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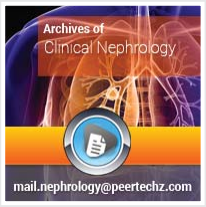

Clinical Group

Archives of Clinical Nephrology

DOI:http://dx.doi.org/10.17352/acn

ISSN: 2581-3870 CC By

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Received: 08 March, 2019
Accepted: 07 May, 2019
Published: 08 May, 2019

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Case Study

Malignant hyperthermia in Lesch-Nyhan disease

Abstract

Lesch-Nyhan disease is a heritable disorder of purine metabolism. Inheritance is X-linked and the disease occurs almost exclusively in males. Defective activity of hypoxanthine phosphoribosyltransferase leads to hyperuricemia and increased quantities of uric acid in the urine. All patients may develop urinary calculi, urate nephropathy, tophaceous deposits and clinical gout. Neurologic disability and abnormal aggressive behavior is characteristically self-injurious.

We report 2 patients with this disease who have been observed to have multiple episodes of hyperthermia which appear to fit the definition of malignant hyperthermia.

Introduction

Lesch-Nyhan disease is a disorder of purine metabolism in which massive overproduction of uric acid is associated with retardation of motor development, choreoathetosis and unusual behavior, the major manifestation of which is self-injury by biting [1]. The molecular defect is in the activity of hypoxanthineguanine phosphoribosyltransferase (HPRT) [2]. The enzyme is coded for by a gene on the X-chromosome [3,4]. More than 400 distinct mutations have been defined [5].

It is the purpose of this report to call attention to the occurrence in this disease of episodes of hyperthermia. They are identical to those of the malignant neuroleptic syndrome, and some of those patients have been treated with neuroleptic agents. However, it is clear that patients have had episodes in the absence of any known neuroleptic agent.

Reports case 1, KB

KB was seen at the University of California San Diego Medical Center at the age of 7 years. Erythrocyte activity of HPRT was absent. A younger brother also had Lesch-Nyhan disease. KG had been diagnosed 2 days before his third birthday.

Self-injurious behavior began early. He began head banging at 1.5 years of age. At 2 years 9 months he began biting his lip and tongue. His teeth were removed at 3 years of age. He was treated with allopurinol from the time of diagnosis. Speech was dysarthic, but understandable; he spoke in sentences. He could use a computer, pushing the keys with an attachment to his forehead. He had had multiple calculi, visualized on ultrasound, and passed one 3 months before admission.

On examination, he weighed 15.3 Kg. Length was 99 cm. He was diffusely hypertonic and had scissoring of the legs. Plasma concentration of uric acid was 1.9 mg/dl. Hemoglobin was 12.3g/L, and cells were macrocytic with MCV of 100.5. Urinary uric acid was 1:24, hypoxanthine 0.94 and xanthine 0.46 mmol/mol creatinine. CSF uric acid was 39.1, hypoxanthine 40.4 and xanthine 9.4 µmol/L.

He began having episodic hyperthermia at the age of 7 years with temperature recorded at 107.2°F/° 41.70°C. Leukocyte count was 17 x 10^3 µL with 82% polymorphonuclear cells. Cultures were negative. Urine was positive for blood. He was treated with intravenous $NaHCO_3$ to render the urine alkaline.

He had multiple similar admissions to the University of Iowa Medical Center, where he carried a diagnosis of malignant neuroleptic hyperthermia syndrome. At 9 years of age, in an episode his temperature was 107° F 41.6°C. Creatinine kinase was 75000 u/µl. Abdominal X-ray revealed ileus.

At 10 years of age, an episode was heralded by a fever of 106°F.

Blood pressure was 132/53. Plasma pH was 7.2 Rhabdomyolysis was recorded in the discharge diagnosis. Six years later he had a fever and Rhabdomyolysis. At 15 years of age, he developed somnolence and visible rhabdomyolysis. He had been admitted 10 days previously with a creatine kinase of 3000u. Temperature was 106°F.

Creatine Kinase was 7500u upon admission, and ranged from 8350u to 15047u. Cultures and chest film were negative. Abdominal X-ray revealed ileus. Myoglobin was documented in the urine.

Citation: Nyhan WL, Lucas M (2019) Malignant hyperthermia in Lesch-Nyhan disease. Arch Clin Nephrol 5(1): 001-002. DOI: http://dx.doi.org/10.17352/acn.000034

During that period, episodes of fever were so frequent a regimen of management at home was developed, employing a cooling blanket, a topical cream to the skin, and valium po. Episodes with temperature up to 107°F 41.2°C. Were managed in this fashion, but in one, myoglobinura was complicated by anuria, which resolved with admission to hospital and vigorous treatment with fluid and $NaHCO_3$.

He was treated with a number of drugs at various times over the years, often with quite a few more than allopurinol. Some of these have been associated with hyperthermia including aripiprazole, but this had been stopped on recommendation of University of Iowa consultant pediatric pharmacologist. They also recommended against the use of any neuroleptics dantelene and risperdal. Other medications included diazepam, trazodone, and propranolol.

Case 2. C.H. was a 25-year-old-patient with Lesch-Nyhan disease when he died in his sleep.

In the last few years of his life, he had had multiple admissions to hospital for unexplained fever. A typical episode at the age of 16 years lasted 10 days. When admitted to hospital, his temperature was 104.5° F, 40.3°C. An intravenous pyelogram revealed no calculi. Prior to treatment with allopurinol he had passed a number of urinary stones.

He displayed classic Lesch-Nyhan behavior. At the age 7 years, all his teeth had been removed. At 8 years of age a calculi was removed surgically. At 14 years of age when he was in an institution for special care, one of his arms was broken by an attendant. At 17 years of age he was burnt by a worker.

He had a huge library of videos he watched. His computer expertise had permitted him to disable the computer of his school such that no one but he could restore its function.

On examination he was wheelchair bound. He had increased deep tendon reflexes and choreoathetoid movements. There were no contractures.

Erythrocyte activity of HPRT was 0 nmol/min/ml protein (normal 202-615) at 20 µm hypoxanthine (normal 234-701). Activity of APRT was 132 (normal 26-101) nmol/min/ml protein. During treatment with allopurinol, his urinary excretion of xanthine and hypoxanthine were 112 and 449 µmol/L. (normal values 11 and 14 µmo/L.

Discussion

The Lesch-Nyhan disease has been characterized by abnormality in behavior, as well as by neurologic features and the major overproduction of purine in the de novo pathway. The behavior is best known for the self-injury, but it is also directed against others and has led to significant injury caused by caregivers. There are positive features to the personality; these are loveable children.

The occurrence of episodic hyperthermia has not previously been recognized as a feature of the disease. In our experience its occurrence has been sufficiently common that the association is clearly not the result of chance. The pattern is that of the malignant neuroleptic hyperthermia syndrome. Some patients have been treated with known neuroleptic offenders; however, it was clear in Case 1 that he had many febrile episodes at times when there were no obvious pharmacologic triggers.

Autonomic imbalance in this disease has been supported by a variety of findings. Abnormality in dopamine function was first indicated by autopsy study of neurotransmitters in the basal ganglia [6]. This was supported by positron emission tomography (PET) studies in vivo [7].

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