

Gout and neurological abnormalities associated with cardiomyopathy in a young man

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Abstract

A 21 year old man with a family history of gout and neurological deficits, developed severe idiopathic congestive cardiomyopathy after a long history of typical gouty attacks and neurological abnormalities. Clinical and laboratory evaluations showed borderline mental retardation, ataxia, sensorineural deafness, marked hyperuricaemia, and excessive uric acid excretion in the presence of impaired renal function. None of the known causes of cardiomyopathy was found. Even though red cell hypoxanthine guanine phosphoribosyltransferase enzyme activity was normal, this case probably represents an inborn error of purine metabolism. The association of cardiomyopathy with gout is very unusual. Previously it has been only once described in a single case.

The description of symptoms and metabolic delineation of the Lesch-Nyhan syndrome has established an association with hyperuricaemia and neurological disease.¹ In men only a complete or partial hypoxanthine guanine phosphoribosyltransferase (HGPRT) enzyme deficiency leads to different degrees of the syndrome, characterised by mental retardation, self mutilation, choreoathetosis, gouty arthritis, and gouty nephropathy.¹⁻³ As far as we know cardiomyopathy has not been found in association with any primary, secondary, or idiopathic gout,^{4,5} except in a single case reported by Rosenberg *et al.*⁶

A further case is described here of a young man with a family history of hyperuricaemia and neurological deficits who presented with severe cardiomyopathy, gouty arthritis, impaired renal function, ataxia, sensorineural deafness, and borderline mental retardation. Red cell HGPRT enzyme levels were normal.

Case report

In July 1988 a 21 year old Greek man was referred to Alexandra Hospital for evaluation of a progressive dyspnoea on exertion, which had started six months earlier. Previous medical history included: several episodes of typical gouty attacks in the last six years, treated with colchicine-allopurinol, and a hearing loss registered progressively in the last three years without any evidence of acoustic trauma. The diagnosis of gout was based on the past typical clinical picture of attacks of acute arthritis of the metatarsophalangeal joints of the great toes.⁷ In addition, polarised microscopy showed needle

shaped, strongly negative birefringent urate crystals free and within leucocytes in aspirated synovial fluid from the left metatarsophalangeal joint and the right knee. The knee was not severely inflamed but he had had an acute attack during his hospital care. During the 11 months before admission he had intermittent diplopia and a short episode of weakness in his right hand and foot, with slight slurring of speech. His family history showed that his mother, aged 41, and her brother, aged 38, had a long history of gout. In addition, at the age of 31 his mother also had diplopia and weakness in hands and feet; these symptoms responded well to a steroid treatment. There were no other children in the family and his father and his uncles had no remarkable medical history.

The patient denied significant smoking and alcohol consumption. Clinical examination showed tachycardia, gallop rhythm, and rales at the bases of both lungs. There was no clinical evidence of previous valvulitis, recent infection, arterial hypertension, or any signs or symptoms of congenital heart disease. Neurological findings included mild tremor of both hands, hyperactive deep tendon reflexes, marked ataxia on finger-nose-finger testing, and a positive Romberg test. He appeared mildly retarded and compulsively bit his lips and fingernails.

Laboratory results showed normal complete blood count, electrolytes, cholesterol, aldolase, serum protein and lipid electrophoresis, and immunoelectrophoresis. Urine analysis showed acidity of the urine and uric acid crystalluria. Blood urea concentrations ranged from 17.8 to 23.2 mmol/l and, the creatinine clearance was 35 ml/min. Serum uric acid concentrations ranged from 595 to 773 $\mu\text{mol/l}$ and the urinary uric acid excretion was over 800 mg/24 hours. All investigations for autoimmune connective tissue diseases, thyroid disease, amyloidosis, toxoplasmosis, syphilis, AIDS, and other viral infections were negative. The activity of HGPRT was measured in dialysed erythrocyte lysates by the method of Kelley *et al.*⁸ and found to be 79.6 nmol/mg of protein for each hour of incubation with hypoxanthine as the substrate (normal value, mean (SD) 90 (11) nmol/mg protein/h). Erythrocyte phosphoribosyl pyrophosphate (PRPP) synthetase activity was determined in addition with Becker's modification⁹ of the two step method of Hershko *et al.*¹⁰ in dialysed erythrocyte lysates and found to be 63.3 nmol/mg protein/h (normal value, mean (SD) 52 (9)).

Radiography of the chest showed cardiomegaly and hilar congestion. Electrocardiography showed 150° axis deviation, left posterior hemiblock, and left ventricular hypertrophy. The

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echocardiogram showed left ventricular dilatation and dysfunction with fractional shortening 9% (normally greater than 28%) and a right ventricular and left atrial dilatation. Radionuclide ventriculography showed wall motion hypokinesia of the left ventricle; the ejection fraction was 28%. The diagnosis of congestive cardiomyopathy was confirmed by haemodynamic studies. Left ventriculography showed diffuse hypokinesia and dilatation with some degree of mitral regurgitation. Coronary angiography showed normal coronary arteries. Endomyocardial biopsy failed to show any specific histological changes; there was no evidence of any infiltrative cardiomyopathy (amyloid, iron, glycogen, glaucoma, neoplasm or vasculitis).

An electroencephalogram, computed tomographic scan of the brain, electronystagmography, and electromyography were normal. An intelligence test using the Weschsler adult intelligence scale showed an IQ score of 79, considered to be borderline. Left sensorineural hearing loss was found by audiometry.

While in hospital the patient developed dyspnoea at rest. He was discharged under treatment with digoxin, frusemide, and allopurinol, and remained under medical observation as an outpatient for the following three months; during these months he developed ataxic gait and mild normochromic, normocytic anaemia and, despite treatment, the serum uric acid concentrations remained high. He died unexpectedly in October 1988 at home; no necropsy was performed.

Our patient's mother and her brother, aged 38, both with long history of gout had been evaluated as follows: serum uric acid concentration ranged from 446 to 541 $\mu\text{mol/l}$ and from 428 to 500 $\mu\text{mol/l}$ respectively. Urinary uric acid excretion was 580 and 560 mg/24 h respectively. The erythrocyte HGPRT⁸ and PRPP^{9, 10} synthetase activities were normal. Renal, mental, and neurological functions were normal. Despite a mild arterial hypertension the patient's mother had no registered cardiac disease.

Discussion

The aggregate of clinical abnormalities in our patient was important. The differential diagnosis included several rare syndromes such as: Alport's syndrome (progressive renal failure, sensorineural deafness),¹¹ Herrmann's syndrome (nephritis, sensorineural deafness, mental retardation),¹² von Gierke's disease (hyperuricaemia, cardiac disease),¹³ Friedreich's ataxia (neurological disease, cardiomyopathy),¹⁴ and some other genetically determined enzymatic abnormalities, which might also have justified the cardiac disease.¹⁵ None of these conditions was compatible with the whole clinical picture and laboratory data described above.

In 1970 Rosenberg *et al* reported a case of a whole family with a syndrome characterised by hyperuricaemia, ataxia, decreased renal func-

tion, and sensorineural deafness; erythrocyte HGPRT activities were normal.⁶ Five members of this kindred had the complete syndrome, and only one of them at the age of 22 has developed congestive heart failure, due to cardiomyopathy.

Obviously our patient has striking similarities with Rosenberg's case, including normal HGPRT activity, but with the difference that our patient had a typical gouty arthritis, mental retardation, and excessive uric acid excretion despite the impaired renal function. Rosenberg's patient in contrast had hyperuricaemia without hyperuricosuria and a normal mental state,⁶ with cardiomyopathy, which was not evident in 21 other members of the kindred.⁶

In conclusion, although the mechanisms responsible for the metabolic, otological, neurological, and cardiac findings described in our patient are not clear, the normal HGPRT and PRPP synthetase enzyme activities, the excessive amount of uric acid excreted, in association with neurological dysfunction and his family history, suggest the presence of an inborn error of purine metabolism. We believe that the above case may be included in the Lesch-Nyhan syndrome variants or phenocopies, in which further cases with an intact HGPRT pathway are included.¹⁶

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