The Lesch-Nyhan Syndrome

FIRST CASE DESCRIPTION IN A SOUTH AFRICAN FAMILY*

Johannesburg

SUMMARY

Two brothers aged 14 and 10 years, presenting with mental retardation, spasticity, athetosis and hyperuricaemia, are described. Red cells of these patients showed a marked decrease in the activity of hypoxanthine guanine phosphoribosyl transferase. This represents the first case description of the Lesch-Nyhan syndrome in a South African family.


In 1964 Michael Lesch, a medical student at Johns Hopkins University, and William Nyhan published a paper entitled, 'A familial disorder of uric acid metabolism and central nervous system dysfunction.' The case concerned a boy who was retarded, spastic, had aggressive self-mutilating behaviour and athetoid movements. He presented as an acute problem with haematuria. Examination of urine showed crystals which at first were thought to be cystine but later were found to be uric acid. Further investigation revealed a marked hyperuricaemia and a marked excess of uric acid from simple precursors such as C-labeled glycine. Subsequently, Seegmiller and his co-workers showed that this syndrome was associated with an almost complete absence of the enzyme hypoxanthine guanine phosphoribosyl transferase (PRT). This discovery led to renewed interest in the study of purine metabolism and added yet another cause for the growing list of central nervous system disorders in childhood.

Renewed interest in the subject has stimulated publication of case histories and it is the purpose of this article to present the clinical and biochemical findings of two brothers who represent the first case description of a South African family with this hereditary metabolic disease.

CASE REPORTS

Case 1

The propositus is a White male aged 14 years who was born after a normal pregnancy and labour at term and weighed 3.63 kg at birth. The child was pink, cried well on delivery, and was found to be normal. During the first 6 months of life his main problem was severe and resistant colic which in no way responded to antispasmodics, sedatives or to changes in his feeds. At the age of 6 months he developed gastro-enteritis with dehydration and was admitted to hospital for intravenous rehydration and treatment.

During the convalescent phase he was found to be spastic. A lumbar puncture showed clear fluid, no increase in cells and normal chemistry. Burr-holes excluded a subdural effusion and an electro-encephalogram showed a general dysrhythmia suggesting a generalized cerebral abnormality of unknown aetiology. From this point onwards, his 'milestones' of development slowed down. His limbs showed marked spasticity. From the age of 4 years he received treatment at the Forest Town School for spasics. During this period he appeared to have lower limb pain which he was unable to localize. At this stage the destructive habit of biting the inside of his cheeks developed. Fortunately this habit was brief, lasting 14 months. Abnormal athetoid movements began at the age of 2½ years but were never very severe. At the age of 14 years he developed an attack of acute abdominal pain which after a week was accompanied by haematuria. His urine showed erythrocytes and crystals of uric acid. The serum uric acid was 11.7 mg/100 ml, and he was diagnosed as a case of gout and treated with allopurinol. The diagnosis was readily acceptable at that time on genetic grounds, as his father was known to suffer from gout.

On allopurinol 100 mg daily, the serum uric acid dropped to 5.9 mg/100 ml, and was maintained within normal limits without difficulty. The patient improved in that there was a disappearance of his abdominal pain (thought to be renal colic), and his limb pain, which was now known to be due to gouty arthritis.

Case 2

A White male and brother of the propositus, aged 10 years, was born after a normal delivery at term. He cried at birth and was pink. He had a normal neonatal period and was examined by a paediatrician who found him to be healthy and normal. The parents became anxious when he, too, developed severe and unresponsive symptoms of colic. Their fear was confirmed when at 6 months of age he failed to sit and was found to be spastic. During his second year of life he showed athetosis and began to chew the inside of his cheeks. This sign subsided after 3-4 months. From this point onwards his progress was similar to that of his brother. Lumbar puncture and burr-hole exploration of his subdural space were negative. An electro-encephalogram was non-specific, showing a generalized dysrhythmia. With growth, his mental retardation and spasticity increased while his athetosis remained mild. Because the brother was found to have increased serum uric acid, he, too, was investigated and found to have a raised serum uric acid level (12 mg/100 ml). Allopurinol treatment, 100 mg daily, resulted in alleviation of limb pain and kept his uric acid levels within the normal range.

The symposium on the Lesch-Nyhan syndrome reported...
in *Federation Proceedings* in July 1968, stimulated our interest and the 2 boys were investigated as possible examples of this condition.

**Assay of Hypoxanthine Guanine Phosphoribosyl Transferase (PRT)**

Red-cell PRT activity was assayed by a method described by Berman et al. In this technique, $^3$H-hypoxanthine is incubated with washed cells from heparinized venous blood. The presence of the PRT enzyme in normal cells enables them to convert the labelled hypoxanthine into inosinate. The cells are then washed with a non-radioactive hypoxanthine solution and the amount of radioactivity remaining in the cells is determined. Red cells obtained from children with the Lesch-Nyhan syndrome have been found by Berman et al. to retain less than 5% of the radioactivity of normal cells. The activity of the erythrocyte PRT enzyme in 3 normal subjects, in the 2 affected siblings (while on treatment with allopurinol), in the father, mother, and in an elder sister, is shown in Table I. It can be seen that the red cell enzyme activity of both affected boys was well below 5% of that found for the control subjects. The parents and the sister of the affected boys had enzyme activities similar to those of the normal controls.

**DISCUSSION**

The combination of the clinical findings and the results of the erythrocyte enzyme assays leave little doubt that the 2 brothers described are suffering from the Lesch-Nyhan syndrome.

There are 4 main characteristics of the disease: mental retardation, neurological abnormalities, obsessive and self-destructive behaviour, and hyperuricaemia.

Mental retardation may be very difficult to recognize during the first 9 months of life but eventually there is a delay in the 'milestones' of development. Failure to sit, to crawl, to stand and to walk appear within the first year. However, attention is drawn to excessive crying during this period, which is often diagnosed as infantile colic, but has since been shown to be due to renal colic caused by the passage of very small uric acid stones. With the passage of time mental retardation becomes more obvious. These children develop a capricious personality and are very likeable children despite their rapidly changing moods.

The neurological abnormalities vary greatly. Spasticity and athetosis are the usual symptoms but their severity varies from case to case. Self-destructive tendencies are an interesting and baffling sign, originally thought to be present in every case. It is now known that patients might show practically no signs of self-destruction whereas in others this might be dominant. Patients showing self-destructive habits appear to have insight into their condition and, when put into restrainers, quieten down as though aware of this measure. When released, they became restless and even terrified as though realizing the compulsive drive to cause themselves hurt and damage. In our two cases this sign was fortunately mild and transient. In severe cases these children suffer from severe anorexia and may die of inanition. Vomiting may be a troublesome symptom.

Treatment is symptomatic only. Allopurinol, while it relieves symptoms of hyperuricaemia, especially abdominal and limb pain, has failed to halt the progress of the disease. Marks and co-workers have diagnosed the abnormality in a neonate, but even though allopurinol was administered at this stage, symptoms of the syndrome appeared several months later.

The clinical and biochemical features of the Lesch-Nyhan syndrome are now known to be due to the virtually complete absence of the PRT enzyme, most tissues being affected. This enzyme plays an important role in the formation of the ribonucleotides, guanylic acid and inosinic acid, in the re-utilization of the purines hypoxanthine and guanine. Although the exact mechanism remains to be elucidated, lack of this enzyme could lead to a depletion of the intracellular purine nucleotides guanylic and inosinic acid, and subsequent lack of feedback inhibition of 5-phosphoribosyl-1-pyrophosphate amidotransferase, which is the first enzyme unique to the pathway of purine (and uric acid) biosynthesis. Furthermore, 5-phosphoribosyl-1-pyrophosphate, which is a substrate for both the PRT and the amidotransferase reaction, would accumulate if the PRT enzyme was lacking and would result in an enhancement of the rate of the amido-transferase reaction. The mechanism whereby lack of PRT affects brain biochemistry and function, however, has yet to be elucidated.

The disorder appears to be inherited in an X-linked fashion, only males being affected through transmission from the mother. On the basis of the Lyon hypothesis of random inactivation of one of the two X-chromosomes present in female somatic cells, it has been shown that heterozygous mothers of affected children have two cell populations in skin fibroblast cultures, one showing a deficiency of the PRT enzyme and the other showing normal PRT activity. Affected males have only a single enzyme-deficient cell population. With a few exceptions, however, it has not been possible to detect obligate female heterozygotes by assay of PRT in erythrocytes. This is borne out in the present study, where the mother of the affected boys (i.e. an obligate heterozygote), was found to have normal PRT activity (Table I).

**Table I. Activity of Erythrocyte Hypoxanthine Guanine Phosphoribosyl Transferase**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Total observed counts/min</th>
<th>Uric acid (mg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
<td>35 400</td>
<td>6,0</td>
</tr>
<tr>
<td>Control 2</td>
<td>38 700</td>
<td>6,0</td>
</tr>
<tr>
<td>Control 3</td>
<td>40 900</td>
<td>6,0</td>
</tr>
<tr>
<td>Case 1</td>
<td>77</td>
<td>6,0</td>
</tr>
<tr>
<td>Case 2</td>
<td>95</td>
<td>4,7</td>
</tr>
<tr>
<td>Father</td>
<td>35 400</td>
<td>6,2</td>
</tr>
<tr>
<td>Mother</td>
<td>36 100</td>
<td>6,2</td>
</tr>
<tr>
<td>Sister</td>
<td>39 700</td>
<td>6,2</td>
</tr>
</tbody>
</table>

Genetic counselling for this disease thus requires demonstration of the heterozygous carrier state in female siblings of affected individuals by demonstration of mosaicism in...
skin fibroblast cultures and, more recently, by the detection of either the heterozygous carrier or an affected male in utero by biochemical studies of cultured amniotic cells at an early period in gestation.²

REFERENCES
7. Nyhan, W. L. (1968); Ibid., 27, 1091.

Fatal Myocardial Necrosis *
PROBABLY DUE TO TOXOPLASMA MYOCARDITIS

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SUMMARY
This report describes a 10-year-old girl, with a congenital neurological abnormality, whose terminal illness was rapid in onset and abruptly fatal.

The patient developed cardiogenic shock from myocardial necrosis. The electrocardiogram showed diaphragmatic myocardial damage, left anterior hemiblock and later features of increasing intraventricular conduction disturbance. Autopsy showed disappearance of myocardial fibres, with interstitial fibrosis and cellular infiltration. Circumstantial evidence suggested a diagnosis of toxoplasma myocarditis.


Extensive myocardial damage is rare in the paediatric age group and the causes are unusual. This is in contrast to the adult, in whom occlusive coronary artery disease is common. This report describes a 10-year-old girl with electrocardiographic evidence of severe transmural myocardial injury due to chronic myocarditis, probably a result of toxoplasmosis.

CASE REPORT
The patient was born in 1960, the third child of normal healthy parents. The pregnancy and labour were normal, birth weight was 3.3 kg and the neonatal course uneventful. Motor development (sitting and walking) and speech development were delayed, and later she was difficult to educate because of an IQ of 58. X-ray studies of the skull, examination of the fundi, urinalysis, a full blood count, the VDRL and Wassermann reactions were normal. An EEG at the age of 5 years was considered normal, but at the age of 7 years an EEG showed a diffuse abnormality in the right temporal area. The serum complement-fixation test tested against Toxoplasma gondii antigen was positive in a dilution of 1:4 and the end titre was 1:8. The indirect toxoplasma fluorescent antibody test was positive (2+) in a serum dilution of 1:25, and at a dilution of 1:400 there was a trace reaction. These results indicated active or recent infection with toxoplasma. The child was treated with pyrimethamine (Daraprim; Burroughs Wellcome) and sulphadiazine for 4 weeks, and 6 months later, when the toxoplasma tests were repeated, they were still positive. Further treatment was not given.

At the age of 10 years she presented with a 25-day history of recurrent vomiting. A full blood count was normal. Seventy-two hours after admission to hospital, during which time she was afebrile, she developed acute peripheral circulatory failure with anxiety, restlessness, cold and sweaty extremities, cyanosis, hypotension; and heart failure with a puffy face, ankle oedema, increasing hepatic enlargement and tachycardia. Cardiac murmurs were not present but a loud pathological 3rd heart sound was heard. The electrocardiogram (Fig. 1) showed sinus rhythm with a PR interval of 0.18 seconds; left atrial hypertrophy, left axis deviation (mean frontal QRS axis of -60°); and incomplete left bundle-branch block. The