. In this form of nephropathy, hypertension, proteinuria, limitation of concentration of the urine and decrease in filtration function can be seen. The use of xanthine oxidase inhibitors and the improved metabolic control have resulted in near normal to normal levels of serum uric acid. Therefore the risk for urate nephropathy and stones may be expected to be low now. However, it is thought that hypercalciuria as seen

in some patients can lead to renal stones and even nephrocalcinosis [10].

Fanconi-like syndrome

Proximal tubular dysfunction has been described in combination with glycogen storage. However, the classic Fanconi syndrome is associated with only one type of glycogen storage in which the glucose-6-phosphatase deficiency has not been confirmed. The enzyme deficiency of this disease, if any, has not yet been identified. Striking features of this disease are generalized aminoaciduria, phosphaturia leading to rickets, and massive glucosuria even during periods of hypoglycaemia. These patients differ further from von Gierkes disease in having galactose intolerance, hypo-uricaemia (due to the proximal tubular defect) and no kidney enlargement [2].

Proximal tubular dysfunction has also been observed in patients with enzymatically proven GSD I [4, 8]. Matsuo et al. [8] described a patient with proximal renal tubular acidosis due to loss of bicarbonate in the urine. In four other children he found hyperphosphaturia, resolving in response to continuous glucose feeding. Chen et al. [4] described three patients with generalized aminoaciduria, hyperphosphaturia and increased excretion of β_2-microglobulin. These three patients had received no other treatment than frequent meals. After starting with intensive therapy the dysfunction improved. These findings suggest that good metabolic control can prevent proximal tubular dysfunction.

Chronic renal disease

Reports of chronic renal disease with advanced glomerulosclerosis, tubular atrophy, interstitial fibrosis and contracted sclerotic kidneys have appeared sporadically, although Steim and Zollinger described the first case already in 1967 [11]. Two years ago Chen et al. [3] published striking and important data of chronic renal disease in his patients. He found proteinuria, hypertension and decreased renal function in a considerable number of his patients. In a group of 20 older patients (13–47 years of age) 14 showed disturbed renal function, while 6 of them developed progressive renal insufficiency. Three patients even died of renal insufficiency. Creatinine clearances determined in 9 patients at the onset of the first sign(s) of renal involvement were increased in 7, indicating hyperfiltration in the period before decline in renal function developed. Baker et al. [1] confirmed the hyperfiltration in his patients, being the only abnormal finding in young children. In his teenager patients a significant increase in urinary albumin excretion was seen and in all three patients over 20 years of age overt proteinuria (2–8 g/day) was present.

Also in 19 of a group of 23 patients we found an increased glomerular filtration rate, while 3 patients older than 15 years had slight but persistent glomerular proteinuria [9]. It seems that in adult patients with GSD I after a period of silent hyperfiltration, proteinuria develops with decline in renal function later on. In this aspect there is a strong parallelism with insulin dependent diabetes mellitus, the factor(s) responsible for the hyperfiltration and nephropathy in this disease have not yet been solved.

Pathology

The predominant pathological lesion found in renal biopsies of patients with signs and symptoms of renal disease is focal segmental glomerulosclerosis. The glomerular lesions being mild to moderate increased mesangial matrix and cells, tuft collapse and hyalinosis [1, 3, 12]. The degree of interstitial fibrosis seems to be proportional to the degree of renal insufficiency [3], in more severe cases attended by tubular atrophy.

Glycogen deposits are especially found in the proximal tubular cells, as already described by von Gierke [5]; glycogen in the distal and collecting tubules is minimal [12].

Verani and Bernstein [12] studied in detail the ultrastructure of the glomerular basement membrane (GBM) in three patients with renal complications. GBM alterations were present in all patients. She found an irregular GBM with thickening and lamellation. Glycogen granules were present in the areas of abnormal GBM. In a patient with chronic renal insufficiency the GMB was thicker than normal for age. In all three patients the glycogen content in the mesangium and in the epithelial, mesangial and endothelial cells was increased. Immunofluorescence showed no evidence of immune deposits [1, 3, 12]. Specific staining showed no uric acid crystals in one series [1].

Conclusion

In conclusion we can say that the risk for gout nephropathy and stones is low now and proximal tubular dysfunction can be prevented by sufficient metabolic control.

However, in recent years it has become clearer that chronic renal disease is a serious risk for patients with GSD I. Many patients exhibit signs of irreversible renal damage such as persistent proteinuria and hypertension possibly leading to chronic renal insufficiency.

References

1. Baker L, Dahlem S, Goldfarb S, Kern EFO, Stanley CA, Egler J, Olshan JS, Heijman S (1989) Hyperfiltration and renal disease in glycogen storage disease type I. Kidney Int 35: 1345–1350
2. Brewer ED (1985) The Fanconi syndrome: clinical disorders. In: Gonick HC, Buckalew VM Jr (eds) Renal tubular disorders. Marcel Dekker Inc, New York, pp 502–504
3. Chen YT, Coleman RA, Scheinman JL, Kolbeck PC, Sidbury JV (1988) Renal diesase in type I glycogen storage disease. N Engl J Med 318:7–11

4. Chen YT, Scheinman JI, Park HK, Coleman RA, Roe CR (1990) Amelioration of proximal renal tubular dysfunction in type I glycogen storage disease with dietary therapy. N Engl J Med 323:590–593
5. Gierke E von (1929) Hepato-Nephromegalia glykogenica. Beitr Pathol Anat Allg Pathol 82:497–513
6. Grantham JJ, Chonko AW (1986) Renal handling of organic anions and cations; metabolism and excretion of uric acid. In: Brenner BM, Rector FC (eds) The kidney, 3rd edn. WB Saunders, Philadelphia, pp 695–689
7. Hers HG, Hoof F van, Barsy T de (1989) Glycogen storage disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The metabolic basis of inherited disease, 6th edn. McGraw-Hill Inc, New York, pp 425–437
8. Matsuo N, Tsuchiya, Cho H, Nagai T, Tsuji A (1986) Proximal renal tubular acidosis in a child with type I glycogen storage disease. Acta Pediatr Scand 75:332–335
9. Reitsma WCC, Troelstra JA, Luijk WHJ van, Smit GPA, Fernandes J (1990) Hyperfiltration in patients with glycogen storage disease type I. Pediatr Nephrol 4:C49
10. Restaino I, Stanley C, Baker L, Weiss R, Kaplan BS (1990) Renal tubular abnormalities and nephrocalcinosis in patients with type IA glycogen storage disease. Pediatr Res 27:337A
11. Steim H, Zollinger HU (1967) Toedliche Schrumpfniere bei Glykogen Speicherkrankheit Typ von Gierke. Klin Wochenschr 45:295–299
12. Verani R, Bernstein J (1988) Renal glomerular and tubular abnormalities in glycogen storage disease type I. Arch Pathol Lab Med 112:271–274