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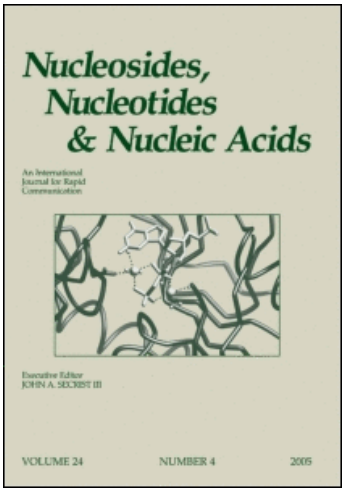

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An Unusual Cause of Renal Amyloidosis Secondary to Gout—the First Description of Familial Occurrence

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AN UNUSUAL CAUSE OF RENAL AMYLOIDOSIS SECONDARY TO GOUT—THE FIRST DESCRIPTION OF FAMILIAL OCCURRENCE

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□ *Background: AA amyloidosis caused by the chronic inflammation accompanying gouty arthritis is extremely rare and familial occurrence has not been described so far. Case report: We present the case of two brothers (47 and 44 years old) with 7- and 10-year history of hyperuricaemia and chronic tophaceous gout with polyarticular involvement. The enzymatic assay performed in their erythrocytes proved the partial hypoxanthine-guanine phosphoribosyl transferase deficiency (Kelley-Seegmiller syndrome), the genetic defect of purine metabolism. Later on they developed proteinuria and chronic renal insufficiency /CRI/. Renal biopsy disclosed the combination of AA amyloidosis and gouty nephropathy in both the cases. Despite the standard treatment the older brother progressed to chronic renal failure. On the contrary, the younger one being longterm treated with oral colchicin have stabilized CRI. Conclusions: Only several cases of AA renal amyloidosis until recently, secondary to gout have been reported. Our case represents the first report of familial occurrence of this extremely rare disease.*

Keywords Familial occurrence; Gout; Hypoxanthine guanine phosphoribosyltransferase (HPRT) deficiency; AA amyloidosis

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INTRODUCTION

Hyperuricaemia and gout have been well known to occur in families. As well as an apparently multifactorial genetic component to classic gout itself—2 rather rare genetic defects of purine metabolism have been defined: overactivity of PPriboseP synthase and hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency. Both defects lead to overproduction of uric acid. HPRT has been mapped to Xq26-27, and mutations occur either as an X-linked recessive disorder or arise de novo.[1] Clinical manifestations are heterogeneous based on the amount of residual HPRT activity as described previously:[2] complete HPRT deficiency (Lesch–Nyhan syndrome), partial HPRT deficiency or Kelley–Seegmiller syndrome. Amyloidosis is a functional disorder characterized by unusual depositions of amyloid protein in various organs and is classified based on its constituent chemical fibrils. Amyloid seen in amyloidosis secondary to chronic infammatory conditions is derived by proteolytic cleavage from an acute phase reactant, serum amyloid A (SAA), and the fibril type is designated AA. Amyloidosis secondary to the chronic arthritis is common, however its association with gout is very rare and was reported for the first time by Litten.[3] Having reviewed the literature we have found only eight further cases.[4–6] Here, we present the case of familial occurrence of AA amyloidosis secondary to gout caused by the partial HPRT deficiency.

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CASE 1

The 48-year old patient with 7-year history of chronic tophaceous gout was regulary hospitalized at the Institute of Rheumatology because of the recurrent acute attacks of arthritis in his first metatarsophalangeals, heels, knees, elbows, carpal and distal interphalangeal joints, and severe hyperuricaemia (more then 800 μmol/l). According to medical report he experienced only one episode of renal colic caused by radiolucent nephrolithiasis 25 years ago. In 1998 nephrotic proteinuria (3.8 g per 24-hour) and advanced chronic renal insufficiency (S-creatinine 209 μmol/l, GFR 0.43 ml/s) appeared and he was sent to our department of internal medicine. On admission the patient was pale, normotensive, with leg oedema and polyarticular gouty involvement with numerous subcutaneous tophi. Laboratory results further revealed megaloblastic anemia, increased erythrocyte sedimentation rate (ESR) to 60 mm/hour, slight increase of CRP (21.5 mg/l) and low levels of paraprotein IgG_{κ} in the serum. Immunological examinations including rheumatoid factor were negative. Since the bone marrow aspiration and trephine biopsy excluded multiple myeloma and no progression during next 8 years occurred benign monoclonal gamapathy was diagnosed. Because of unsure etiology of chronic renal insufficiency renal biopsy was indicated. The pathologist described

advanced AA amyloidosis, gouty nephropathy with numerous small urate tophi in the interstitium and severe atrophy of renal parenchyma. The type of amyloid fibrils was confirmed immunohistochemically. Other common causes of AA amyloidosis were excluded. Despite the intensive standard treatment of nephrotic syndrome chronic renal insufficiency slowly progressed. In 2002, acute renal failure due to the septic complications of left leg thrombophlebitis occurred. Renal function did not recover and regular hemodialysis treatment had to be initiated.

CASE 2

The 44-year old patient (younger brother of the Case 1) with 10-year history of chronic polyarticular arthritis, polyneuropathy, recurrent renal colics caused by radiolucent nephrolithiasis and proteinuria was admitted to our department in 2002 because of clinical symptoms of nephrotic syndrome. The physical examination revealed leg oedema. Bigger tophi were present on the right elbow and small cream-yellow finger pad tophi 2 to 3 mm of size on the finger pulps on his hands and feet. The examination of tophus aspirate confirmed the presence of uric acid crystals. Hyperuricaemia (612 μmol/l), increased ESR (92 mm/hour) and CRP (56.5 mg/l), nephrotic proteinuria (10.1 g/24 hour) were the most alarming from the laboratory results. His renal functions were normal. Immunological examinations including rheumatoid factor showed negative results. X-ray depicted erosive bone changes in the knees, wrists, interphalangeal and metatarsophalangeal joints. Chronic tophaceous gout was diagnosed. Because of unexplainable nephrotic proteinuria renal biopsy was performed, which confirmed AA amyloidosis and chronic urate nephropathy with only mild atrophy of renal parenchyma. The biopsy of rectal mucosa showed amyloid deposits as well. While being next 3 years on longterm treatment with oral colchicin (1.5 g/day) his proteinuria decreased to 2.0 g/24 hours but he developed slight renal insufficiency, which is stabilized.

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MATERIAL AND METHODS

Uric acid in serum and urine was measured by a specific enzymatic method. Creatinine in plasma and urine was measured by the Jaffé reaction adapted to the autoanalyser. Endogenous urinary purines and purine enzymes activities in lysed erythrocytes were measured as described.[7] SAA was not analyzed.

RESULTS AND DISCUSSION

Because of familial occurrence of gout genetic defect of purine metabolism was suspected. The diagnosis of the partial HPRT deficiency

was confirmed by finding low activity of HPRT in the erythrocytes, whereas activity of phosphoribosylpyrophosphate synthetase was within the normal range. Subsequent molecular-genetic testing proved the mutation in exon 3 of the HPRT gene—215A>G, Tyr 72Cys(Y72C). Identical changes were detected in both the brothers. Although gout is a very common disease, its association with amyloidosis is rare and only several such cases have been published. The possible explanations for this uncommon association have been suggested by Rubinow and Sonnenblick.[5] Gout attacks are characterized by intensive but self–limited inflammation with short duration in contrast to rheumatoid arthritis, in which the acute phase reactants, including SAA, are persistent. Another possible explanation is based on the heterogeneity of human SAA since not all the SAA types appear to be amyloidogenic. Based on the facts we can conclude that only individuals with persistently high SAA levels and probably some other conditions are prone to develop amyloidosis. The combination of AA amyloidosis and gout based on the genetic defect of purine metabolism is very unusual. As far as we know, this is the first report of the familial occurrence of AA amyloidosis due to chronic polyarticular gouty arthritis resulting from severe form of partial HPRT deficiency, one of the two well-known genetic defects of purine metabolism.

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