Hyperuricosuric Encephalopathy without Hyperuricaemia

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We have recently studied a girl with hyperuricosuric encephalopathy in whom the clinical manifestations corresponded to those found in the classical form of encephalopathy with hyperuricaemia, but in whom the biochemical investigations revealed a disturbance of the purine biosynthesis different from that observed in the classical form. The disease is probably inherited as an autosomal recessive trait.

Case Report

This girl (B.C.) was 3 years old when first admitted for assessment of psychomotor retardation and behaviour problems.

She was born in November 1962, after a normal and full-term pregnancy, birthweight 3500 g. Initially, the mother noticed nothing particular except that, compared with her older brother, feeding was more difficult and weight gains were slower. Gradually, a delay in psychomotor development became obvious. At 10 months she could hardly sit upright and only when prompted to do so. At 14 months, she could scarcely stand when supported. From the age of 1½ years, she started crying continuously, and considerable mental deterioration set in. Social contact was practically absent, the child was unmanageable and very choleric, letting out sudden loud screams and moaning for hours. Extreme anorexia developed and motor development practically ceased. A pink staining of the nappies was occasionally noted.

The parents were first cousins: their mothers were sisters (Fig. 1). There were 3 other healthy children. One child died from a congenital heart defect when 5 days old. There were no other similar cases in the family.

On physical examination at the time of admission, at the age of 3 years, her weight was 8800 g., her height 89 cm., and her head circumference 49 cm. She was undernourished, very backward, and irritable. Sudden attacks of crying occurred both during the day and at night. She hardly uttered any distinguishable sounds and could not even pronounce the most elementary words. She bit her hands until she cried with pain,

bit the inner side of her cheeks, and knocked her head against the edge of the bed, causing bruises and abrasions. Auscultation of heart and lungs was normal. Palpation of the abdomen revealed nothing particular; the liver and spleen were not enlarged. Neurological examination showed a marked hypertonicity, hyperactive tendon reflexes, and normal plantar responses. Finally, choreo-athetotic movements of the extremities were noted which sometimes resulted in violent spasms and opisthotonos.

X-rays of the skull, electroencephalography, and funduscopy were normal. Routine laboratory data also showed nothing particular. Haemoglobin was 13.4 g./100 ml., white cell count 11,000 per cu.mm., with a normal differential, red cells 4,450,000 per cu.mm., reticulocytes 10% and platelets 344,000 per cu.mm. Urinalysis revealed a constant proteinuria, a constant microscopic haematuria, and large amounts of uric acid crystals in the sediment. Plasma electrolytes, blood pH, and blood levels of bicarbonate, urea, creatinine, calcium, phosphate, alkaline phosphatases, serum lipids, and cholesterol were all within normal limits. Serum total proteins were 6.9 g./100 ml., with a normal differentiation. The renal concentrating capacity was 1020. Creatinine clearance was 177 ml./min. per 1.73 sq.m., phosphate clearance 15 ml./min. per 1.73 sq.m., and tubular phosphate reabsorption 87%. Paper chromatography showed a normal pattern of urinary amino acids. An intravenous pyelogram was normal. Culture of peripheral blood cells showed a normal number of 46 chromosomes, with a normal female karyotype.

Investigation of Purine Metabolism

Purine metabolism was extensively studied in this child, for which purpose she was kept on a purine-low diet during five days preceding the biochemical studies.

The blood uric acid was always normal, varying from 3.5 to 5 mg./100 ml. The 24-hour urinary excretion of uric acid was estimated on 6 occasions: it varied from 35 to 45 mg./kg. body weight per 24 hours, with a mean of 41 mg./kg. (normal range for this laboratory, 10-25 mg./kg. per 24 hours). The incorporation of labelled glycine was also investigated. Glycine ¹⁴C (specific activity 8.2 µCi/mM) was administered intravenously, the dose being 2 µCi/kg. 12-hour

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FIG. 1.—Pedigree of family.

FIG. 2.—Specific activity of the urinary uric acid after intravenous administration of glycine ^{14}C . FIG. 3.—Cumulative excretion of labelled urinary uric acid after intravenous administration of glycine ^{14}C .

urine specimens were collected. Urinary uric acid was isolated, purified, and crystallized, and the specific activity was measured according to the method of Lesch and Nyhan (1964). The specific activity of the urinary uric acid was maximal on the fifth day after injection (Fig. 2). The cumulative urinary excretion of labelled uric acid after 7 days was 1.7% of the injected dose (Fig. 3). This is about 200 times the rate of excretion in normal children.

A treatment with a purine-low diet was started, from which all substances known to contain purines in appreciable amounts were eliminated. After five to six weeks, there was an undeniable improvement in the child's condition. Whereas she had previously remained apathetic and taken no interest in the outside world, she now sat upright, took notice, and even smiled at her parents. Her appetite improved and the weight gain was obvious (Fig. 4). The self-destructive urge decreased

though it did not completely disappear; biting of the hands ceased, but she still bit the inner side of the cheeks. Long-standing periods of screaming no longer occurred. The frightened expression also disappeared. After 2 months she could walk without support. After 6 months of treatment the girl was placed in an institution. We have not yet been able to reinvestigate her.

Discussion

The clinical picture in this girl is that of the classical form of hyperuricosuric encephalopathy with hyperuricaemia, a disease entity described by several authors (Balis *et al.*, 1967; Catel and Schmidt, 1959; Hoefnagel, 1965; Hoefnagel *et al.*, 1965; Jeune *et al.*, 1966; Laplane, Polonovski, and Graveleau, 1967; Lesch and Nyhan, 1964; Marie,

FIG. 4.—Development of weight before and during diet.

Royer, and Rappaport, 1967; Nyhan, 1965; Nyhan, Oliver, and Lesch, 1965; Nyhan *et al.*, 1967; Polonovski *et al.*, 1966; Seegmiller *et al.*, 1961; Seegmiller, Rosenbloom, and Kelley, 1967). In these children development is normal during the first months of life, though in the previous history minor feeding difficulties and a decreased motor development can be detected. Later on, the psychomotor retardation becomes extreme; these patients never learn to walk alone and are able only to utter some sounds. Neurological examination shows a marked hypertonicity which is more pronounced on the lower extremities, a generalized hyperreflexia, involuntary movements of the extremities, episodic jerking of the legs, and choreo-athetotic movements of the arms. Dysarthria is also present: the children are able only to utter inarticulate sounds. A very important symptom, which becomes apparent only when the child reaches the age of 2 to 3 years, is self-mutilation. This consists in biting the fingers and lips and, as a result, painful screaming. Acute abdominal pain, tophi, and enlargement of the joints, other less constant features of the classical form, were absent in our patient, but pink coloration of the nappies was seen.

The pertinent clinical and biochemical data from the literature are summarized in the Table.

Though the majority of the clinical manifestations found in the classical form of encephalopathy with hyperuricaemia were present in our patient, two unusual clinical features and one important biochemical finding allow us to differentiate the disease from the classical type. First, the propositus was

a girl, whereas all the cases described hitherto were boys; and secondly, the parents were first cousins. Despite extensive anamnestic investigation, we were unable to find other similar cases in the child's family.

From the biochemical point of view, in contrast to all previously reported cases, hyperuricaemia was never observed.

The results of the biochemical investigations showed, without doubt, that there was a disturbance of the biosynthesis of the purines. As in the classical form, large amounts of uric acid crystals were seen in the urinary sediment as well as an increased urinary excretion of uric acid, with values between 35 and 45 mg./kg. per day. Also in our patient, the cumulative excretion of the labelled urinary uric acid during the 7 days following intravenous administration of labelled glycine was enhanced and reached values that were 200 times higher than those found in normal children. An important difference, however, was that the specific activity of the urinary uric acid was maximal at 120 hours, with 72 counts/min. per mg. urinary uric acid, whereas in the classical form, first described by Lesch and Nyhan (1964), maximal activity is reached after 12 to 24 hours.

There are no available data in the literature on the long-term effects of a purine-free diet.

Considering the results of these biochemical investigations, we think that we are dealing with another form of encephalopathy due to a disturbance in the biosynthesis of purines, namely an encephalopathy with hyperuricosuria without hyperuricaemia. In view of the cousin relationship of the parents

TABLE
Clinical and Biochemical Data in Patients described in Literature, and in Propositus

Reference	Sex	Parental Consanguinity	Other Cases in Family	Blood Uric Acid (mg./100 ml.)	Urinary Uric Acid (mg./kg. per day)	Cumulative Excretion After 7 Days (%)	Maximal Specific Urinary Uric Acid (counts per min.)
Catel and Schmidt (1959)	M	No	4 males	9.9-15.5	—	—	—
Hoefnagel (1965)	M	No	No	11.0-13.0	37.0-46.0	—	—
Hoefnagel <i>et al.</i> (1965)	Family A	M	No	10.5-12.4	55.6-32.4	—	—
	Family B	M	No	8.6-9.4	37.8-53.0	—	—
Jeune <i>et al.</i> (1966)	M	—	6 males	7.0-12.5	35.0-60.0	—	—
Laplane <i>et al.</i> (1967)	M	—	2 males	12.0-14.2	—	—	—
Lesch and Nyhan (1964)	Case A	M	No	16.8	46.8	2.30	240 (12 hr. after injection)
	Case B	M	Brothers	9.9-11.2	43.7	2.10	115 (12 hr. after injection)
Marie <i>et al.</i> (1967)	M	No	No	12.6-14.0	25.0-30.0	—	—
Nyhan <i>et al.</i> (1967)	Family A	M	No	7.4-9.9	36.4-56.5	2	118 (12 hr. after injection)
	Family B	M	No	11.7	—	—	—
Nyhan <i>et al.</i> (1965)	M	No	8 males	9.2-13.3	57.5	2	80 (12 hr. after injection)
	M	No	1 male	—	—	—	—
Polonovski <i>et al.</i> (1966)	M	No	—	12.0-14.2	—	—	—
Our case	F	First cousins	—	3.0-5.0	35.0-45.0	1.7	72 (120 hr. after injection)

and the absence of other similarly affected cases in the family, it seems probable that the disease is inherited as an autosomal recessive trait.

Summary

A 3-year-old girl is described, presenting with the majority of the clinical manifestations found in the classical form of encephalopathy with hyperuricaemia and hyperuricosuria. The clinical picture differed from the latter in the following ways: the patient was a girl, the parents were first cousins, and no other members of the family were affected.

From the biochemical point of view, an increased urinary excretion of uric acid was observed, values varying from 35 to 45 mg./kg. daily. Uri-caemia, however, was always normal. After intravenous administration of labelled glycine, specific activity was maximal at 120 hours with 72 counts per minute per mg. urinary uric acid, while the cumulative excretion after 7 days was 1.7% of the injected dose.

It was concluded that the encephalopathy was due to a disturbance of the biosynthesis of purines, differing from the classical type. The disease is probably inherited as an autosomal recessive trait.

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