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MASTER

JUVENILE HYPERURICEMIA WITH
NEUROLOGICAL MANIFESTATIONS¹

by

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FOOTNOTES TO TITLE PAGE

1. Two of the four patients reported here were admitted to the Clinical Research Center, supported by FR-55, USPHS. The other two were studied in the Argonne Cancer Research Hospital. A 16 mm color movie showing the neurological manifestations in the two patients studied in the Clinical Research Center has been made and persons interested in viewing the film should contact the authors.
2. Supported by a Career Research Development Award (K3-NB-7, 389) from the National Institute of Neurological Diseases and Blindness, USPHS.
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Primary gout is an uncommon disease of childhood. Among such cases, however, a number have been described in recent years which present not only with the manifestations of hyperuricemia but with marked neurological impairment as well (Catel and Schmidt, 1959; Riley, 1960; Lesch and Nyhan, 1964; Nyhan, Oliver and Lesch, 1965; Hoefnagel, 1965; Hoefnagel, Andrew, Mireault and Berndt, 1965; Sass, Itabashi and Dexter, 1965; Shapiro, Shephard, Dreifuss and Newcombe, 1966; and Seegmiller, Rosenblum and Kelley, 1967a). These cases have been regarded as representing a syndrome as distinct metabolically from adult gout on the one hand and from other instances of juvenile hyperuricemia by their neurological manifestations on the other (Lesch and Nyhan, 1964). The purpose of this communication is to present four additional cases of this syndrome in order to call further attention to the characteristics of the syndrome and the variations which may occur within the group.

CASE REPORTS

Michael I. -- This thirteen-year old boy is the elder of two brothers. Little information is available regarding their past history, as he has been abandoned by his parents. For the same reason no family history is available, nor are details concerning the pregnancy or delivery. It is stated, however, that this child was said at birth by the physician attending to have cerebral palsy. Thus, he is the only one in the series whose neurologic manifestations were apparently evident at an early age. His development was consistently retarded, and he has never achieved any significant

milestones in motor skills. He is able to speak, although at times is difficult to understand. He is not toilet-trained, does not walk, does not feed himself, and in no way is able to care for his own needs. It is said that he has had several urinary calculi in the past, but there is no other information available about his general health. Early in his life it was noted that he exhibited a tendency toward self-mutilation. He had bitten off the major portion of his upper and lower lips; self-mutilation also involved the upper extremities, and he had bitten off all but a small portion of the proximal phalanx of the thumb in the right hand. Because of the tendency toward self-mutilation, it was necessary to keep this child in restraints. He was usually happy and well-disposed to be cooperative and attentive, although on occasion he would spit at someone speaking to him. Self-mutilation in this boy was of particular interest in that it seemed to be a compulsive rather than a voluntary activity. As noted above, when restrained he was quite happy, but if the restraints were removed he became increasingly agitated, and his hands would immediately begin to move toward his mouth, and if allowed to go on he would begin to bite himself despite the fact that he cried out in pain and was evidently greatly disturbed by his own behavior. If he were then restrained again, he would quiet down and return to his normal state. This could be repeated over and over again, and whenever he was unrestrained he became agitated, obviously fearful, and would compulsively move one member or another toward his mouth, where it would obviously have been mutilated if this were not prevented.

General physical examination was unremarkable save for the evidence of self-mutilation. Again, as noted above, very little of his upper or lower lip

remained, and that which was present was heavily scarred. In addition he was missing most of his right thumb and had other scars on his hands. On examination of the abdomen a well-healed scar was found along the lower mid-line.

On neurological examination this boy showed evident mental retardation. It was not clear, however, how much of this was due to his rather severely impaired motor ability and how much represented truly diminished intelligence. He would perform simple movements to command, and could answer simple questions in the affirmative or negative. He ate without difficulty, but had no accomplishments beyond apparent recognition of his surroundings and of individuals. He did become attached to certain members of the nursing staff and quite evidently interacted with some individuals on a primitive level. In addition to the retardation he showed evidence of severe disturbance of movement, and a marked choreoathetosis with an associated double hemiparesis. The deep tendon reflexes were considerably increased, and both plantar responses were extensor. There was some sustained clonus at the ankles. There was a consistent increase in muscle tone, which seemed to be a combination of both spasticity and rigidity. When up on his feet the boy made walking movements with a scissor gait, but was unable to stand or walk by himself. He showed no evidence of sensory defect.

Mark I. -- This is the second of the two brothers, and was born on June 2, 1960. This boy, who is six years of age, is less severely afflicted than his older brother. As is the case with his brother, the history is sketchy because of the unavailability of a parent or similarly informed historian. The child was said to have been slow in his development from the beginning. It is not known, however, whether he showed

any clear abnormality at birth, and nothing is known of the history of the pregnancy or delivery. He is said to have passed a kidney stone earlier in his life but the details of this are not known. He has never walked, nor has he been able to care for himself in any manner. He is not toilet-trained, he does not feed himself nor dress himself. He is able to talk and interacts more with people than does his elder brother. He recognizes things shown to him in books and will carry on rudimentary conversations with individuals. He clearly recognizes people and interacts with his surroundings. He is able to play somewhat and will catch and throw a ball. Unlike his brother he has never shown any tendency toward self-mutilation, and can be maintained without restraints. It is noted that he is usually tied into a chair or a bed, though, because with his disorder of motility he has a tendency to fall out and to injure himself.

The general physical examination was normal. On neurological examination, the findings were primarily those of mental retardation with a disorder of motility. In the case of this child the retardation seemed moderate to mild. Again it was difficult to judge this because his difficulty with movement certainly impaired his performance, and his understanding and intelligence may be greater than is apparent from this performance. In contrast to his brother, he showed no choreic movement, but had marked athetosis. He held his head in a position of hyperextension, often with rotation to the right, and there was athetotic posturing and movement of the upper extremities, which was greater on the left than on the right. He was unable to sit without support and could not walk. Deep tendon reflexes were all considerably increased and the plantar responses were extensor. He also showed a combined spasticity and rigidity which were difficult to separate one from the other. He demonstrated

no sensory abnormality. The neurological syndrome in this boy, thus, was one of a combined mental retardation with athetosis and a mild double hemiparesis. He did not demonstrate any evidence of self-mutilation.

David T. -- This seven year old boy was born August 10, 1958, after an uncomplicated, full-term pregnancy. He was the second child in the family, and the family history is unremarkable except that the older brother died at the age of 3 months with a diagnosis of uremia. He was not known to have had hyperuricemia and no neurological abnormality had been noted. This child appeared normal to the mother until the age of 6 months, when she noted that he appeared to experience severe pain when touched over his back. In retrospect his development seemed retarded from the beginning. He did not recognize his mother until 4-5 months of age, and rolled over by himself at 10-11 months. He has never held his head up by himself, nor has he sat, crawled or stood. He does not speak but does make some attempts to play rudimentary games. He has attempted to feed himself but is not able to accomplish this. At the age of one year his mother noted some material in his diaper which had the appearance of sandy gravel. At the same age she also noted self-mutilating behavior, and restraint was required to prevent him from harming himself. At the age of two years he was first noted to have jerking movements of his arms and legs, and these have continued. His neurological status has been stable for some years. In 1965 he had an operation for the removal of kidney stones.

General physical examination showed a small boy who appeared younger than his reported age, but the only other abnormality was evidence of self-mutilation. Neurological examination showed findings which were predominantly those of an

extrapyramidal disorder of motility. The primary manifestation of this was athetotic posturing of the arms and head with moderately severe slow athetotic movements. Some rigidity was present both in the arms and legs, and the deep tendon reflexes were increased. The plantar responses were extensor on both sides, and it was not possible to determine whether there was any sensory abnormality. He was clearly severely retarded and evidenced only slight appreciation of his surroundings and a very modest ability to obey simple commands. He showed no control over his own movements. In addition there was marked loss of the tissue of the lower lip from self-mutilation. He was kept in restraints in order to prevent mutilation of the extremities, and became quite agitated when the restraints were removed.

Carl M. -- This thirteen year old boy was first admitted to the University of Chicago Clinics on January 24, 1966. His early history was unremarkable, and he was believed to be perfectly normal until the age of three, when he was noted to have uric acid crystals in the urine, on a routine urinalysis done when he had an upper respiratory infection. At the age of five he had abdominal pain and vomiting, and again was found to have uric acid crystals in the urine. He was relatively well until the age of ten, when he had another episode of abdominal pain and vomiting and on this occasion was found to have hematuria. Such episodes have recurred several times in the last few years. In September of 1965, during a flare-up of this difficulty he was found to have a uric acid of 26 mg% and a BUN of 56 mg%. The retrograde pyelogram done at this time showed hydroureter and hydronephrosis. In December of 1965 he had another episode of abdominal pain and vomiting and was found at this time to have a BUN of 172 mg% and a serum uric acid of 33 mg%. Urine again showed uric

acid crystals, and he was treated at that time with high fluid intake, sodium bicarbonate and Diamox. His BUN fell to 25 mg% and his uric acid to 9 mg%, at which time he was transferred to the University of Chicago Clinics from the University of Wisconsin, where the diagnosis of juvenile gout had been made.

Family history was unremarkable. General physical examination was normal except that he showed a patch of alopecia over the vertex of his skull. On neurological examination he was found to have an intact mental status, with the exception that he seemed somewhat dull. Psychological testing (Stanford-Binet Intelligence Scale Form LM) showed an IQ of 80. The remainder of the neurological examination was normal with the exception that he showed clear choreiform movements in his arms, but no abnormality of tone or posture. These movements were sometimes present at rest, but could be most easily elicited by having him hold his arms outstretched, when they were quite evident. The movements were clearly abnormal for a boy of his age.

METABOLIC STUDIES

The size of the miscible pool of uric acid and its rate of turnover were determined after intravenous injection of uric acid-2- C^{14} (Sorensen, 1960). The incorporation of a precursor into purines was assessed by determining the concentration of C^{14} in urinary uric acid following intravenous injection of glycine-1- C^{14} (Sorensen, 1966). Plasma and urine uric acid and its immediate precursors, hypoxanthine and xanthine, were determined by enzymatic spectrophotometric methods.

Table I summarizes the results of the metabolic studies in the four boys and

in the asymptomatic mother of D. T. Grossly excessive uric acid synthesis is evident. When the data were adjusted for the differences in body weight, the patients were found to have a daily uric acid production of from 42.8 to 62.2 mg/kg of body weight as compared to a normal value of 10 mg/kg. On a purine-free diet D. T.'s mother excreted 641 mg of uric acid per day, which is nearly twice the average value for normal women. However, uric acid production measured with isotopic uric acid was only modestly increased.

From Table I it can be seen that the percentage of the dose recovered as urinary uric acid- C^{14} agrees well with the estimate based on the mean daily urate excretion and the computed daily turnover. The amounts of uric acid excreted in the urine represented from 72.5 to 78.1 per cent of the total amount formed daily as indicated by the turnover rate. This relationship is consistent with the findings in normal subjects and is indicative of normal handling of uric acid at the renal level in our patients.

Intravenous injection of glycine- $l-C^{14}$ into the four patients resulted in a rapid and excessive incorporation of precursor into urinary uric acid, maximum isotope concentration being reached within 18 hours after the administration of glycine. This pattern has been taken as evidence of a shunt pathway whereby precursor is incorporated into uric acid more promptly than in normal man by bypassing nucleic acid purines. The cumulative recovery of isotope in urinary uric acid over a seven day period after the administration of glycine was strikingly accentuated, ranging from 1.35 to 2.08 per cent of the injected dose. This represents a 10 to 15-fold increase in the utilization of glycine for production of uric acid as compared to normal control subjects.

No evidence for a shunt pathway was found in the case of the mother of D.T., and the cumulative recovery of C^{14} in urinary uric acid was grossly normal.

Adult patients with gout characterized by overproduction of uric acid show a similar, but less marked pattern of incorporation of glycine into uric acid. It has been shown that in the adult type of gout the shunt pathway can be abolished by administration of the synthetic purine azathioprine (Imuran) with ensuing marked lowering of plasma and urinary uric acid (Sorensen, 1966). Two of the boys (C.M. and Ma. I.) received azathioprine for a period of ten days in a daily dose of 4 mg per kg body weight. In contrast to the situation in adult gout with overproduction of uric acid, azathioprine failed to reduce either the plasma uric acid level or the urinary excretion of uric acid (Fig. 1). Furthermore, the pattern and extent of glycine incorporation into urinary uric acid during treatment with azathioprine were remarkably similar to those obtained during the control period (Sorensen and Benke, 1967).

Allopurinol (Zyloprim[®]), an isomer of hypoxanthine, is a potent inhibitor of xanthine oxidase, the enzyme which catalyzes the oxidation of hypoxanthine and xanthine to uric acid. This compound produced a dramatic reduction in both plasma and urinary uric acid, but simultaneously there was an increase in the precursors of uric acid so that the total excretion of urinary oxypurines remained constant. With allopurinol, the cumulative recovery of carbon-14 in urinary uric acid was decreased, but when this figure was corrected for the simultaneous increase in hypoxanthine and xanthine, the incorporation of glycine- C^{14} into all oxypurines was comparable to the control value.

DISCUSSION

The striking neurological manifestations associated with remarkable aberration in uric acid metabolism indicate that these patients have a unique disorder. Patients with this syndrome have a four to six-fold increase in uric acid production when compared to control subjects of similar age and weight. This degree of overproduction of uric acid is far greater than that encountered in the adult type of gout. Whereas azathioprine in a dose of 4 mg per kg body weight per day abolished the shunt pathway in gouty men, this drug had no effect on uric acid metabolism in children with this disorder (Sorensen and Benke, 1967; Seegmiller et al., 1967a).

Recently Seegmiller et al. (1967a) have demonstrated virtually complete absence of the enzyme hypoxanthine-guanine phosphoribosyltransferase (E. C. 2.4.2.8.) in hemolyzates of washed erythrocytes as well as in fibroblasts grown in vitro from skin biopsies obtained from children with this syndrome. This enzyme converts the free bases hypoxanthine and guanine to their respective ribonucleotides by reaction with 5-phosphoribosyl-1-pyrophosphate. Seegmiller et al. have suggested that this enzyme plays an important role in the normal regulation of purine biosynthesis.

All patients with this syndrome have been boys. Published data on the pedigrees indicate an X-linked recessive pattern of inheritance as the most likely mode of transmission for the disorder (Hoefnagel et al., 1965; Shapiro et al., 1966). The mothers of affected children show no abnormalities on physical examination. Two carrier mothers reported by Hoefnagel et al. (1965) and by Shapiro et al. (1966) had elevated urinary uric acid outputs in the face of normal serum uric acids. The mother reported by us was also a hyperexcretor of uric acid. However, uric acid dynamics evaluated by the incorporation of glycine into urinary uric acid and by turnover studies

with uric acid-C¹⁴ were not grossly abnormal, thereby excluding metabolic isotope studies as a means of detecting the carrier state.

Seegmiller et al. (1967b) have demonstrated that female carriers show mosaicism for the defect in the enzyme hypoxanthine guanine phosphoribosyltransferase. They cultured fibroblasts from skin biopsies obtained from a carrier mother and found that approximately half of the cells incorporated tritiated hypoxanthine, whereas the other half did not. This suggests that abnormal chromosome distribution has occurred post-meiotically and that both abnormal daughter cells and normal cells coexist in the same person. The evidence presented supports the hypothesis proposed by Lyon (1962) to explain the lack of dosage effect of X-linked genes and the unusual variability of gene expression in females heterozygous for an X-linked gene.

The uniformity of the features of choreo-athetosis, double hemiparesis, mental retardation and self-mutilation has been repeatedly emphasized (Lesch and Nyhan, 1964; Hoefnagel, 1965; Nyhan et al., 1965; Hoefnagel et al., 1965; Sass et al., Shapiro et al., 1966). The cases presented here are of interest in that they show a disparity in the neurologic manifestations of the syndrome. Two patients (David T. and Michael I.) are typical in most respects. Both exhibit the marked pyramidal and extrapyramidal signs, are mentally retarded, and evidence self-destructive biting. The latter manifestation, as noted by others (Lesch and Nyhan, 1964; Shapiro et al., 1966), is unusual and deserves further mention. Although occasionally seen in non-hyperuricemic children with severe mental retardation it is rarely, if ever, as marked or as persistent. When kept restrained these children are docile and happy. If the restraints are removed, however, they become agitated and compulsively move an

extremity to the mouth where it is mutilated, obviously with great pain. The genesis of such complex behavior is unclear. In addition these patients appear to have more intellectual defect than, for example, the less severely affected brother (Mark I.). The more severely affected brother (Michael I.) is remarkable in that his signs were evidently sufficiently gross to be noted at birth. This would argue that the defect in purine metabolism is present and of consequence in utero. If this is the case, it would suggest that the primary defect might be an isolated enzyme defect analogous to what has been found in the neurolipidoses. Hypoxanthine-guanine phosphoribosyltransferase is present in brain normally and is especially concentrated in the basal ganglia (Seegmiller et al., 1967b). Since oxypurines accumulate abnormally in the cerebrospinal fluid of these patients (Seegmiller et al., 1967b), it would seem reasonable to suggest that this enzyme is absent or reduced in the brains of severely affected children. A deficiency of hypoxanthine-guanine phosphoribosyl has been established by assaying the brain of one of Dr. Nyhan's original patients, who died recently (Seegmiller et al., 1967b). Two of our patients (Mark I. and Carl M.), however, demonstrated less than the full-blown neurologic picture. In one (Carl M.) there were only mild choreic movements evident and he has normal intelligence. In the other (Mark I.) the disorder of motility was apparent but not as marked as in the severely involved patients and he showed borderline intelligence and no self-mutilation. It might be postulated that in these patients there is only a partial enzyme defect in the brain with concomitantly altered function. Such a concept would also be consistent with the fact that neuropathologic studies have not shown lesions consistent with the neurologic picture (Sass et al., 1965). The neurologic manifestations could, then, be viewed as the result of a functional alteration in neuronal metabolism which, since it does not involve structural elements, is not evidenced by an anatomic abnormality in the affected cells.

SUMMARY

This report concern the clinical and biochemical features in four boys (ages 6 to 13 years) from three families, suffering from a sex-linked neurological disorder associated with excessive purine synthests.

The disorder of movement was manifested by both pyramidal and extra-pyramidal involvement. Three patients exhibited the results of self-mutilation.

The biochemical characteristics include (1) a four to six-fold increase in uric acid production; (2) a strikingly accentuated incorporation of glycine-C¹⁴ into urinary uric acid with an isotope pattern signifying the presence of a shunt pathway; and (3) failure of azathioprine to suppress de novo biosynthesis. Allo-purinol produced dramatic reduction in both plasma and urinary uric acid, but simultaneously an equivalent rise in the excretion of uric acid precursors. No significant derangement in urate metabolism was found in one asymptomatic carrier female.

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TABLE 1

Summary of Data on Uric Acid Metabolism in Four Patients with Juvenile Hyperuricemia and Neurologic Manifestations and in One Carrier Female

Pt.	Age	Wt. kg	URIC ACID							C ¹⁴ -gly- cine in urine uric acid (7 days) % of dose
			Plasma	Miscible pool	Turnover		Recovery from Urine			
			mg%	mg	mg/day	mg/day kg	mg/day	% of turn- over	% C ¹⁴ uric acid	
Ma. I.	6	20	8.85	695	1,244	62.2	907	72.9	71.5	1.60
Mi. I.	13	26	8.74	869	1,454	55.9	1,054	72.5	77.4	1.47
C. M.	13	56	12.45	2,695	2,396	42.8	1,741	72.7	76.9	1.35
D. T.	8	16	7.73	---	---	---	840	---	---	2.08
N. T.*	33	80	4.58	850	821	10.3	641	78.1	82.1	.21

* Mother of D. T.

FIGURE LEGEND

Fig. 1. --Plasma uric acid and urinary oxypurines during a control period and during treatment with azathioprine and allopurinol in a boy with a syndrome of a neurological disorder associated with excessive purine synthesis. Oxypurines, comprising hypoxanthine, xanthine, and uric acid, are expressed as mg of uric acid.