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Functional Hyperactivity of Hepatic Glutamate Dehydrogenase as a Cause of the Hyperinsulinism/Hyperammonemia Syndrome: Effect of Treatment

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Pediatrics 2000;106;596-600
DOI: 10.1542/peds.106.3.596

EXPERIENCE AND REASON—Briefly Recorded

"In Medicine one must pay attention not to plausible theorizing but to experience and reason together. . . . I agree that theorizing is to be approved, provided that it is based on facts, and systematically makes its deductions from what is observed. . . . But conclusions drawn from unaided reason can hardly be serviceable; only those drawn from observed fact." Hippocrates: *Precepts. (Short communications of factual material are published here. Comments and criticisms appear as letters to the Editor.)*

Functional Hyperactivity of Hepatic Glutamate Dehydrogenase as a Cause of the Hyperinsulinism/Hyperammonemia Syndrome: Effect of Treatment

ABSTRACT. *Objective.* **The combination of persistent hyperammonemia and hypoketotic hypoglycemia in infancy presents a diagnostic challenge. Investigation of the possible causes and regulators of the ammonia and glucose disposal may result in a true diagnosis and predict an optimum treatment.**

Patient. **Since the neonatal period, a white girl had been treated for hyperammonemia and postprandial hypoglycemia with intermittent hyperinsulinism. Her blood level of ammonia varied from 100 to 300 μmol/L and was independent of the protein intake.**

Methods. **Enzymes of the urea cycle as well as glutamine synthetase and glutamate dehydrogenase (GDH) were assayed in liver tissue and/or lymphocytes.**

Results. **The activity of hepatic GDH was 874 nmol/(min·mg protein) (controls: 472–938). Half-maximum inhibition by guanosine triphosphate was reached at a concentration of 3.9 μmol/L (mean control values: .32). The ratio of plasma glutamine/blood ammonia was unusually low. Oral supplements with *N*-carbamylglutamate resulted in a moderate decrease of the blood level of ammonia. The hyperinsulinism was successfully treated with diazoxide.**

Conclusion. **A continuous conversion of glutamate to 2-oxoglutarate causes a depletion of glutamate needed for the synthesis of *N*-acetylglutamate, the catalyst of the urea synthesis starting with ammonia. In addition, the shortage of glutamate may lead to an insufficient formation of glutamine by glutamine synthetase. As GDH stimulates the release of insulin, the concomitant hyperinsulinism can be explained. This disorder should be considered in every patient with postprandial hypoglycemia and diet-independent hyperammonemia.** ***Pediatrics* 2000;106:596–600; *hyperammonemia, hyperinsulinism, plasma glutamine, glutamate dehydrogenase.***

ABBREVIATIONS. HIHA, hyperinsulinism/hyperammonemia; GDH, glutamate dehydrogenase; GTP, guanosine triphosphate; CG, carbamylglutamate; ADP, adenosine diphosphate; CSF, cerebrospinal fluid.

Received for publication Nov 10, 1999; accepted Jan 19, 2000.
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Neonatal or infantile hypoketotic hypoglycemia with persistent hyperammonemia has been associated with only a few inherited conditions, ie, either defects of the carnitine transport system such as carnitine acylcarnitine carrier deficiency[1] or unusual forms of hyperinsulinism.[2] In affected patients coma and/or convulsions may rapidly develop. Therefore, immediate adequate treatment is required.

The more common cases of isolated hyperinsulinism may be the result of genetic defects in the insulin secretion by the pancreatic β cells.[3] These defects may reside in the plasma membrane sulfonylurea receptor (SUR 1) or an associated potassium channel (Kir 6.2) of the pancreatic β cells. Other causes of hyperinsulinism have also been described. These classic types of hyperinsulinism are not accompanied by elevated blood ammonia levels.

Recently, 10 patients with hyperinsulinism combined with hyperammonemia (HIHA) have been described.[2,4–10] Both sporadic and dominantly inherited cases were observed. The clinical histories more or less resembled those of leucine-sensitive hypoglycemia,[11] although disorders related with the ammonia disposal have not been reported in the latter condition. The HIHA syndrome has been studied in lymphoblasts. This syndrome was shown to be either the result of hyperactivity of glutamate dehydrogenase (GDH)[10] or impaired inhibition of GDH by guanosine triphosphate (GTP).[5] GDH catalyzes the conversion of glutamic acid into 2-oxoglutaric acid.

In this article, we report our attempts to treat a patient with HIHA in whom the primary defect could be established in liver tissue.

CASE REPORT

The female patient was born as the second child of healthy, nonconsanguineous parents after an uneventful pregnancy and delivery. Neither parent had ever experienced protein intolerance or a tendency to hypoglycemia. Her birth weight was 3840 g (75th centile [P75]), head circumference 36 cm (P75), and Apgar score 8/9. She was admitted on the twelfth day of life because of convulsions and cyanosis, associated with hypoglycemia. During the hypoglycemic episodes, which recurred after discontinuing the parenteral glucose supply, no ketone bodies were found in the urine. Hyperinsulinism was diagnosed on the finding of insulin levels of 28 and 45 μU/L at glucose concentrations of 2.8 and 2.7 mmol/L, respectively. When measured at low blood glucose levels, the 24-hour C-peptide excretion was 8.1 nmol (controls: 1.0–5.5). Blood ammonia was repeatedly elevated and varied from 100 to 200 μmol/L in the initial period (neonatal controls <80). All other routine clinical chemical analyses were normal.

An electroencephalogram did not show any epileptic changes, a computed tomography scan was performed at the age of 2 months and revealed widened ventricles as well as hypodensities of the frontotemporal white matter.

Feeding difficulties became a major clinical problem, necessitating gavage feeding from the age of 6 weeks. She was discharged at 14 weeks. At that time, treatment consisted of diazoxide (2 × 8 mg/day), a high-carbohydrate, and a protein-restricted diet [1.5 g/(kg·day)]. Arginine (and later citrulline, 5 × 1000 mg/day) and sodium benzoate (4 × 1500 mg/day) were administered to reduce the blood ammonia levels.

At the age of 2 years, the patient was referred to the University Children's Hospital and her condition was reevaluated. Her length was 84.5 cm (50th centile [P50]), body weight was 15 kg (>P90), and head circumference was 48 cm (P50). Her motor development was 7 months delayed; she showed a marked retardation of speech development. Blood ammonia was 312 μmol/L (controls: <50); no further clues to a diagnosis were found. Despite the high ammonia levels no clinical signs of hyperammonemia were noted (such as drowsiness, lethargy or ataxia). A brief trial with an extreme dietary protein restriction [.5 g/(kg·day)] did not have any effect on the ammonia levels. Plasma-free carnitine was 12 μmol/L (controls: 25–60), total carnitine 13 μmol/L (controls: 30–65). Carnitine supplements (2 × 750 mg/day) were administered. The treatment was adjusted by replacing the oligoglucose formula by uncooked cornstarch. Over the years, the diazoxide treatment was gradually adjusted to the requirements, reaching a dose of 4 × 50 mg/day at the age of 6 years.

As a result of the mitigated carbohydrate intake and the resulting decrease of fat deposits, the patient's adipose appearance markedly improved. However, her development showed a slow progress and the feeding difficulties persisted. These problems led to the decision to install a gastrostoma at age 5. During this intervention, a surgical liver biopsy was taken for diagnostic purposes. After the final diagnosis, treatment with oral supplements of carbamylglutamate (CG) (4 × 500 mg/day) was started. Blood ammonia levels tended to be lower on this regimen, but did not normalize completely. At the age of 6.5 years, her psychomotor development was estimated to be at a level of 4.5 to 5 years (not formally tested).

MATERIALS AND METHODS

Quantitative amino acid analysis was performed with a Biochrom 20 amino acid analyzer (Amersham Pharmacia Biotech, Cambridge, United Kingdom). Organic acids in urine were analyzed by gas chromatography/mass spectrometry (MD800, Fisons, Manchester, United Kingdom) of the ethoximated methyl esters after ethylacetate extraction. Orotic acid in urine was measured using a colorimetric assay.[12] Profiling of plasma acylcarnitines was performed by fast-atom bombardment mass spectrometry after solid-phase extraction and butyl ester formation.[13] All other clinical chemical analyses, including all aspects of insulin homeostasis, were performed by standard methods.

Glutamine synthetase activity was assayed in lymphocytes, leukocytes, and liver homogenate of the patient according to Rowe[14] with slight modifications. The synthesis of 1-^{14}C-glutamine from 10 mM 1-^{14}C-potassium glutamate was measured. The reaction mixture contained 10 mM phosphoenolpyruvate, 50 μM imidazole-hydrochloric acid (pH 7.2), 10 mM 2-mercaptoethanol, 1 mM ethylenediaminetetraacetic acid (pH 7.2), 20 mM NH_4Cl, 20 mM $MgCl_2$, 10 mM sodium adenosine triphosphate (pH 7.4), 5 μg (1 IU) pyruvate kinase and 3 μM rotenone. The total volume was 100 μL; incubation at 37°C was conducted for 30 or 60 minutes. After stopping the reaction with 400 μL of ice cold 4 μM imidazole-HCl (pH 7.2) plus 10 μM glutamine, the reaction product was isolated on a .5 × 7 cm AG-1x8 (200–400 mesh) ion exchange column, which was in the acetate form. GDH activity was assayed in a liver biopsy homogenate, essentially as described by Wreszcynski and Colman.[15] The reaction of 2-oxoglutarate with ammoniumchloride forming glutamate and the simultaneous oxidation of NADH was followed spectrophotometrically at 340 nm. Stimulation of the enzyme activity was achieved by adding 200 μM adenosine diphosphate (ADP), whereas the effects of the regulatory GTP were studied at concentrations of .01 to 10.0 μM.

Ornithine carbamoyltransferase and carbamoyl phosphate synthetase activities were measured in a liver biopsy specimen by spectrophotometric methods.

RESULTS

Because of the persistent hyperammonemia, detailed studies of the urea cycle were performed. Both fasting and postprandial plasma and urine amino acid concentrations were always normal. In particular, citrulline, arginine, and ornithine were not decreased, However, the ratio of plasma glutamine versus blood ammonia was unusually low (Fig 1), unlike that observed in patients with various urea cycle defects.[16] Plasma glutamate averaged 54 ± 25 μmol/L (controls: 30 ± 14), and was therefore not decreased. Urinary orotic acid excretions were inconsistent; at no occasion did we find a striking increase. Urinary organic acids, including 2-oxoglutarate, have always been normal. Cerebrospinal fluid (CSF) amino acids revealed a normal glutamine level (421, 732, and 800 μmol/L on 3 occasions, controls: 614 ± 241) and markedly increased levels of ammonia (100, 149 and 161 μmol/L, controls <11). The patient was treated with various regimens aimed at reducing the ammonia level. Neither a drastic reduction of the dietary protein to .5 g/(kg·day), nor supplementation with sodium benzoate and arginine or citrulline, led to changes of blood ammonia levels (Fig 2). In addition, treatment with neomycin remained without effect (data not shown).

At various occasions, simultaneous measurements of blood glucose and insulin were performed, clearly indicating hyperinsulinism. Early morning blood glucose was always in excess of 3 mmol/L; glucose levels during the day went down to 2.7 mmol/L with a concomitant insulin of 45 μU/L. On one occasion, blood glucose and insulin were checked before and after a meal. Glucose was 2.8 mmol/L before and 3.5 mmol/L 2 hours after the meal; simultaneous insulins were 28 and 101 μU/L, respectively.

The activities of hepatic carbamoyl phosphate synthetase and ornithine carbamoyl transferase were 463 nmol/(h·mg protein) (control: 587) and 36.9 μmol/(h·mg protein) (control: 45.5), respectively; both values were normal. Glutamine synthetase was assayed in leukocytes and liver, which resulted in values of

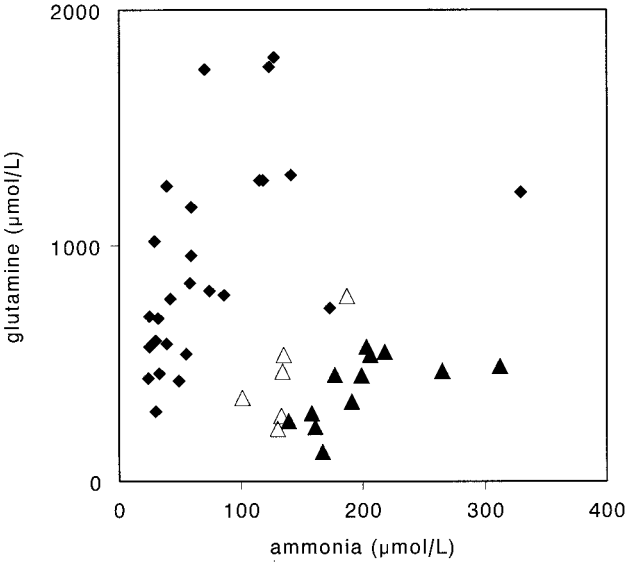

Fig 1. Relationships between blood ammonia and plasma glutamine in a patient with a regulatory defect of GDH on conventional treatment (▲), on treatment with CG (△), and in some patients with ornithine carbamoyltransferase deficiency (♦).

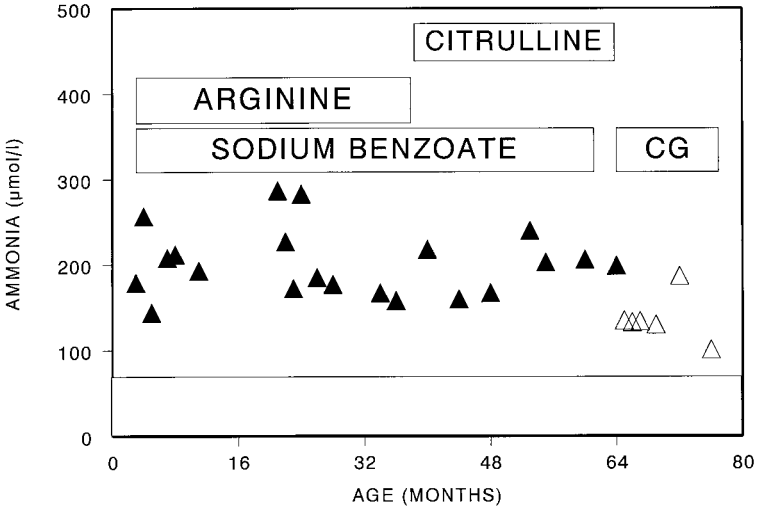

Fig 2. Blood ammonia levels in a patient with a regulatory defect of GDH under various regimens of treatment without (▲) and with (△) CG. No influence whatsoever of the amount of dietary protein could be observed. At this point the CG treatment had been given for 10 months.

.175 nmol/(min·mg protein) and 7.15 nmol/(min·mg wet weight) respectively. Control values for leukocytes and liver were .115 and 3.41, respectively.

The results of the GDH assay in liver are shown in Fig 3. Under standard conditions with ADP stimulation, the patient had a normal activity [874 nmol/(min·mg protein), controls 472–938 (n = 3)]. After addition of the inhibitor GTP, this activity decreased more slowly than in the control. Half-maximum inhibition was reached at a GTP concentration of 3.9 µmol/L (control mean: .32). Histologically, the liver tissue was normal; there were minimal signs of fibrosis. GDH in fibroblasts was normal [19.4 nmol/(min·mg protein); controls 7.9–26.8 (n = 3)]. The GTP inhibition was not tested in these cells.

Following the diagnosis, the patient was given a trial with oral CG (4 × 500 mg/day). This treatment was based on the hypothesis that she might suffer from a shortage of glutamate necessary for the synthesis of *N*-acetylglutamate. Blood ammonia levels were regularly checked during 10 months of follow-up and were found to be consistently lower than before the onset of the treatment (Fig 2).

DISCUSSION

Recurrent periods of hypoglycemia in infancy without the concurrent availability of alternative energy substrates such as ketone bodies or lactate, represents one of the most important metabolic abnormalities in young children. The same applies for hyperammonemia. A relatively mild increase of blood ammonia levels for short periods of time presumably leads to cerebral damage. Our patient, having only a moderate mental retardation, has had hyperammonemia with ammonia levels in blood and CSF of 100 to 300 µmol/L for 6 years in combination with episodically occurring nonfasting hypoketotic hypoglycemia. The latter was in fact the first presenting symptom, accompanied by convulsions. Subsequently hyperinsulinism was diagnosed and this was

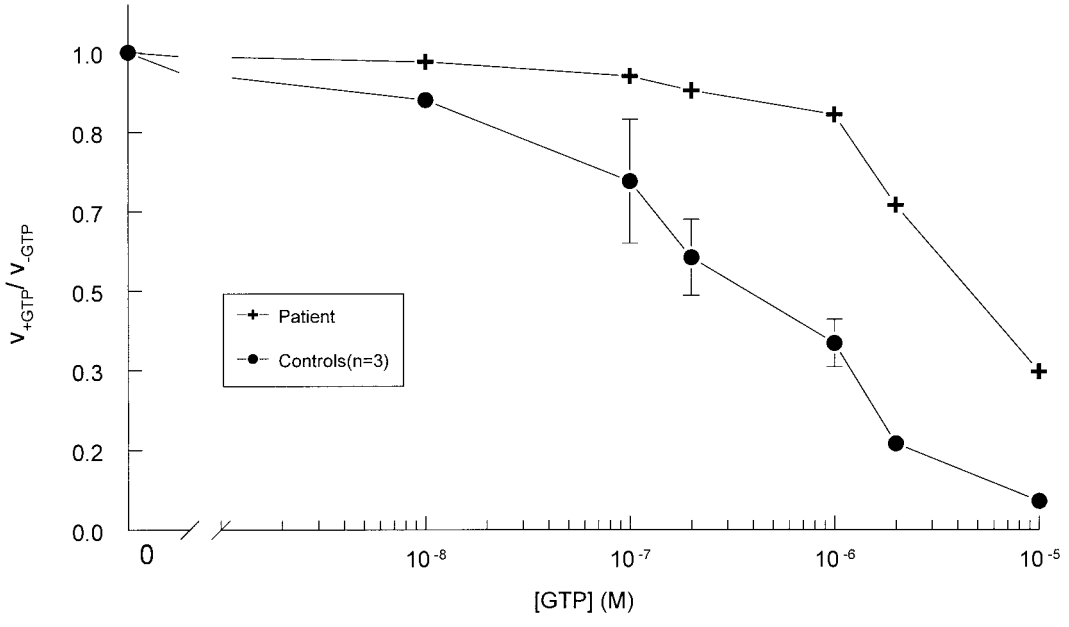

Fig 3. Inhibition of GDH by GTP in a liver homogenate. For comparison the basal activities of a patient with a regulatory defect of this enzyme (+) and three controls (●) were made to match. Absolute values of the basal activities are in the text.

treated successfully with diazoxide. It was clearly shown that the hypoglycemias were most prominent after a protein-containing meal, similar to the observations made in leucine-sensitive hypoglycemia.[11]

As there were no diagnostic clues to the hyperammonemia, treatment was originally directed at alleviating the symptoms by administrating citrulline (originally arginine) for stimulation of the urea cycle, and sodium benzoate for the direct removal of ammonia in the form of hippurate. When we found the aberration in the GDH, implying that in this patient the function of the urea cycle was not compromised, conventional treatment was stopped, and replaced by CG treatment.

Recently, the HIHA syndrome has been identified.[2] Not long thereafter, Stanley et al[5] disclosed regulatory mutations of the GDH gene in some of the patients. Thus far, 3 out of 10 patients, whose clinical history has been published, showed the GDH insensitivity toward GTP in lymphoblasts. The patient reported by Yorifuji et al[10] had a different mutation resulting in a permanent hyperactivity of GDH. No studies in liver were reported. Our data originating from liver tissue show that the basal GDH activity in the patient was normal, in accordance with the lymphoblast findings in sporadic cases.[5] In contrast, the basal GDH-activity in familial cases was moderately decreased. The half-maximum inhibitory concentration of GTP in the patient's liver was approximately 10-fold higher than in control liver tissue. This difference was more pronounced than previously found in the patients' lymphoblasts.[5] Presumably, GTP is present in hepatic tissue at a level that is sufficient to inhibit normal GDH. Mutant GDH—needing a much higher concentration of GTP for its inactivation—is supposed to be fully active when the GTP level is not decreased. There are only a few conditions in which the intracellular GTP concentrations are decreased, eg, hypoxanthine phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome) or purine nucleoside phosphorylase deficiency. Neither of these conditions is associated with a deranged GDH activity leading to hyperinsulinism or hyperammonemia.

Hepatic glutamine synthetase activity in our patient's liver was increased. This may be considered as a compensatory mechanism for the removal of ammonia. However, glutamine synthetase is a high-affinity, low-capacity enzyme and is apparently not capable of removing all excess ammonia. The CSF ammonia levels in our patient were quite high, although accompanied by normal glutamine levels. This result again raises the question of ammonia/glutamine toxicity to the brain. We have the impression that a single elevation of brain ammonia—without glutamine—showed a less deleterious effect on the brain than a combined increase. Hyperammonemic rats, treated with the glutamine synthetase inhibitor methionine sulfoximine, had less brain edema than untreated hyperammonemic rats.[17] Other reports have shown that brain glutamine synthetase is a saturable enzyme and that ammonia encephalopathy progresses only after saturation of this enzyme.[18] It remains to be established whether brain glutamine synthetase in the present patient was actually exhausted. We do not have information about CSF ammonia levels in patients with urea cycle defects.

The clinical spectrum of HIHA, as deduced from our patient and the literature,[2,4–10] is rather uniform. None of the patients was severely retarded. In general, moderate mental retardation or even normal development was reported. Convulsions—possibly the result of hypoglycemia—were invariably the presenting symptom. Although symptoms are expected to start in the first week of life, most patients were detected between 2 and 7 months. Blood ammonia levels were comparable in all patients, ranging from 75 to 350 μmol/L. None of the authors reported abnormalities of plasma amino acid profiles. There were 2 reports on increased 2-oxoglutarate levels in the urine.[8,9] It was not mentioned whether these patients had a decreased sensitivity of GDH inhibition by GTP. So there seems to be some biochemical heterogeneity of the HIHA syndrome. Thus far, all patients with a proven defect of GDH had a normal 2-oxoglutarate excretion, including the patient with a permanent hyperactivity of GDH reported by Yorifuji et al.[10]

Treatment of the hyperinsulinism varied from simple diazoxide administration (as in the present patient) to subtotal pancreatectomy. It has been shown that glutamate stimulates insulin secretion in rats.[19] The mechanism of this reaction is not entirely clear, but an enhanced oxidation of glutamate by GDH may be a contributing factor.[5] Recently, it has been shown that insulin secretion can be stimulated by leucine, which activates GDH.[20]

The differential diagnosis of infantile nonketotic hypoglycemia has been extended. It is now clear that in every case of suspected hyperinsulinism blood ammonia levels should be determined, preferably together with plasma amino acids. The HIHA syndrome may prove to be less rare than originally believed.

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ACKNOWLEDGMENTS

We thank Dr O. P. van Diggelen (Erasmus University Rotterdam) for the assay of the urea cycle enzymes; N. van Rossum-de Jong and L.M. Hussaarts-Odijk for the assay of GDH and glutamine synthetase; and R. Jankie for the amino acid analyses.

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Herbal Vitamins: Lead Toxicity and Developmental Delay

ABSTRACT. A case of lead poisoning from an Indian herbal vitamin is presented. The patient who was developmentally delayed was given an herbal vitamin from India to strengthen his brain. The tablet contained large amounts of lead and mercury, leading to significant lead burden. Vulnerability of families and lack of awareness of health care professionals of dangers of unknown herbal supplementation are discussed. *Pediatrics* 2000; 106:600–602; *herbal vitamins, lead poisoning, developmental delay.*

ABBREVIATIONS. EDTA, ethylenediaminetetraacetic acid; BAL, dimercoprol.

Low levels of lead ingestion can lead to cognitive deficits and even long-lasting neurodevelopmental deficits.[1] In the United States the most common source of lead is paint, whereas, in other countries, folk remedies are a significant source.[2] Families with developmentally delayed children are always seeking ways to improve their child's status. This quest makes families especially vulnerable to nonstandard medical intervention and to folk remedies. Many immigrant families are acculturated to non-American remedies. Many of these products have become available and are being used in the United States.

We present a case of chronic lead poisoning in the United States in an Indian child who had an established neurodevelopmental delay. His mother was giving him a natural medication to strengthen his brain.

CASE REPORT

S.P. is a 5-year-old Indian boy with static encephalopathy, seizures, and developmental delay from neonatal asphyxia. He was referred to a hematologist for persistent anemia (hemoglobin: 9.2 g/dL) without basophilic stippling, refractory to iron therapy. Initial investigation revealed normal iron stores and normal hemoglobin electrophoresis. To complete the workup, a blood lead level was obtained, which was 86 μg/dL. He was admitted to Childrens Hospital Los Angeles for chelation with calcium disodium ethylenediaminetetraacetic acid (EDTA) and dimercoprol (BAL). On physical examination he was alert and active but nonverbal. He was able to stand with support but not ambulate and had no focal neurologic defects. Skeletal and abdominal radiographs revealed no lead lines and no gastric lead particles. His lead level at the end of the chelation was 25.6 μg/dL. A 24-hour-urine collection (1245 mL) on day 3 of chelation revealed a lead level of 4480 μg/L or 5578 μg/24-hour (normally none detectable).

The mother who is well-educated and whose English is excellent, initially denied any exposure to lead or use of any folk medications. On further investigation, the mother had been giving S.P. a Tibetan Herbal Vitamin, in the form of tablets, 3 times per day for the past 4 years of his life. A traditional medicine healer told the parents that these tablets were pure medicinal herbs and plants that were prepared according to ancient Tibetan pharmacological traditions. These tablets were said to be free from any harmful or toxic substances and would actually promote brain growth and improve his mental capabilities. The tablets were produced in India and each was individually wrapped (Fig 1). The tablets were analyzed by the Los Angeles County Environmental Toxicology Laboratory for lead, arsenic, cadmium and mercury content (Table 1). It was estimated that S.P. ingested approximately 63 g of lead over the 4-year period. The radiographs of the tablets (Fig 2) were consistent with high lead and mercury content. The 24-hour-urine sample (1245 mL) was also analyzed for mercury (23 μg/L; 28.64 μg/24-hour) and arsenic (undetectable). Blood level of mercury was undetectable at <.5 μg/dL, and blood arsenic was .2 μg/dL (range: 0–3.0 μg/dL). Public health investigation of the home was negative for other sources of lead.

He was followed as an outpatient and chelated with succimer without incidence. Seven months after his first admission, his

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Received for publication May 3, 1999; accepted Dec 22, 1999.

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Fig 1. Individually wrapped vitamins.

TABLE 1. Analysis of Vitamins

Sample	Lead mg/kg	Mercury mg/kg
Tablet 1	35 300.0	12 800.0
Tablet 2	5 780.0	65.5
Tablet 3	54.8	3.0
Tablet 4	72.0	3.8

blood level was 76 μg/dL and he was readmitted for EDTA and BAL chelation. On day 2 of chelation he had a 1-minute tonic clonic seizure. On day 2 random urinary lead was 2310 μg/L and his blood lead level on discharge was 41.3 μg/dL. During the next 4 years S.P. underwent a total of an additional 6 chelations with succimer when his lead levels were >45 μg/dL. He had no other complication of chelation and after 4 years, his latest lead level was 24.5 μg/dL. He has maintained his growth parameters and made developmental progress, achieving ambulation with minimum assistance and he understands simple directions but remains nonverbal.

DISCUSSION

Alternative medicine and folk remedies are widely used and accepted by the general public. It is estimated that in 1990 $13.7 billion was spent on unconventional therapy.[3] Many academic centers have started programs to study and teach the use of alternative forms of therapy. When traditional therapies and medications cannot cure or significantly improve a chronic condition, families and patients are motivated to try alternative approaches. Children with developmental disabilities are especially vulnerable to the introduction of alternative therapies and medications. Past movements such as megavitamin therapy for retardation[4] and the Doman-Delacato technique for brain-damaged children[5] are examples of alternative interventions which were widely used in the United States without proven efficacy. Families in ethnic communities that have a tradition of alternative medicine and folk remedies will seek and support their use and availability in the community.

In our patient's case, the pressure on the family to use traditional medication arose from both the immediate family and from the community that had a great deal of experience and faith in the use of traditional medications from India. In discussing this with the mother, the perceived efficacy of these individually wrapped and colorful vitamins was enhanced by their designation as a Tibetan herbal medication.

In India, a form of traditional medicine called Ayurveda is usually made of vegetable products, occasionally from animal products and less often from metals and minerals.[2] The metals usually consist of lead, mercury, arsenic or, rarely, gold. Analysis of the patients' tablets demonstrated a variable and inconsistent amount of lead and mercury in each tablet. Although previous reports have identified Indian herbal medications as a source of lead, mercury, and arsenic poison, this is not widely appreciated by the lay population or medical community.[6–9] The vitamins had been obtained directly from a relative in India, costing approximately $40 for a 3-month supply. The mother was told it was formulated by a physician who was close to the Dalai Lama. The mother was very compliant with all traditional therapeutic interventions as she was with administering and securing a steady supply of the vitamin.

S.P.'s baseline developmental delay made the detection of the lead toxicity especially difficult. The effect of lead exposure during brain development has been well-documented.[1] The impact on S.P. of this level of toxicity over 4 years, in the context of a prior neonatal asphyxia, is not quantifiable. Two months after chelation the patient was able to walk with minimal support and was more communicative. Within 6 months of stopping the herbal vitamin, and after chelation, his mother and grandmother felt that he made significant progress in social interactions characterized by more awareness and joy of others, and responsiveness to directions. The persistence of the high lead levels after multiple chelations is not surprising given the estimated 63 g of lead

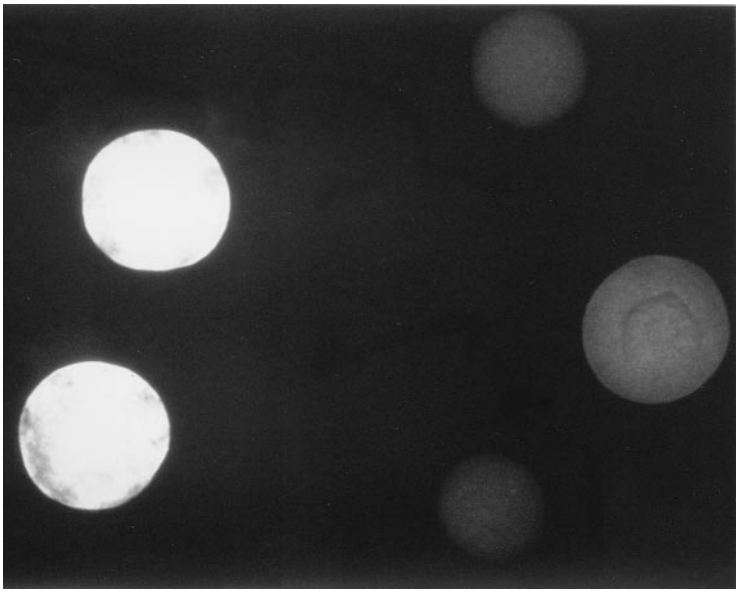

Fig 2. Radiograph of vitamins.

ingested and the known half-life of lead in bone of approximately 10 000 days.[10]

Physicians who treat diverse ethnic populations need to become aware of traditional herbs as an alternative treatment. There is also increasing use by the general population of natural and folk remedies as alternatives or enhancements to traditional medical interventions and prescriptions. Physicians need to inquire about their use, and be knowledgeable about benefits and risks. This awareness is especially needed when working with families who have developmentally disabled children.

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Human Granulocytic Ehrlichiosis Presenting as Abdominal Pain

ABSTRACT. Human granulocytic ehrlichiosis (HGE) is an emerging infectious disease that primarily affects adults. Typical clinical features include fever, headache, and myalgias. This case represents the youngest reported patient with HGE. Her clinical presentation was unusual in that she presented with severe abdominal pain. In addition, she did not develop the typical spectrum of laboratory abnormalities that has been reported in adults. This patient's course suggests that the presentation of HGE may be more varied than previously reported. ***Pediatrics*** **2000;106:602–604;** ***human granulocytic ehrlichiosis, abdominal pain, acute abdomen, fever, tick bite.***

ABBREVIATIONS. HGE, human granulocytic ehrlichiosis; PCR, polymerase chain reaction; IFA, indirect fluorescent antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CT, computed tomography (scan); IgG, immunoglobulin G; IgM, immunoglobulin M.

Human granulocytic ehrlichiosis (HGE) is an emerging infectious disease caused by an organism closely related or identical to *Ehrlichia equi* and *E phagocytophilia*.[1,2] In the northeastern United States the organism is transmitted by the deer tick, *Ixodes scapularis*, which is the same vector that transmits the cause of Lyme disease, *Borrelia burgdorferi*. In contrast to Lyme disease, however, HGE is rare in patients <20 years old and most cases occur in males.[3] Clinical features of the illness include fe-

Received for publication Oct 4, 1999; accepted Jan 27, 2000.
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ver, headache, and myalgias, although there are no consistent physical findings.[4–6] Laboratory hallmarks are neutropenia, thrombocytopenia, and mildly elevated liver transaminases.

The diagnosis of HGE can be confirmed by finding cytoplasmic inclusion bodies (morulae) in granulocytes on a Wright-stained blood smear. Typically, morulae are found in 1% to 6% of granulocytes,[1] although a sensitivity as high as 80% has been reported.[6] Polymerase chain reaction (PCR) to the 16S rDNA sequence has been shown to be rapid, sensitive (86%), and specific (100%).[7] However, PCR testing is not widely available. At the present time, the diagnosis of HGE is most often confirmed by either a fourfold rise between acute and convalescent sera in the indirect fluorescent antibody (IFA) titer to *E equi* or a single titer ≥1:80.[8]

The following case is a very young patient with HGE who had an unusual presentation with acute abdominal pain.

CASE REPORT

A 5-year-old girl presented to the emergency department with a 2-week history of fever and a 2-day history of abdominal pain. There was no vomiting or diarrhea. Another physician had begun treating her with amoxicillin 1 week before for presumptive Lyme disease. There was no history of a tick bite or erythema migrans and her Lyme antibody titers obtained at that time were subsequently reported to be negative. In the emergency department her physical examination was notable for a temperature of 103°F and right lower quadrant tenderness on deep abdominal palpation. Laboratory results included a normal urinalysis, a hemoglobin of 11.2 g/dL, a hematocrit of 32%, a white blood count of 13 400/mm^3 (59% neutrophils, 7% bands, 26% lymphocytes with rare atypical forms, 7% monocytes, and 1% eosinophils), and a platelet count of 287 000/mm^3. A blood culture was obtained. The pain resolved without treatment and she was discharged.

She returned to the emergency department about 12 hours later with a temperature of 103.6°F, pallor, abdominal distension, and diffuse abdominal tenderness. A repeat complete blood count was significant for a hemoglobin of 9.1 g/dL, a hematocrit of 27%, a white blood cell count of 8000/mm^3 (59% neutrophils, 5% bands, 26% lymphocytes, and 10% monocytes), and a platelet count of 278 000/mm^3. The serum electrolytes, prothrombin time, partial thromboplastin time, and a urinalysis were all normal. The aspartate aminotransferase (AST) was minimally elevated (42 U/L), but the alanine aminotransferase (ALT) was normal (36 U/L). Abdominal radiographs and a computed tomography (CT) scan of the abdomen with intravenous contrast were significant for mild hepatosplenomegaly. In view of the persistent high fever, specimens were obtained for serum antibodies to *B burgdorferi*, *E chaffeensis*, and the HGE agent, as well as for PCR testing for the 2 causative agents of human ehrlichiosis. The patient was admitted to the hospital.

The next day, the white blood cell count was 8900/mm^3 (68% neutrophils, 26% lymphocytes, and 6% monocytes), the platelet count was 298 000/mm^3, and an abdominal ultrasound revealed fluid-filled loops of bowel in the right lower quadrant without any free fluid. Intravenous ceftriaxone therapy was initiated. On the third hospital, day the fever, abdominal pain, and distension persisted, and guarding and rebound were noted on abdominal palpation. A repeat abdominal CT scan with oral contrast showed distended loops of small and large bowel without any masses or free fluid. In view of a concern about a possible perforated appendix, an exploratory laparotomy was performed. At surgery, mild nonspecific serositis of the vermiform appendix was found along with a 7-mm lymph node, which subsequently was reported to show nonspecific reactive changes. Postoperatively, her electrolytes and liver function tests were normal (AST: 38 U/L; ALT: 31 U/L), but the white blood cell count had decreased to 3600/mm^3 (69% neutrophils, 29% lymphocytes, and 2% monocytes) and the platelet count was 195 000/mm^3. The following day (hospital day 4), the New York State Department of Health laboratory reported that the PCR was positive for the presence of HGE agent 16s rDNA and negative for *E chaffeensis*. Treatment with doxycycline was started and the patient was afebrile the next day.

Subsequently, the acute polyclonal IFA for *E equi* was reported as nonspecific, but a convalescent specimen obtained 23 days later was positive, with a titer of 320. Four months after the hospitalization the patient was well. At that time her IFA for *E equi* immunoglobulin G (IgG) was positive (1:512), but the immunoglobulin M (IgM) was negative (<1:20). Both IgG and IgM IFA titers for *E chaffeensis* were negative.

DISCUSSION

This case has several unusual features. First, to our knowledge, this the youngest patient reported with documented HGE.[4,5] The diagnosis was confirmed by the elevated IFA to *E equi*, the positive PCR for the HGE agent, and the increase in IFA *E equi* IgG titer between the acute and convalescent specimens. The vast majority of cases of HGE have been reported in adults, with very few diagnosed during the first 2 decades of life. This is in sharp contrast to Lyme disease, in which the incidence is much higher in children than adults. There is no clear explanation for this age discrepancy, despite the fact that the same vector spreads the agents that cause both HGE and Lyme disease.

Second, although many of the patient's symptoms were typical for HGE, there have been no previous reports of HGE mimicking acute abdominal pain in any age patient. In fact abdominal symptoms are unusual, although Wallace et al[5] did report 3 patients with gastrointestinal hemorrhages.

Finally, our patient did not manifest the spectrum of laboratory abnormalities typically seen in adults with HGE.[6] She did have leukopenia, but her platelet count remained normal and she had only a minimal, transient increase in her AST. Once other young patients with HGE are reported, it will be interesting to see whether the clinical presentations are different in children and whether they develop the characteristic laboratory abnormalities noted in older patients. If HGE is suspected, prompt treatment with doxycycline is indicated, pending laboratory confirmation.[9,10]

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NO HELP IN SIGHT FOR THE POOR

With globalization, goods, capital, culture, and knowledge readily diffuse across borders, but political and social institutions often lag a step behind. Among populations increasingly interconnected, infectious spill over borders but afflict the poor and excluded disproportionately. For those less fortunate, the boundaries seem only semipermeable to the drugs and technologies that are life-saving . . . and the benefits of globalization may come late, or not at all.

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Submitted by Student

Functional Hyperactivity of Hepatic Glutamate Dehydrogenase as a Cause of the Hyperinsulinism/Hyperammonemia Syndrome: Effect of Treatment

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Pediatrics 2000;106;596-600
DOI: 10.1542/peds.106.3.596