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The Clinical Findings in a Patient with Nonketotic Hyperglycinemia

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Extract

A male infant with hyperglycinemia presented with neonatal seizures and lethargy, but had neither ketosis nor hematologic abnormalities. Treatment with a low protein diet and glycine-binding agents was instituted at the age of 2 ½ months. Although greater alertness and reduced irritability were noted immediately, the treatment failed to prevent severe developmental retardation and persistent seizures.

Speculation

The structural and metabolic basis for the severe neurological damage seen in this rare hereditary metabolic defect is unclear. It seems imperative, however, that prompt diagnosis and therapy be instituted if one expects to offer a better prognosis. Attempts to maintain normoglycinemia by using a low-protein diet and glycine-binding agents may be useful if serum glycine levels are monitored carefully.

Introduction

In 1961 the first case of hyperglycinemia was described by CHILDS *et al.* [4]. The disorder was characterized by the neonatal onset of periodic ketosis, hyperglycinemia, and marked hyperglycinuria. Other features included persistent neutropenia, occasional thrombocytopenia, repeated infections, and subsequent developmental retardation, osteoporosis, and seizures. Several additional reports [5, 12] have described similar patients with progressive deterioration and, with some exceptions, death within the first year of life. A striking feature of this form of the disease was intolerance to ketogenic amino acids, particularly leucine. In 1965 GERRITSEN [6] reported a five-year-old male with seizures, developmental retardation, hyperglycinemia and hyperglycinuria, but without the other manifestations of the disease, i.e., acidosis, ketosis, neutropenia and osteoporosis. Other differences from previous case reports included a diminished excretion of oxalic acid in the urine and a failure to exhibit ketosis after a leucine load.

At least three other patients who resembled the nonketotic form of the disease clinically have been reported in detail [2, 7, 11] and other cases have been cited [3, 10]. The literature, however, reveals that the case of GERRITSEN is the only one which was well documented. The purpose of this report is to present the clinical features and some of the laboratory data in another case of the nonketotic form of hyperglycinemia. It serves as a clinical companion report to another paper describing the biochemical pathology in this disease [1].

Case Report

Historical and Physical Findings

This Caucasian male was the fourth child of nonconsanguineous parents and the product of a full-term, uncomplicated pregnancy and delivery. The birth

weight was 4 kg; the infant breathed spontaneously at birth and appeared healthy and vigorous. Although initial feedings were taken well, on the third day of life the infant became lethargic and refused feedings. Later that day, several generalized seizures were noted and treatment with phenobarbital was started. During the next two days, the infant remained lethargic and had two generalized seizures, each lasting several seconds. No family history of a similar disorder was elicited. Examination at seven days of age showed normal vital signs, a body weight of 3.6 kg, and an occipital-frontal head circumference of 36 cm. He was lethargic, with unsustained sucking, a depressed Moro response, and moderate generalized hypotonia. The fontanelle was flat and transillumination of the cranium was normal. Tendon reflexes were symmetrically brisk and there was no evidence of paresis. The funduscopic examination was normal. The heart, lungs, abdomen and genitalia appeared normal and no congenital anomalies were found.

Laboratory Data

Hematocrit was 52; white blood count was 11,600 with 21 % polymorphonuclear leukocytes and 78 % lymphocytes. BUN was 6 mg %; fasting blood sugar, 80 mg %; serum chloride, 104 mEq/l; carbon dioxide, 23.5 mEq/l; calcium, 10.9 mg %; phosphorus, 6.5 mg %; albumin, 3.7 g %; and globulin, 2.2 g %. The urine was negative for acetone, reducing substance and phenylpyruvic acid. Glucose levels in blood obtained one, two and three hours postprandially were 81, 69 and 91 mg % respectively. X-rays of the skull were normal. The spinal fluid showed slight xanthochromia with 195 red blood cells mm^3 and no leukocytes; the protein, 95 mg %; and the sugar, 46 mg %. Culture was negative. Bilateral subdural taps yielded no fluid. An EEG showed repeated spike activity over the right posterior head region. A two-dimensional paper chromatograph of urine for study of amino acids showed an excessive output of glycine, and a one-dimensional chromatogram of serum showed a striking elevation in the glycine level. These abnormal laboratory findings were confirmed by quantitative amino acid analysis, which showed a level of glycine in plasma of 11.3 mg/100 ml (controls 0.65 ± 0.23/100 mg [4]) and in urine of 313 mg/24 h (controls 12.9–117.3 mg/24 h [4]).

Laboratory data from subsequent hospitalizations at 3, 9 and 13 months of age revealed the following: blood leukocyte counts of 12,500 with 32 % lymphocytes and 64 % polymorphonuclear leukocytes; 6,900 with 78 % lymphocytes and 22 % polymorphonuclear leukocytes; and 14,300 with 46 % lymphocytes and 43 % polymorphonuclear leukocytes. The following values in mEq/l were found in serum: sodium, 145; potassium, 5.2; chloride, 109; and carbon dioxide, 25.4. Roentgenograms of the extremities showed a slight decrease in bone density and muscle mass. The cerebrospinal fluid contained no cells; the protein was 26 mg % and the glucose was 43 mg %. The fluid was clear under normal pressure. The cerebrospinal fluid glycine level was 1.01 mg/100 ml (control 0.07 mg/100 ml [6]). The findings of several electroencephalograms can be summarized as showing marked abnormalities, with diffuse symmetrically slow background activity and intermittent diffuse and shifting focal epileptiform discharges. A pneumoencephalogram at 3 ½ months of age revealed slight ventricular dilatation.

Table I. Comparison of clinical findings in two patients with nonketotic hyperglycinemia

	Case of GERRITSEN *et al.* [6]	Authors' case
Onset	'early postnatal period'	third day
Symptoms	listlessness, lack of spontaneous movements, failure to thrive and seizures	lethargy and generalized seizures
Physical signs	at 5 years: irritability, cachexia, microcephaly and severe developmental retardation, opisthotonus and hyperreflexia	at 33 months: irritability, good state of nutrition, borderline microcephaly, severe developmental retardation, hypotonia and hyporeflexia
Pneumoencephalogram	'porencephaly'	slight ventricular dilatation
Acidosis *Neutropenia* *Thrombopenia* *Osteoporosis*	absent	absent

Course

Initially, the patient remained in the hospital for fifteen days, during which time he remained lethargic and poorly responsive, but seemed to take feedings well. No further seizures were observed except for one episode of twitching of the right arm and right side of the face.

After the diagnosis of hyperglycinemia was established at approximately 2 ½ months of age, the patient was placed on a 1 % soybean protein formula [13]. In an effort to bind glycine, sodium benzoate, 2 g/day, and acetylsalicylic acid, 600 mg/day, were added to the regimen. On this therapy the patient seemed more alert and less irritable. Periodic examinations carried out over the next two years showed moderate generalized obesity, slowly failing head growth (at 33 months of age the occipital-frontal circumference was 48.0 cm, compared with a normal mean of 50.2 cm), and continued severe developmental retardation. The child demonstrated unawareness of his environment, wandering dysconjugate eye movements, and incessant turning of the head from side to side. There were decreased spontaneous limb movements, poor head and trunk control, diffuse hypotonia and hyporeflexia. No focal deficit was detected. The seizures, which initially were controlled with phenobarbital, recurred periodically, necessitating the addition of diphenylhydantoin to his therapeutic program. In spite of the anticonvulsants, both major and minor seizures continued at irregular intervals, often associated with feeding. Between ages 21 and 33 months, the seizures were more easily controlled, requiring the use of only phenobarbital. The patient was continued on the low protein diet, to which sodium benzoate and acetylsalicylic acid were added and appeared to tolerate the regimen well. When last seen at 36 months of age, he was still unable to roll over or sit unassisted and was unresponsive to social stimulation.

Discussion

When one compares the clinical findings in our patient with those of GERRITSEN [6] (table 1), some differences are noted. For example, hypotonia, hyporeflexia, and the normal nutritional state in our patient contrasts with the severe spasticity, opisthotonus and cachexia in GERRITSEN's case. These differences may reflect the variable spectrum of clinical manifestations seen in many metabolic diseases (e.g., phenylketonuria). The neonatal onset of listlessness and seizures is a common occurrence in hyperglycinemia, regardless of type, and subsequent severe developmental retardation with seizures seems to be uniform in those patients who survive beyond the neonatal period. Hypooxaluria was reported in GERRITSEN's case and was thought to be a characteristic finding in the nonketotic form of hyperglycinemia [6]. Oxalic acid excretion studies were carried out in our case, but this single study before and during dietary therapy is inadequate to warrant conclusions regarding oxalic acid metabolism. Normal levels of circulating leukocytes were found in both cases of the disease, as contrasted with the ketotic form of hyperglycinemia, in which intermittent leukopenia and neutropenia are common findings.

Although severe central nervous system changes are apparent clinically, observations on structural changes in the brain in both types of hyperglycinemia are limited to a brief autopsy report and the findings on one pneumoencephalogram. A neuropathological report on one patient with the ketotic form of the disease showed bilateral symmetrical encephalomalacia in the putamen and globus pallidus [9]. GERRITSEN's patient showed 'porencephaly' on pneumoencephalogram at six weeks of age [6]. The pneumoencephalogram in our patient showed slight ventricular dilatation, suggesting mild cerebral atrophy.

It has been suggested that careful dietary control is of benefit in this disorder, since one patient with the ketotic form of hyperglycinemia has been reported in whom strict dietary control begun in the neonatal period was of advantage [8]. Normal growth, development and intellectual function were recorded in this patient at three years of age. In our patient, the effect of the 1 % soybean diet with added sodium benzoate and acetylsalicylic acid is difficult to assess. Efforts to maintain normoglycinemia were not initiated until the age of 2 ½ months, by which time the patient had already shown definite signs of developmental retardation. There seemed little doubt, however, that our patient was less irritable and more alert on the restricted diet than on a more liberal diet, and his nutritional state was better than that described in GERRITSEN's untreated patient [6]. It is unfortunate that we were unable to measure the effects of the dietary regimen upon levels of glycine in plasma and urine.

Therefore, like many other metabolic disorders, nonketotic hyperglycinemia presents the challenge of early diagnosis and carefully monitored dietary control, if one expects to prevent irreversible central nervous system damage.

Summary

Hyperglycinemia and hyperglycinuria were discovered in a newborn infant who presented with convulsions and lethargy, and without acidosis or hematologic abnormalities. Treatment with a soybean formula and agents intended to bind circulating glycine was instituted at 2 ½ months of age. These measures reduced

the infant's irritability and heightened his state of alertness. At three years of age, the baby was in good nutrition but severely retarded, with mild microcephaly and occasional seizures. It seems likely that earlier institution of special dietary therapy might reduce the severity of the neurological deficit.

References and Notes

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