A greater risk of Down’s syndrome in the offspring of persons who are carriers of a pericentric inversion of a G chromosome, is suggested.

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BIBLIOGRAPHY


A New HGPRT-deficient Phenotype?

Seizures were a retrospective neurological finding in one of 18 patients with gout, hyperuricaemia, and partial deficiencies of hypoxanthineguanine phosphoribosyltransferase (HGPRT) (Kelley et al., 1969). Seizures also accompany the clinical expression of hyperuricaemia associated with the complete enzyme deficiency, i.e., the Lesch–Nyhan syndrome of mental retardation, spasticity, choreoathetosis, and self-mutilation (Michener, 1967; Dreifuss et al., 1968), but are not especially common. We describe a non-gouty, retarded, 14-year-old negro boy with hyperuricaemia and HGPRT deficiency, in whom seizures were not only the presenting sign, but were the main clinical feature of his disorder.

Case Report

The propositus was the product of a full-term, uncomplicated pregnancy, and normal delivery. Birth weight was 2636 g. His early developmental milestones were somewhat delayed; he sat at 1 year, walked at 16 months, and spoke single words only at 15 months. Speech developed slowly thereafter and was 'dysarthric' at age 5½ years when evaluated.

Seizures, which began at 5 years, were a mixture of generalized major motor, psychomotor, minor motor, and akinetic spells, almost from the onset; the latter 2 types occurring 15 times or more a day. At 5½ years, his height and weight were normal, 117 cm and 22 kg, respectively. Hyperactive and distractible, he was slightly unsteady on tandem gait and displayed mild dysmetria and dysdiadochokinesia. Cranial and sensory nerve examinations and deep tendon reflexes were normal. Spasticity and choreoathetosis were absent. His IQ was 86 on the Stanford-Binet Test, which revealed deficiencies in verbal and perceptual-motor skills. Electroencephalograms (EEG) consisted of diffuse 2-4 cps spike-and-wave, almost continuous, activity.

Treatment with phenobarbital, dilantin, tridione, myosin, triple bromides, zaronit, peganone, and valium in appropriate combinations and full therapeutic doses throughout the years failed to alter the frequency of his seizures appreciably, and the EEGs remained virtually unchanged.

At 14 years, his dysarthric, slurred speech persists. He may have deteriorated mentally, as his full scale IQ on the Wechsler Intelligence Scale for Children (which is not directly comparable to the Stanford-Binet scale) was 48 (verbal IQ 63 and performance IQ below 44) at the age of 11½ years. The main deficit, as before, was in perceptual-motor functioning.

Finger-nose-finger testing reveals mild cerebellar incoordination, and attempts at posture-holding during the last year or two provoke very minimal choreiform jerks of the outstretched fingers.

He weighs 41·6 kg and is 155 cm tall (25th centile). His head circumference is 53 cm (20th centile).

Uricacidemia of 10–13 mg/100 ml was discovered recently as a chance finding on routine screening. Subsequent laboratory studies revealed 24-hour uric acid excretion averaging 20 mg/kg body weight, a rate in excess of normal, but less than that of the Lesch–Nyhan syndrome (Kelley, 1968). The following blood values were normal: calcium, phosphorus, glucose, urea nitrogen, cholesterol, total protein, lactic dehydrogenase, and glutamic-oxalic transaminase. A sickle-cell preparation was negative. Electromyogram and nerve conduction studies were normal. Urinalysis and urinary amino-acid screening were normal. Radiology showed a thickened calvarium, a finding not present on initial x-rays at age 5½ years, and a consequence, perhaps, of chronic dilantin administration (Kattan, 1970). Haemoglobin was 13-14 mg/100 ml, and reticuloeyte counts were 1·5-3·9. Glucose-6-phosphate dehydrogenase (G6PD) was deficient in the fluorescent spot test (Beutler, 1966).

His negro parents, who are in their late 30's, and a 9-year-old sister are healthy. The father's serum uric acid was 5-0 mg/100 ml, 3-7 mg/100 ml in the mother, and 3·9 mg/100 ml in the sister. A paternal uncle has renal disease not related to hyperuricaemia, gout, or arthritis. Other family history is not pertinent. The mother's erythrocyte G6PD was also deficient; those of the father and sister were normal.

Treatment with allopurinol has reduced the uric acid concentration in his serum to 5–6 mg/100 ml and his uric

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acid excretion to less than 7 mg/kg/24 hr, without effect, however, on the seizures or neurological status (Dreifuss et al, 1968; Marks et al, 1968).

### Enzyme Studies

HGPRT activities in the patient, his parents, and sister were estimated by a method for dried blood samples (Fujimoto, Greene, and Seegmiller, 1968). Filter paper discs of the dried blood were shaken in 0·01 M Tris buffer, pH 7·4, for 30 minutes and incubated with substrate containing hypoxanthine-8,14C (1·37 mM, specific activity of 3·8 mc/mmole), or guanine-8,14C (1·06 mM, specific activity of 12·6 mc/mmole; Seegmiller, Rosenbloom, and Kelley, 1967), 1·8 mM 5-phosphoribosyl-1-phosphate, 0·01 M Tris buffer, pH 7·4, and 0·01 M MgCl2. The samples were incubated with hypoxanthine for 30 minutes at 25°C and with guanine for 45 minutes at 37°C (Berman, Balis, and Dancis, 1968). Inosinic and guanylic acids were separated by high voltage electrophoresis on Schleicher and Schuell No. 2043-B Chromatography Paper at 3000 volts in a Camag chamber with water-cooled jacket and located under short-wave ultra violet (Ultraviolet Products View Box). The paper segment containing the 14C-labelled product was cut out, taped into position in an aluminium planchet and counted for β-radiation for 5 minutes in an ultra-thin window planchet counter (Nuclear Chicago, Model 4334). Activities were expressed in cpm per mg of haemoglobin to correct for the variable concentrations of haemoglobin in blood spot samples, especially from anaemic patients. HGPRT in 6 healthy laboratory workers ranged from 6000 to 14,000 cpm/mg Hb with hypoxanthine as substrate and from 4400 and 6100 cpm/mg Hb with guanine as substrate. In mailed samples, the activities ranged from 5000 to 12,000 cpm/mg Hb with hypoxanthine.

### TABLE I

<table>
<thead>
<tr>
<th>Source</th>
<th>Hypoxanthine (cpm/mg Hb)</th>
<th>Guanine (cpm/mg Hb)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample 1</td>
<td>Sample 2</td>
</tr>
<tr>
<td>Proposito</td>
<td>95</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Mother</td>
<td>---</td>
<td>3100</td>
</tr>
<tr>
<td>Father</td>
<td>---</td>
<td>8000</td>
</tr>
<tr>
<td>Sister</td>
<td>---</td>
<td>9240</td>
</tr>
<tr>
<td>Daily control</td>
<td>7100</td>
<td>8500</td>
</tr>
</tbody>
</table>

Little or no transferase was detected in the patient’s samples, measured with either substrate (Table I). HGPRT activities in the mother’s dried blood ranged from 32% of normal with hypoxanthine to 76% of normal with guanine. Activities of the father’s and sister’s transferases were normal with both substrates.

The patient’s fibroblasts, cultured and examined by Dr Joseph Dancis, displayed ‘moderate’ HGPRT activity.

The fraction of leucocyte enzyme in the dried blood sample was estimated by measuring transferase activities in white cells, which were separated from whole blood of normal persons by fibrinogen flotation (Skog and Beck, 1956), reconstituted in serum, and dried on filter paper discs in volumes equivalent to those of white cells in the dried blood samples. Activities with hypoxanthine as substrate were expressed as cpm per filter paper spot of white cells and compared with those in spots made with 8·5 μl of whole blood.

No more than 1% of the total transferase activity of the dried blood samples was due to that from leucocytes, in contrast to the greater proportion of leucocyte enzyme in estimates of whole blood transferase (Balis, 1968; Berman et al, 1968).

### Discussion

The patient’s disease differs from other phenotypes associated with HGPRT deficiency in clinical and biochemical features. Intractable convulsions are a presenting sign in neither Lesch–Nyhan syndrome (Dreifuss et al, 1968) nor gout with partial transferase defect (Kelley et al, 1969). The differential activity of his erythrocyte and fibroblast transferase is also unusual and suggests a chimeric distribution of the defect, and, in turn, the development of a forme fruste. Gout, a manifestation of uncontrolled hyperuricaemia in either HGPRT-deficient phenotype (Kelley et al, 1969), or choreoathetosis and self-mutilation, 2 of the later signs of Lesch–Nyhan syndrome (Dreifuss et al, 1968), may yet appear.

Expression of the mother’s probable heterozygosity through erythrocyte enzyme is unique, as the partial defects of carriers in other pedigrees showing HGPRT deficiency are apparently recognizable only in cultured fibroblasts (Dancis et al, 1968; Kelley, 1968; Nyhan et al, 1970). Variable expression of abnormal biochemistry among carriers, however, is a clue to a disease’s genetic heterogeneity and, in our family, detection of the probable carrier’s erythrocyte defect may reflect a severe form of HGPRT deficiency, as it may in allelic forms of G6PD deficiency (Henderson et al, 1969).
On the other hand, our procedures differed somewhat from those in the study of other pedigrees and may have influenced the mother's 'expression' of her unique biochemical trait. The use of dried blood samples, for example, excluded the possible masking of a partial erythrocyte defect by leucocyte enzyme, which is fully active in carriers (Dancis et al., 1968) and contributes one third the transferase activity of whole blood (Balis, 1968; Berman et al., 1968). Measurements with both purine substrates, furthermore, are now a corollary to the interpretation of recent kinetic data which suggest that HGPRT's structure is not homogeneous (McDonald and Kelley, 1971). A property of bacterial mutant transferase (Kalle and Gots, 1961), substrate sensitivity or specificity may regulate the activity of man's transferase and explain, perhaps, the rare instances of atypical activity in HGPRT-deficient families (Kelley, 1968; Henderson et al., 1969; Kelley et al., 1969). The transferase in our patient's family, however, resembles that in the majority of pedigrees reported in its similar activities with alternate purine substrates.

Summary

Hyperuricaemia and hypoxanthineguanine phosphoribosyltransferase (HGPRT) deficiency in a retarded, 14-year-old negro boy with a seizure disorder of long standing suggest he expresses a variant form of the HGPRT-deficiency syndromes, transmitted through the maternal line.

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