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.)*

Severe Ethylene Glycol Ingestion Treated Without Hemodialysis

ABSTRACT. Fomepizole (4-methylpyrazole, Antizol) is being increasingly used in the treatment of ethylene glycol toxicity in adults. Little experience exists with this drug, however, in the pediatric population. We present a case of ethylene glycol poisoning in a child where use of fomepizole averted intravenous ethanol infusion and hemodialysis, limited the duration of intensive care monitoring, and decreased the overall cost of treatment. *Pediatrics* 2001;107:172–174; 4-methylpyrazole, fomepizole, Antizole, ethylene glycol, pediatric.

ABBREVIATION. ADH, alcohol dehydrogenase.

f all alcohols, ethylene glycol has the greatest clinical toxicity. In 1998, >5376 ethylene glycol exposures were reported in the United States, with 1538 exposures occurring in the pediatric population.¹ Formerly, treatment for ethylene glycol poisoning required intravenous ethanol infusion, hemodialysis, or both. Fomepizole (4-methylpyrazole, Antizol) was recently approved by the Food and Drug Administration as an antidote for ethylene glycol poisoning in adult patients.² In selected patients, fomepizole may eliminate the need for ethanol therapy and dialysis with attendant cost savings.3-5 Although clinical experience with fomepizole has been expanding, pediatric use remains uncommon.^{6–9} We report a case of ethylene glycol poisoning in a child treated with fomepizole. Fomepizole obviated the need for intravenous ethanol infusion and hemodialysis, limited the duration of intensive care monitoring, and decreased the overall cost of treatment.

CASE REPORT

A 13-year-old female ingested approximately 4 fluid ounces of antifreeze after an argument with her father. She was brought to a local emergency department approximately 30 minutes after the ingestion. Initial vital signs were temperature, 99.4°F; pulse, 115 beats per minute; blood pressure, 144/76 mm Hg; respiratory rate 20 breaths per minute. She weighed 80 kg. The physical examination was normal with no evidence of intoxication.

Initial laboratory evaluation revealed a white blood cell count of 9900/mm³, hemoglobin 11.8 g/dL, and platelets of 317 000/ mm³. Serum chemistries were sodium 144 mg/dL, potassium 4.3 mg/dL, chloride 105 mg/dL, bicarbonate 25 mg/dL, blood urea

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nitrogen 11.0 mg/dL, creatinine 0.8 mg/dL, and glucose 105 mg/dL. Anion gap was 14 mg/dL. An arterial blood gas showed pH 7.38, Pco_2 38 mm Hg, and Po_2 116 mm Hg. Aspirin, acetaminophen, blood alcohol, and pregnancy tests were negative.

An initial urinalysis was unremarkable, although the urine fluoresced beneath a Wood's lamp. The serum osmolarity was 351 mosM/L; the calculated osmolarity was 298 mosM/L, yielding an osmolar gap of 53 mosM/L. The measured serum ethylene glycol concentration was 103 mg/dL.

Transfer to a tertiary care center was arranged. Before transfer, however, the patient became ataxic and dysarthric. She therefore received an intravenous ethanol bolus of 600 mg/kg, followed by a continuous infusion of 20% ethanol administered at 30 mL/ hour. She promptly became obtunded after the bolus and required orotracheal intubation for airway protection. On arrival at the referral intensive care unit she had a serum ethanol concentration of 144 g/dL, and an arterial blood gas of pH 7.34, PCo₂ 38 mm Hg, and Po₂ 277 mm Hg. Urinalysis revealed calcium oxalate crystals.

Six hours after the ingestion she received a 15 mg/kg intravenous loading dose of fomepizole. Arterial pH remained above 7.35. She was successfully extubated and transferred to a general medical floor approximately 12 hours after arrival. Intravenous fomepizole, 10 mg/kg, was administered every 12 hours. A serum ethylene glycol concentration drawn 24 hours after ingestion was 23 mg/dL. By 36 hours after ingestion it had decreased to 13 mg/dL. At discharge on the third hospital day, she had a blood urea nitrogen of 10 mg/dL and a serum creatinine of 0.6 mg/dL. Psychiatric follow-up was arranged on an outpatient basis. During her hospitalization she required a total of 5 doses of fomepizole. A copy of the patient's hospital charges was reviewed. Based on the hospital's current cost structure, an analysis of intensive care versus general medical floor fees (excluding physician's charges) is provided in Table 1.

DISCUSSION

Ethylene glycol is found in radiator antifreeze, deicing solutions, and other formulations. Pure ethylene glycol, which has a slightly sweet taste, is odorless and colorless. After ingestion, ethylene glycol is rapidly absorbed from the gastrointestinal tract. The presence of ethylene glycol in blood produces the osmolal gap.¹⁰ Nontoxic itself, ethylene glycol is converted enzymatically to toxic compounds. More than 85% of ethylene glycol is oxidized to glycoaldehyde by alcohol dehydrogenase (ADH). Acidosis is attributable to the presence of glycolic, glyoxylic, and oxalic acids.¹¹ Ethylene glycol is unique among alcohols in that a significant amount is eliminated unchanged in the urine.¹²

The diagnosis of ethylene glycol poisoning is supported by the clinical findings of mental status alteration, metabolic acidosis, and oxalate crystals in the urine. The diagnosis is established, however, by the measurement of serum ethylene glycol concentration or by an estimate of the toxin's concentration extrapolated from the osmolal gap.¹⁰ Antidotal therapy is reserved for serum ethylene glycol concentrations >20 mg/dL. Ethanol, preferably a 10% solution, is

Intensive Care Unit		General Medical Floor	
Bed cost:	\$ 8034	Bed cost:	\$ 3864
Laboratory		Laboratory	
(hourly ethanol level:	\$ 2000	(daily ethylene glycol level):	\$ 660
(daily ethylene glycol level):	\$ 660		
Therapy		Therapy	
1. Ventilation, oxygen:	\$ 3558	Fomepizole	\$ 5000
2. Ethanol drip:	\$ 27	1	
Consults (for dialysis):	\$ 200	Consults:	None
Dialysis:	\$ 1244	Dialysis:	None
Total cost:	\$15 723	Total cost	\$ 9524

TABLE 1. Cost Comparison of Treating Ethylene Glycol Ingestion With Conventional Therapy

 Versus Fomepizole
 Fomepizole

administered as a 600 mg/kg intravenous bolus followed by continuous infusion. The goal of therapy is to achieve a minimum serum ethanol concentration of 100 mg/dL; at this level and above, ethanol inhibits ADH and prevents the metabolism of ethylene glycol. Hemodialysis, in conjunction with ethanol therapy, is recommended for patients with ethylene glycol levels >50 mg/dL.^{5,12,13}

Fomepizole, a competitive inhibitor of ADH, has been approved as an antidote for ethylene glycol intoxication in adults.² Like many pharmaceuticals, fomepizole is not approved for use in children. Independent of patient age, fomepizole potentially offers a significant advantage because it eliminates the need for intravenous ethanol therapy with its attendant problems. In children, the hyperosmolarity of an ethanol solution (1713 mosM/L) often requires central venous access.¹⁴ Side effects of ethanol in young children include obtundation, hypoglycemia, and hypothermia.⁴ Maintaining a serum ethanol concentration of 100 mg/dL is a difficult task that requires frequent monitoring. An ethanol infusion may itself produce frank intoxication as a result of individual variations in metabolism and response to ethanol. As this case illustrates, even appropriate ethanol doses may inadvertently produce obtundation. In contrast, fomepizole does not cause hypoglycemia and has no sedating side effects.² Also, fomepizole is administered as an intravenous infusion every 12 hours; serum fomepizole concentrations do not require monitoring. Consequently, fomepizole has substantially greater safety and ease of administration compared with ethanol therapy.²

As this case also illustrates, fomepizole can eliminate the need for hemodialysis in those with severe ethylene glycol poisoning. In addition to the risks associated with its invasiveness, hemodialysis is more technically demanding for children than adults. Also, hemodialysis has relatively limited availability for pediatric patients.13 Having an affinity for ADH >8000 times that of ethanol, fomepizole interrupts the enzymatic metabolism of ethylene glycol so that the parent compound can be eliminated in the urine.¹⁵ In our patient, maintenance of urine output during fomepizole therapy was sufficient to avert hemodialysis, despite an elevated ethylene glycol concentration. Current recommendations still call for hemodialysis in those who have already developed metabolic acidosis.⁵

Finally, fomepizole offers significant cost savings

over existing therapies. Current protocols require that patients receiving ethanol infusions be admitted to an intensive care unit.5 Because of the sedating effect of ethanol, these patients may require intubation for airway protection and ventilatory support. As Table 1 indicates, fomepizole has the potential to reduce the cost of treating this intoxication by at least 40%. Moreover, Table 1 does not include costs typically associated with intensive care monitoring, such as portable chest radiographs and serial arterial blood gases. In addition, nursing costs for hemodialysis and intensive care, typically much higher than those for general floors, are not included in the analysis. Finally, the recommended course of fomepizole requires approximately 4 multiuse vials, at a cost of \$4000. Because our institutional pharmacy does not permit successive withdrawal of medicine from a single vial, an additional container was required at a cost of \$1000. The aforementioned estimate is therefore conservative. As a result, the actual cost savings of fomepizole are more significant than described here. Although the patient in this report did not enjoy all the cost savings described above, primarily because of complications of ethanol therapy, fomepizole shortened her intensive care unit course and decreased her cost of hospitalization.

As pediatric experience with fomepizole grows, the drug is being shown to be safe and effective. For children it offers the added benefits of eliminating ethanol administration and, potentially, hemodialysis. Cost savings from fomepizole can be substantial.

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Glutaric Aciduria Type 1 and Nonaccidental Head Injury

ABBREVIATIONS. NAI, nonaccidental injury in childhood; GA1, glutaric aciduria type 1.

Subdural hemorrhage has been a recognized manifestation of nonaccidental injury in childhood (NAI) since 1860.¹ The presence of subdural collections, often with coexisting retinal hemorrhages, fractures, and multiple traumatic injury, greatly raise the clinical index of suspicion for child abuse.^{2–5} The finding of subdural blood in an infant presents a difficult and important diagnostic challenge for pediatricians given the legal and social import of child abuse.

Glutaric aciduria type 1 (GA1) is a relatively rare inborn error of metabolism that presents in infancy with a range of neurological features. It is increasingly recognized that GA1 is associated with acute subdural hemorrhage and chronic subdural collections.^{6–8}

We present a case of an infant with bilateral subdural hematoma in whom a diagnosis of NAI was initially made. Subsequent metabolic investigation of the child led to a diagnosis of GA1 with important therapeutic, social, and legal consequences.

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CASE REPORT

An 8-week-old white male infant was referred to this hospital by his general practitioner after a head injury. The history from the mother was that the infant was upstairs being carried by his 7-year-old brother who fell, dropping the infant against a wall. She was downstairs and was alerted by the infant's cry. The infant vomited and was noted to be drowsy. He was then taken immediately to the general practitioner's office.

The infant was born by spontaneous vaginal delivery at 38 weeks' gestation after a normal pregnancy. He was noted to be asymmetrically growth retarded with weight below the 10th percentile and head circumference on the 50th percentile. The infant was bottle-fed from birth, received the first diphtheria, tetanus, and pertussis-polio-*Haemophilus influenzae* type b vaccination, and was well until the day of presentation.

The family consisted of this infant and 2 older half-siblings, aged 4 and 7, who were well. All 3 children were from different nonconsanguineous partners. The mother was a 25-year-old, unemployed, and unsupported lone parent with learning difficulties who was known to social services.

On presentation the infant was noted to be well-grown, quiet, and pale, but alert. The head circumference was now over the 97th centile. The anterior fontanelle was large and full with splaying of the coronal sutures. There was some erythema over the right parietal region but no evidence of bruising or external injury. The systemic examination, including neurologic examination, was unremarkable.

A skull radiograph showed no fractures. Routine laboratory investigations including coagulation studies were within normal limits. A transcranial ultrasound scan revealed bilateral subdural collections. On the evening of admission the infant developed right-sided focal seizures that required treatment with phenobarbitone and phenytoin.

A computed tomography scan was performed (Fig 1). This showed bilateral frontal subdural collections larger on the right side, with some effacement of the cortical sulci. Additionally there was a fresh subdural hemorrhage high in the left parietal region. The ventricles were rather small in size. Diffuse low-density white matter changes in both hemispheres were also reported.

The infant underwent emergency drainage of blood-stained fluid from both subdural collections. He had no further seizures. A radiographic skeletal survey was conducted. It was reported that there was a fracture through the midshaft of the right radius and a metaphyseal fracture of the distal right radius with significant periosteal reactions. Formal ophthalmologic review revealed 1 pinpoint hemorrhage on the right fundus.

In view of the history and the pattern of clinical and radiologic findings, it was decided that the infant had probably been subjected to NAI. Child protection procedures were instituted. Police investigations resulted in a criminal charges being brought against the mother by the Crown Prosecution Service. The infant was discharged into interim foster care after 2 weeks in hospital at which point he was well and seizure-free.

When reviewed at 6 months of age the child was noted to have macrocephaly and global developmental delay, particularly in gross motor function. He had bilateral conductive hearing deficit with some sensorineural deficit. He showed marked left-sided preference. Urine organic acid analysis was performed and gas chromatography-mass spectrometry showed markedly elevated excretion of glutaric acid and 3-hydroxyglutaric acid, with glutaric acid concentration 1500 μ mol/mmol creatinine.

The diagnosis of GA1 was confirmed enzymologically by demonstrating absent glutaryl-CoA dehydrogenase activity in cultured fibroblasts. The child's glutaryl-CoA dehydrogenase activity was 0.01 μ mol/h/g protein with a control range of 5.0 \pm 1.6 μ mol/h/g protein.⁹ Two experts reviewed the radiographs and concluded that the supposed radial fracture was a nutrient artery; however, the periosteal reactions were confirmed and still caused concern that there had been inappropriate handling of the infant.

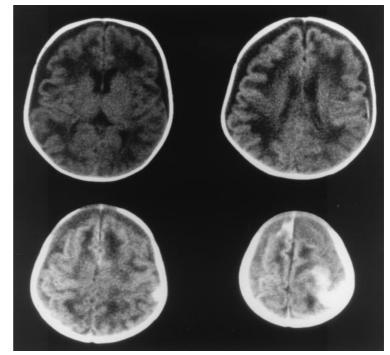
The infant was commenced on a reduced lysine/tryptophan diet with carnitine supplementation, and appropriate management of intercurrent illnesses. The child has had 4 hospital admissions to date with mild catabolic illnesses. He remains markedly globally delayed but has not yet developed any new neurologic features.

In light of the new diagnosis, Crown proceedings against the natural mother were temporarily suspended. A court hearing

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Fig 1. Axial computed tomography from the infant on the day of presentation. There are bilateral frontal subdural collections with some cortical effacement and a fresh high left parietal collection. Diffuse white matter signal attenuation is seen in both hemispheres.



raised doubts about the mother's ability to maintain a safe environment for the infant and the child remained in the care of social services with the hope that he would be adopted.

DISCUSSION

GA1 is an autosomal recessive disorder of lysine, hydroxylysine, and tryptophan catabolism caused by deficiency of mitochondrial glutaryl-CoA dehydrogenase, first described in 1975.¹⁰ The population frequency has been estimated at 1 in 30 000 neonates in a Scandinavian study.¹¹ It is biochemically characterized by elevated urinary excretion of glutaric acid, 3-hydroxyglutaric acid, and glutarylcarnitine, reduced plasma carnitine, and reduced or absent glutaryl-CoA dehydrogenase activity in fibroblasts and leukocytes (11 for review). Molecular studies show that a wide variety of mutations in the human glutaryl-CoA dehydrogenase gene are responsible for causing the disease.¹³

Such allelic heterogeneity may underlie the wide phenotypic variations seen in this neurometabolic disorder. Unlike other organic acidemias, metabolic and lactic acidosis, hyperammonemia and hypoglycemia are rarely present. The 'typical' presentation is within the first 12 months of life of an acute metabolic encephalopathic crisis followed by loss of motor skills and development of a dystonic-dyskinetic movement disorder often with preservation of intellectual function. Orofacial dyskinesias with concomitant feeding difficulties are notable. A prominent clinical findings is of macrocephaly, often not present at birth, but rather an abnormal increase in head circumference during infancy. Retinal hemorrhages are found in 20% to 30% of patients.¹² Seizures are seen in 20% of children with GA1.¹⁴

Earlier presentations are with less florid neurological symptoms such as hypotonia, irritability, and mild encephalopathic episodes with few sequelae.

Undiagnosed, the disorder progresses to develop-

ment of cerebral atrophy with pyramidal tract signs and mental retardation. Anorexia, insomnia, hyperthermia, and hyperhidrosis are common symptoms. Approximately 25% of children, however, present with subacute motor delay, insidious development of dystonia (often diagnosed as cerebral palsy), and mental retardation; encephalopathic episodes in this group are absent or milder.^{14,15} There are reports of completely asymptomatic children with GA1.⁸

Therapy is directed at dietary manipulation. A reduced lysine/tryptophan diet, carnitine and ribo-flavin supplementation, and aggressive management of catabolic states including episodes of fever or vomiting are said to modify the progress of the disease.^{12,18} This dietary control needs to be instituted early or in presymptomatic patients, although clear benefits of low protein diets beyond the age of 4 years are still to be shown.^{12,15}

Neuroradiologic findings in GA1 are increasingly well-documented.6-8,16-20 Consistent findings are of macrocephaly and frontotemporal cerebral atrophy with widening of the Sylvian fissures. Transient subependymal pseudocysts, diffuse white matter signal attenuation, and basal ganglia changes affecting the caudate nucleus are also well-described. The presence of acute and chronic subdural collections in GA1 was initially thought to be a rare association, but some large series report that 20% to 30% of patients with GA1 will have subdural collections.¹⁴ The pathogenesis of subdural hemorrhage remains unclear but it is thought to arise from stretching of bridging veins attributable to cerebral atrophy-increased fragility leads to bleeds with minimal trauma. Alternatively, hemorrhage may occur from the outer membrane of a subdural effusion.^{6,21}

The clinical features of subdural collections of different ages, retinal hemorrhages, and nonspecific symptoms in the absence of a history of adequate trauma may lead clinicians to suspect NAI in a child with undiagnosed GA1.^{15,23}

In our case, GA1 was diagnosed later because urine was sent for metabolic screen, requested because of macrocephaly and neurodevelopmental delay at follow-up. The diagnosis of GA1 provided 1 explanation for the subdural collections found in this infant. The expert review of the radiographic skeletal survey showing the presumed radial fracture to be a nutrient artery further weakened the evidence for NAI.

The periosteal reactions seen on radiograph remain unexplained. This, together with the atypical presentation with early seizures and marked neurodevelopmental sequelae in the absence of an encephalopathic episode, continues to raise the possibility of NAI. Children with neurometabolic disorders are at increased risk of NAI injury; heightened awareness of child protection issues should not end once a diagnosis of GA1 has been made.²³

In the context of the general pediatric population subdural hemorrhages in infancy are common. A recently reported incidence is of nearly 21/100 000 children per year.²² Subdural hemorrhages are associated with poor outcomes and nonspecific presentation, and more than four fifths of cases are highly suggestive of abuse with evidence of coexisting injury or a history of previous child abuse within the family.

It has been suggested that multidisciplinary social assessment, expert ophthalmoscopy, radiographic skeletal survey supplemented by either a bone scan or repeat survey, coagulation screening, and neuro-radiologic investigations should be mandatory in the investigations of infants with subdural hemorrhage.^{22,24,25}

We propose that screening for GA1 should be added to these investigations. Urine organic analysis, glutarylcarnitine measurement on blood spots, and plasma total and free carnitine estimations, followed by confirmatory enzymology, have been recently suggested as the best screen.²³

The devastating social and legal consequences for a family facing a charge of child abuse place the onus on the attending pediatrician of meticulous exclusion of alternative diagnoses to NAI. It is additionally important to diagnose a potentially modifiable albeit rare metabolic disorder.

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Carbamazepine Overdose Recognized by a Tricyclic Antidepressant Assay

ABSTRACT. Altered mental status in an adolescent presents a diagnostic challenge, and the clinician depends on clinical evaluation and laboratory studies to determine therapy and prognosis. We report the case of

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an adolescent with altered consciousness caused by carbamazepine overdose with a positive tricyclic antidepressant level to alert clinicians to the cross-reactivity of carbamazepine with a toxicology screen for tricyclic antidepressants. *Pediatrics* 2001;107:176–178; *coma*, *carbamazepine*, *tricyclic antidepressants*.

ABBREVIATIONS. TCA, tricyclic antidepressants; CBZ, carbamazepine; ECG, electrocardiogram; QRS, electrocardiographic wave.

The differential diagnosis of altered mental status in an adolescent is broad. It can be difficult to eliminate trauma, ingestion, or infection as the cause in any presentation of alteration of consciousness. The initial assessment and resuscitation are directed at the management of the patient's airway, breathing, and circulation.

Decreased level of consciousness is the most common serious complication of drug overdose. Toxicology screens for central nervous system depressants and for potentially lethal but treatable substances such as acetaminophen, aspirin, and tricyclic antidepressants (TCA) should be considered in diagnostic testing. However, the treatment of poisoning often must proceed without the results of extensive screening. Fortunately, in most cases, the correct diagnosis can be made after a careful history, clinical assessment, and limited laboratory testing.

We report a case of carbamazepine (CBZ) overdose in which knowledge of the cross-reactivity between CBZ and tricyclic antidepressants was the key to the diagnosis of the cause of altered mental status.

CASE REPORT

A 16-year-old girl with a remote history of childhood seizures and a tic disorder presented in a coma.

She was last seen awake at approximately 11 pm the previous evening. At that time, she had been complaining of abdominal discomfort for which she reportedly took Pepto-Bismol, ibuprofen, and St John's Wort. In addition, she took her regular dose of clonidine (0.1 mg) which was used to control the tic disorder. There was no history of fever or other systemic symptoms. Her family reported recent social stressors but no change in behavior or suicidal threats. Her family denied knowledge of alcohol, illicit drug use, or any other medication exposure.

The next morning, the patient was found unresponsive, slumped over the side of her bed. She was transported to Children's Hospital, Boston for additional evaluation.

On presentation she was minimally responsive to pain, having a Glasgow Coma Scale of 7. Temperature was 37.2°C, pulse 100 beats/minute, respiratory rate 16 breaths/minute, and blood pressure of 90/58 mm Hg. Respirations were spontaneous and adequate. There were no obvious signs of trauma. Pupils were dilated at 9 mm bilaterally and were reactive to light. Her cardiac and pulmonary examinations were normal. Her neurologic examination was nonfocal except for her depressed mental status.

The patient was intubated for airway protection. Activated charcoal was given via a nasogastric tube. A head computed tomography scan revealed no evidence of intracranial pathology. An electrocardiogram (ECG) was normal for age. Her complete blood count, electrolytes, liver function tests, and urinalysis were unremarkable. Serum osmolality, acetaminophen, aspirin levels, a qualitative tricyclic antidepressant screen, and a comprehensive toxicology screen were obtained.

In discussion with the patient's parents, they were confident that she did not have access to any medications in the home other than her prescribed clonidine. They assured the treatment team that the clonidine vial had the appropriate number of remaining tablets.

The patient was admitted to the intensive care unit where she initially remained responsive only to painful stimulus. An electroencephalograph revealed abnormalities consistent with drug toxicity or metabolic defect. A lumbar puncture was performed which had a normal opening pressure and examination of the cerebral spinal fluid did not reveal any abnormality. Acyclovir was initiated pending herpes polymerase chain reaction results.

Shortly after transfer to the intensive care unit, the patient's serum screen for TCA was reported as positive. A repeat ECG showed no evidence of QRS or axis deviation. Over the subsequent days she was extubated and her mental status normalized. On recommendation from the clinical toxicology service, a serum CBZ level was obtained because of the possibility of a cross-reactivity of CBZ with the TCA screen. The CBZ level was elevated at 17 μ g/mL (therapeutic range: 4–12 μ g/mL).

Psychiatry and toxicology consults were involved, and supportive care continued. By hospital day 3, the patient was transferred to the medical floor with a CBZ level of 9 μ g/mL. She was subsequently discharged from the hospital with outpatient psychiatry follow-up.

DISCUSSION

Antidepressant medications are among the most common used in self-poisonings and suicide attempts. TCAs are the most toxic and represent a major cause of poisoning, hospitalizations, and deaths. TCA toxicity may cause 3 major syndromes: anticholinergic, cardiovascular, and neurologic. Anticholinergic effects include sedation, delirium, coma, dilated pupils, dry skin and mucous membranes, absent bowel sounds, and urinary retention. Cardiovascular toxicity manifests as abnormal cardiac conduction and arrhythmia. Seizures are common with TCA overdose. Studies have shown that specific ECG changes are correlated with TCA overdoses. A prolonged QRS interval, ≥ 100 milliseconds, and a terminal 40 millisecond right axis deviation, ≥120 degrees are reliable predictors of serious cardiovascular and neurologic toxicity.¹ In this case, the ECG showed no evidence of ORS widening or deviation of the axis in the terminal segment. Although TCA ingestion was a possible cause of the depressed mental state, the ECG results were inconsistent with this cause. Therefore, it was unlikely that the positive TCA assay explained the altered consciousness in this patient. In contrast, although CBZ is structurally similar to TCAs it does not cause rhythm disturbances, alterations in heart rate, changes in QRS duration, or terminal segment axis deviation.²

Toxicology screens are increasingly becoming part of an evaluation of the pediatric patient with altered mental status. The most commonly used screen is a urine immunoassay for drugs of abuse. In addition, a serum immunoassay for TCA, aspirin, acetaminophen and other specific therapeutic medications may be part of an initial screen. A complete understanding of the basic principles of the screen allows for a proper interpretation of a positive or negative result. There are multiple types of immunoassays distinguishable by the marker of free drug in the sample. For example, in the enzyme-linked immunoassay performed at our institution, a drug-specific antibody binds to free drug. Therefore, the presence of the drug limits the antibody available to bind to the enzyme in the assay. The free enzyme produces a detectable product.³ This is an effective and inexpensive screen for drugs in serum or urine. However, there is the possibility of false-positive results from structural similarity of substances.

Examples of drugs with structural similarity include amphetamines with phenylephrine and ranitidine, opiates with poppy seeds, phencyclidine with diphenhydramine, dextromethorphan and ketamine, and TCAs with CBZ and diphenhydramine. Each of these drugs may cause false-positives on the immunoassay screen for the cross-reacting substance. If the patient's clinical presentation is inconsistent with the assay result, it may be necessary to obtain confirmatory testing for the positive result of an immunoassay screen. This can be done using gas chromatography coupled with mass spectrometry. However, it is a more expensive and labor-intensive study and therefore is used as a confirmatory test of a positive immunoassay result.

CBZ is a neutral lipophilic iminostilbene derivative with structural similarity to the tricyclic antidepressant imipramine. Schindler and Hafinger synthesized the compound in 1952.⁴ This structural similarity allows for cross-reactivity of the TCA immunoassay with CBZ. The reported cross-reactivity of the TCA immunoassay for CBZ is 0.3% with the Abbott assay.^{5,6} The TCA assay can be positive in therapeutic as well as toxic ingestions of CBZ.

CBZ is most commonly used for prevention of seizures, analgesia for trigeminal neuralgia and affective disorders, particularly bipolar disorder. There is a relatively elevated risk of super-therapeutic ingestion of this substance because of the underlying conditions being treated. In a review of >400 patients diagnosed with CBZ overdose, Schmidt and Schmitz-Buhl⁷ revealed that the level of lethality is low particularly in patients under the age of 15 years. Coma, somnolence and cerebellar syndrome were the most common symptoms in overdose, with an increased incidence of seizures and respiratory depression in the lethal overdose group.

Management of CBZ overdose is mainly supportive. There should be a low threshold for intubation in patients with borderline mental status because of frequent emesis and neurologic compromise. Cardiovascular and respiratory monitoring is essential.⁸ Repeat doses of activated charcoal may increase the clearance because of enterohepatic circulation. The half-life of serum CBZ can be significantly shortened by multiple doses of activated charcoal.⁹ Charcoal hemoperfusion is effective and may be considered for severe intoxication refractory to standard therapies.

This case illustrates that an understanding of the method and interpretation of drug screens, including the possibility of false-positive results attributable to cross-reactivity, is important when using toxicology screens as part of a patient evaluation. The knowledge of cross-reactivity between the TCA assay and CBZ resulted in the diagnosis in this case of toxic ingestion.

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Laxative-Induced Dermatitis of the Buttocks Incorrectly Suspected to Be Abusive Burns

hild abuse should be considered as a possible diagnosis in young children who present with burns. Often the history or the absence of a history provides the clue to a correct diagnosis. We recently evaluated 4 children (at 4 different medical centers) who each presented with large buttock burns that were initially diagnosed as abusive scald burns. In each case, a more detailed history revealed that the child's burn was not attributable to immersion in hot water, but rather resulted from the ingestion of Ex-Lax (Novartis, Summit, NJ). To our knowledge there are no previous reports of this type of injury in children.

CASE REPORTS

Case 1

A previously healthy 23-month-old boy was brought to the emergency department of Yale-New Haven Children's Hospital by his mother with a blistering "rash" on his buttocks. The child's mother reported that she had bathed him at approximately 8 pm the night before admission and at that time the patient had no rashes or blisters. The next morning when she changed the child he had a large diarrheal stool in his diaper, and she noticed a pinkish area with a few small blisters on his buttocks. The mother was concerned about the diarrhea because she had discovered 6

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Fig 1. Case 1: 23-month-old demonstrating ruptured bullae, diamond-shaped distribution, and sparing of perianal area.



Fig 2. Case 2: 27-month-old demonstrating bullae, diamond-shaped distribution, and no sparing of perianal area.

empty Ex-Lax wrappers on the floor of her room that had not been there previously. She had left the Ex-Lax on a dresser that the child sometimes climbed on; therefore, she was concerned that he had ingested the medicine while playing.

Throughout the day the child continued to have red-brown diarrheal stools and worsening blisters on his buttocks. On evaluation in the emergency department, the child was found to have a sharply demarcated area of erythema with multiple bullous lesions over the buttocks. The erythema and bullae extended 5 cm peripherally from the anus. There was sparing of the skin around the anus and the perineum. The child was estimated to have a second-degree burn of 4% of his body surface area. Past medical history revealed that the patient had been to the emergency department 6 months before with an electrical burn to his lip. Because of concern that the child's burn was attributable to an immersion injury, he was admitted to the hospital and Child Protective Services was notified.

During the child's hospitalization, the mother provided a similar history to several different interviewers. On reexamination of the child, the bullae had sloughed and the erythema along the left buttock formed a linear demarcation that was closely aligned with the inner absorbent pad of the child's diaper (Fig 1). Child Protective Services and the police investigated the child's home and were able to retrieve the foil from the Ex-Lax wrappers but not the box of Ex-Lax. They then accompanied the mother to the store who was able to demonstrate which box she had purchased. The box contained 9 squares of Ex-Lax wrapped in foil, and each square contained 15 mg of senna as the active ingredient. Novartis Company, the manufacturer of Ex-Lax, was contacted and had 1 case on file with no details in which a 5-year-old child had sustained burns to the buttocks after ingesting a box of Ex-Lax.

Based on this information, the hospital's child abuse team concluded that the child's injury was a chemical/contact dermatitis secondary to the ingestion of Ex-Lax containing senna. The involved skin was treated with local care (aquaphor and xeroform gauze). The patient was discharged to the care of his mother, who applied silver sulfadiazine topical treatment. Child Protective Services kept the case open. At follow-up 3 days after the hospitalization, the erythema was still present but less pronounced.

Cases 2 Through 4

The clinical features of the other 3 cases are similar to case 1. The children were ages 27 (Fig 2), 29, and 42 months old, respectively. In each case, the child ingested Ex-Lax, and on the next day when the diaper was changed, diarrheal stool was noted by the caretaker. The presence of erythema and blisters were noted at that time or developed over the next several hours. The blisters eventually developed into large bullae. On physical examination, the area around the anus and the gluteal cleft were spared in 2 of the 3 cases, the lesion appeared diamond- or pear-shaped on the buttock rather than circumferential, and the lateral borders

aligned with the outer edge of the diaper. In 2 of the cases, the incident was reported to Child Protective Services because of suspected child abuse resulting from an immersion burn, and in one of these cases the child was placed in relative care under protective supervision.

DISCUSSION

These 4 cases highlight the importance of a detailed history in determining the cause of an apparent injury. Although the findings on physical examination were suggestive of an immersion burn, on more careful examination there were 3 findings that were unusual: the diamond-shaped lesion on the buttock, the linear borders that lined up with the diaper edge, and the sparing of the perianal tissue and the gluteal cleft. In general, sparing of skin folds and creases in the diaper area is consistent with an irritant contact dermatitis.

The use by adults of laxatives, such as Ex-Lax, is certainly common, and it is likely that many young children have ingested Ex-Lax. Our cases were between 23 and 42 months old; such young children are at the highest risk of ingesting medications or poisons. The preparation of Ex-Lax that was ingested seems to be particularly attractive to young children because it comes as chocolate squares wrapped in foil.

It is unclear, however, how frequently the skin reaction that we noted occurs. The pathogenesis of this reaction also is unclear. In each case, the buttock area had been exposed for a period of a few hours to diarrheal stools resulting from the ingestion of the Ex-Lax. The active ingredient in Ex-Lax is senna, which is an anthraquinone laxative and has been used in children for decades. The active ingredient in Ex-Lax had been phenolphthalin, but this was replaced by senna in 1997. This recent product reformulation is likely the reason why this adverse event had not been reported previously.

An important characteristic of the anthraquinone laxatives is that the active ingredient interacts with microorganisms in the large intestine to produce its laxative effect.¹ What role this interaction might play in the development of the lesions is uncertain. A possible pathogenic mechanism to explain the dermatitis is injury from digestive enzymes.² The diarrhea resulting from the laxative overdose could have increased the concentrations of these enzymes because of increased gut transit time. Because anthraquinones are partially absorbed from the gastrointestinal track and are excreted in the urine, the irritant effects that resulted in the dermatitis may have been attributable to this excretion. This explanation, however, seems less likely because of the location of the lesions on the buttocks area.

Although there have been no previous reports of reactions to senna, laxative-induced dermatitis from Danthron (an anthraquinone) has been reported in 2 elderly patients³ and in 1 infant.⁴ In each case, there was erythema, but no blisters or bullae, as in our patients.

The identification of these cases at separate medical centers was facilitated by SIGCA-MD-L, a child abuse Internet mailing list for physicians, which is located at Cornell University and co-managed by Ann S. Botash and Tom Hanna. The presentation of one of these cases on the list-serv prompted a discussion of the injury and aided the physician in making the correct diagnosis. This same discussion brought the 4 cases together and resulted in this report.

CONCLUSION

In summary, we report 4 children who sustained chemical/contact dermatitis of their buttock region after ingesting Ex-Lax. In each case, although an abusive scald burn was initially suspected, the history of the ingestion provided the necessary information to clarify the correct diagnosis. These cases also highlight the importance of Internet-facilitated communication among physicians in helping make the correct diagnosis in unusual cases.

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Factitious Hypoglycemia: A Tale From the Arab World

ABSTRACT. The mother is usually the one who narrates the patient's history to the pediatrician. Listening and eliciting the parent's story is an art. One of the essential attributes of a good pediatrician is the readiness to believe the parent's story. Mothers are good historians

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and careful observers. The axiom that the mother is always right is true in most instances. However, occasionally the clinician is deliberately misled by the storyteller, resulting in numerous and potentially dangerous diagnostic investigations. We describe a boy with recurrent hypoglycemic coma in whom the diagnosis of factitious hypoglycemia was delayed as it is believed to be nonexistent in our community. We emphasize that in all patients with recurrent hypoglycemia, estimation of C-peptide and insulin should be performed even when the clinical settings are not in favor of the diagnosis of Munchausen syndrome by proxy. *Pediatrics* 2001;107:180–182; *Munchausen syndrome by proxy, hypoglycemia*.

ABBREVIATION. MSP, Munchausen syndrome by proxy.

The term Munchausen syndrome by proxy (MSP) was introduced by Meadow in 1977¹ to describe a unique form of child abuse that was often easily overlooked. In this condition children are the victims of illness, ingenuously fabricated or actively induced by parents, usually the mother.^{2,3} In MSP the director of the fictitious play is the socially deprived or psychologically disturbed mother and the actor is the child who may be a passive or an active participant in this folly.

CASE HISTORY

A.A. first presented to accident and emergency department at the age of 3.5 years with a 1-week history of fever and abdominal pain. Within few minutes of arrival he became very lethargic and profusely sweaty. Blood glucose was 1.1 mmol/L. He was managed with intravenous glucose infusion. Clinical examination revealed a left gluteal abscess, soft hepatomegaly of 3 cm. The gluteal abscess was drained and he was treated with antibiotics. He improved within a few days and was discharged with advice to undergo further investigations for hypoglycemia at a later date. He was lost to follow-up. He presented again after a long gap of 2 years with 3 episodes of hypoglycemic convulsions in a period of 3 months. Despite rather extensive investigations, the diagnosis remained unclear and he was referred to the endocrine unit for further evaluation.

Review of his previous hypoglycemic episodes showed that each of these episodes occurred in the middle of the night after a good dinner without any history of preceding febrile illness. On each occasion, there was severe hypoglycemia, and a minimum of 36 hours of high concentration glucose infusion was required before an euglycemic state was reached. The results of laboratory findings at the time of previous hypoglycemic episodes were as follows: serum electrolytes, venous blood gas analysis, liver function tests, blood lactate, and blood acylcarnitine were normal. Urine was consistently negative for ketones and organic acids. Serum cortisol was appropriately elevated and serum C-peptide was similarly low for the blood glucose level. He was subjected to 20-hour of controlled fasting study as a part of protocol for the investigation of hypoglycemia. At the end of fasting the lowest blood glucose concentration recorded was 4.5 mmol. The fasting urine sample showed traces of ketones and was negative for organic acids.

He was later readmitted twice within a short interval of few days with hypoglycemia. The results of both serum C-peptide and insulin levels estimated at the time of above hypoglycemic attacks were as follows: serum insulin was 70 mU/L and 473 mU/L and C-peptide was <214 pg/L on both occasions. Urinalysis did not show the presence of any oral hypoglycemic agent.

Family and Social History

A.A., the youngest in a sibling ship of 3 lived with his mother, (henceforth called R.). His parents are divorced. The family lived with his grandmother, who is a diabetic on insulin. R. is 1 among 9 siblings. She lost her father at an early age and discontinued her studies after primary school. From her early teens she has a history of hysterical attacks and depressive episodes. She has been treated by faith healers and traditional remedies for what have been described as attacks by evil spirits.

In her early teens she was married to a distant relative many years her senior. This marriage ended in a divorce within few months. Within a year of her divorce, R. married again. Her second husband was her first cousin, a man much older than herself. He had 2 living wives and several children. This marriage also ended in a divorce. However, R. remarried the same man shortly afterward. The reconciliation was short-lived, and they separated again after A.A. was born. R. and her children have been living with her mother in an extended kinship that includes her second husband, his other wives, and their children. She is unemployed.

After her mother was diagnosed to have diabetes, R. has learned the technique of giving insulin injection and helps her mother in the day to day care of diabetes. A.A. appears to be a very hyperactive child. He has a very close relationship with his mother and will not interact with the medical staff except in the presence of his mother.

DISCUSSION

In a tradition-bound society, it seems almost heretical to doubt the axiom that the mother is a child's best historian and that she would do nothing to harm her child. In the case of A.A., all evidence seemed to point to the contrary.

The course of each episodes of hypoglycemia in the hospital was stereotyped. All the documented hypoglycemic episodes occurred in middle of the night. The duration of each hypoglycemic episode was prolonged, lasting >24 and 30 hours, despite continuous intravenous infusion of 10% dextrose, intermittent boluses of 25%, 10% dextrose, and the unusual quantity of food and drinks he was taking. Episodes of hypoglycemia were not related to stress or inter-current illness. All the hypoglycemic spells occurred after the dinner. Hypoglycemia was not associated with metabolic acidosis or lactic acidemia and urine was consistently negative for ketones, despite severe and prolonged hypoglycemia. In between these spells of hypoglycemia he was in perfectly good health.

The history, clinical picture, results of the basic investigation, and the course in hospital did not correspond with the disorders of glycogenolysis, Neoglucogenesis, fatty acid oxidation, endogenous hyperinsulinemia, pituitary, and adrenal insufficiency. Exogenous insulin administration or poisoning with hypoglycemic drugs were the only explanations for the clinical picture of intractable hypoglycemic episode refractory to treatment. The source of insulin was unlikely to be endogenous, because of episodic nature, it did not bear any temporal relationship to fasting, additionally, the hypoglycemia always occurred in the middle of the night shortly after a good dinner. The endogenous hyperinsulinism was excluded by appropriately low C-peptide concentration during hypoglycemia.

Insulin abuse has been widely reported among adults⁴ and in children.^{5,6} The triad of hyperinsulinism, low C-peptide, and hypoglycemia is diagnostic of exogenous insulin.⁷

The mother's passive and unconcerned behavior to the medical management, easy access to insulin at home, and her good knowledge about insulin and insulin injection clearly suggested that the mother was the perpetrator. However, what was unusual was that the mother has only secondary school education; her knowledge of medical matters is limited to what she has been taught about the management of her mother's medical condition.

In the tradition-bound Arab society, women are always kept under the protection of the extended family. Their access to external influences, outside their kinship, is limited. In modern, progressive societies, MSP has been attributed to the stresses and strains of single parenthood, with little support from the partner.³ Our patient demonstrates that MSP can occur even in a large extended family that follows traditional tribal rules.

When the mother was confronted with evidence of factitious nature of A.A.'s illness, she denied giving the injection to her son. Although family members were aware of her abnormal personality, appropriate medical help was not sought. Strangely, male members of the family refused to participate in counseling. It was only after much persuasion that the child was moved to a paternal uncle's house. There is as yet no system of community health follow-up and statutory laws for child protection in the country.

In a child with unexplained and intractable hypoglycemia administration of parenteral insulin as a form of child abuse should always be considered even when it is least likely and simultaneous estimation of C-peptide and insulin is the only way to establish the diagnosis of fictitious hyperinsulinemia.

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Complete Spontaneous Resolution of Childhood Chiari I Malformation and Associated Syringomyelia

ABSTRACT. The diagnosis of Chiari I malformation and associated syringomyelia is often made in childhood. Since the advent of magnetic resonance imaging, these abnormalities are increasingly detected incidentally. Despite incomplete understanding of the natural history of asymptomatic Chiari I malformations, the current recommendation is to consider prophylactic surgical intervention in those with an associated syringomyelia. This case report presents a complete spontaneous resolution of a Chiari I malformation and syringomyelia in a child. It illustrates the possibility that asymptomatic children with Chiari I malformations and syringomyelia may be followed conservatively. *Pediatrics* 2001;107:182–185; *Chiari I malformation, resolution, syringomyelia, pediatric.*

ABBREVIATIONS. MRI, magnetic resonance imaging; CSF, cerebrospinal fluid.

Thiari I malformation is the congenital downward displacement of the cerebellar tonsils into the cervical canal. It is often associated with syringomyelia, which is a cavitary dilation of the spinal cord. The diagnosis is often made in childhood and symptomatic children respond favorably to surgical treatment. Magnetic resonance imaging (MRI) has facilitated the diagnosis and an increasing number of incidental Chiari I malformations are seen.¹ The natural history of an asymptomatic Chiari I malformation in children is not known. Nevertheless, it is generally accepted that the presence of a syringomyelia with Chiari I malformation warrants consideration of a surgical decompression, even in an asymptomatic child.² We present a child whose incidental Chiari I malformation and associated cervical syringomyelia spontaneously and completely resolved over a 7-year interval. This case illustrates a variable natural history of Chiari I malformations with syringomyelia and the option of conservative management in asymptomatic children.

CASE REPORT

A 7-year-old boy was evaluated for a 1-month history of headaches, which occurred daily after exercise, or awoke the patient in the morning. These headaches were bitemporal in nature and described as throbbing. The most severe episodes were associated with nausea and occasionally vomiting. There was no association between the headaches and Valsalva maneuvers. His neurologic examination was nonfocal. There was a strong family history of migraine headaches and the child was diagnosed with common migraine headaches. As part of the initial evaluation for his headaches, the patient underwent a MRI of the head. This MRI showed a Chiari I malformation and an associated cervical syringomyelia

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(Fig 1A). The brain was otherwise normal. He was seen in neurosurgical consultation and underwent a repeat brain and cervical spine MRI with contrast to rule out enhancement. The repeat MRI confirmed the presence of Chiari I malformation with associated syringomyelia. There was no enhancement. This was felt to be an incidental finding and the patient was treated for migraine headaches and monitored.

The patient's headaches initially improved with dietary modification alone, in particular the removal of chocolate. At age 13, the severity and duration of the infrequent headaches increased despite the institution of medication. The patient had grown from 122 cm at age 7 to 156 cm at age 13, and he had become sexually mature. A repeat MRI was performed to evaluate the Chiari I malformation. It was read as normal by the neuroradiologist: the Chiari I malformation completely resolved and the associated syringomyelia disappeared (Fig 1B). At the time this article was submitted, he was 16 years old and he continues to have recurrent severe migraine headaches every 2 to 3 months. He is being treated with Inderal prophylaxis and acute interventions. The neurologic examination remained nonfocal and the physical examination unremarkable.

DISCUSSION

In 1891, Chiari described 4 congenital anomalies of the lower brainstem and inferior cerebellum.³ The type I malformation consists of downward herniation of the cerebellar tonsils through the foramen magnum. Herniation of the tonsils >5 mm below the foramen magnum on MRI is considered diagnostic.⁴ A Chiari I malformation may also be occasionally acquired from increased intracranial pressure in conditions such as head injury, hydrocephalus, or craniosynostosis. Syringomyelia has been noted to accompany 50% to 70% of patients with Chiari I malformations.¹ Obstruction of cerebrospinal (CSF) flow at the craniocervical junction from the tonsillar herniation has been shown to create perivascular movement of CSF from the spinal subarachnoid space into the spinal cord with each Valsalva maneuver and systole to form the syringomyelia.⁵

The Chiari I malformation and resulting syringomyelia can cause a host of neurologic manifestations. The most common presenting symptom from a Chiari I malformation is pain, which can be a headache or nonradicular pain in the shoulder, back, and limbs. The headache differs from migraine and other forms of headaches in that it is usually suboccipital and upper cervical in location and is exacerbated by Valsalva maneuvers. Impaction of the tonsils against the cervicomedullary structures can cause brainstem dysfunction, sensory disturbance, and motor loss. The syringomyelia is associated with the development of a painful, rapidly progressive, or left-curving scoliosis. The cavitation within the central gray matter can produce a segmental or suspended sensory loss of pain and temperature by interrupting crossing fibers of the spinothalamic tract while preserving touch and the deep sensibility whose fibers ascend ipsilaterally in the dorsal column before entering the gray matter. Further compression by the Syrinx can affect the long tracts in the white matter and lead to spastic quadriparesis. Presentation during childhood is increasingly recognized.5-7 A detailed neurologic evaluation is essential, as the im-

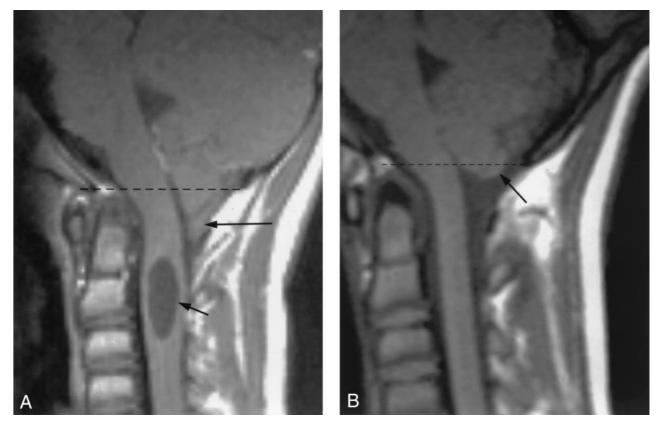


Fig 1. Sagittal T1-weighted MRI with contrast demonstrating a Chiari I malformation with 13 mm of tonsillar herniation below the foramen magnum (large arrow). There is an associated cervical syringomyelia without enhancement (small arrow, A). Follow-up image reveals resolution of the Chiari I malformation with the tonsils <2 mm below the foramen magnum (arrow) and complete disappearance of the cervical syringomyelia (B). Dotted lines represent the foramen magnum.

pairments may be subtle and the onset insidious. Symptomatic patients can be successfully treated by a variety of surgical decompression techniques to restore CSF dynamics across the craniocervical junction.^{6–8} Failing a decompression, a persistent syrinx can also be directly addressed by shunting.^{9,10}

The ability of MRI to visualize the craniocervical junction and spinal cord has facilitated the diagnosis of Chiari I malformations and associated syringomyelia. As a result, Chiari I malformations with or without syringomyelia are now increasingly encountered as incidental findings.¹ Although there is a pattern of progressive neurologic impairment in most symptomatic patients,11 the natural history of asymptomatic patients with a Chiari I malformation and syringomyelia is not well-defined. Cases of acute neurologic deterioration, syncope, cardiac arrest, and even sudden death have been reported as the presenting event in patients with medullary compression and large syringomyelia from a previously undetected Chiari I malformation.12-15,16 However, most of these cases were symptomatic well before their catastrophic presentations. Only Minorat¹¹ has reported 1 case of a 4-year-old child without a history of weakness, scoliosis, or paroxysmal complaints who presented with cardiopulmonary arrest and was found to have a Chiari I malformation and large holocord syringomyelia on MRI. There was no autopsy. Sudden death after minor trauma have also been reported in adults and children with Chiari I malformations; but as reviewed by James, ¹⁷ all cases were previously symptomatic Chiari I malformations or involved additional confounding factors such as alcohol use or congenital cervical abnormalities. So, collectively, these case reports do not necessarily provide a compelling rationale to treat asymptomatic Chiari I malformations. But once an associated syringomyelia has developed with a Chiari I malformation, obstructed CSF dynamics at the foramen magnum from the tonsillar herniation would theoretically lead to progression of the syrinx and eventual symptoms. And once neurologic deficits develop from a syringomyelia, they do not typically reverse completely with surgery.¹⁸ Consequently, the small risk of prophylactic surgery including stroke, CSF leakage, infection, and delayed craniocervical instability is felt to be justifiable. The degree of apparent brainstem compression at the foramen magnum and size of the syringomyelia are also considered when evaluating an otherwise asymptomatic patient. Presently, very few patients with a significant syringomyelia associated with Chiari I malformation are left untreated.¹⁹

On the other hand, cases of spontaneous radiographic improvement of childhood Chiari malformations and syringomyelia have been recently reported. In symptomatic children, 3 cases of spontaneous resolution of Chiari I malformation and improvement of syringomyelia on follow-up MRI have been reported.^{20–22} The neurologic deficits were improved in 1 case and unchanged in the other 2 cases. In asymptomatic children, the spontaneous resolution of an incidental Chiari I malformation alone without an associated syringomyelia has been reported by

Castillo²³; and Avellino²⁴ described the spontaneous resolution of an incidental Chiari I malformation with marked reduction in size, but not total disappearance, of an associated cervical syringomyelia from age 6 to 10. The patient presented here has migraine headaches but otherwise has had no signs or symptoms referable to the Chiari I malformation or syringomyelia. Consequently, this patient represents a complete spontaneous resolution of an incidentally discovered, asymptomatic childhood Chiari I malformation and associated syringomyelia. The Chiari I malformation normalized and the syringomyelia totally disappeared over 6 years on follow-up MRI. Although the tonsillar herniation was significant, the cervical syrinx in our patient is relatively small at 30 mm \times 12 mm as compared with the holocord syringomyelia in the 4-year-old patient with cardiopulmonary arrest reported by Martinot.

The cerebellar tonsils normally ascend with age.²⁵ Therefore, in the pediatric population, Chiari I malformations can conceivably resolve from axial growth.²³ Our patient grew 34 cm from the age of 7 to 13. The relative skeletal growth across the craniocervical junction, along with some enlargement of the posterior fossa, may have pulled the tonsils out of the foramen magnum. Once the tonsillar are pulled up sufficiently to restore normal CSF dynamics across the craniocervical junction, the result can be a complete resolution of the syringomyelia. In the absence of any intracranial pathology, the prognosis of a completely resolved asymptomatic Chiari I malformation and syringomyelia should be excellent. However, recurrence of a spontaneously resolved symptomatic Chiari I malformation and fluctuation in the size of the syringomyelia was seen one of the reported cases.²² Rupture of the syringomyelia into the subarachnoid space has also been proposed to account for the spontaneous decompression of a large holocord syrinx in an adult.26 The Chiari I malformation and neurologic deficits in that patient remained. Given the relatively small size of the syringomyelia in our patient, the lack of neurologic deficits, and concurrent resolution of the Chiari I malformation, spontaneous decompression through a tear in the spinal cord seems less likely.

At present, a prophylactic decompression is generally considered for an asymptomatic child with Chiari I malformation in the presence of an associated syringomyelia. Our case adds to the small body of emerging evidence which demonstrates that the natural history of asymptomatic Chiari I malformations and associated syringomyelia is not universal progression. Conservative management with serial imaging and close neurologic monitoring may be considered in asymptomatic childhood Chiari I malformations with associated small to moderately sized syringomyelia.

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Perinatal Renal Ischemia Resulting in Hypertensive Cardiomyopathy

ABSTRACT. Three neonates presented with malignant hypertension during the first week of life; 2 of them had congestive heart failure. Although none had indwelling umbilical artery catheters, unilateral renovascular lesions were diagnosed by nuclear perfusion scans. Angiotensin-converting enzyme inhibitor therapy produced rapid recovery. Hypertension must be included in the differential diagnosis of infants presenting with congestive heart failure and acidosis. Ultrasonography is not sensitive enough to exclude renovascular lesions. We emphasize the importance of early diagnosis and treatment. *Pediatrics* 2001;107:185–187; *neonatal, renovascular hypertension, congestive heart failure, converting enzyme inhibitors, renal artery stenosis.*

ABBREVIATIONS. CHF, congestive heart failure; ^{99m}Tc, technetium 99; MAG₃, mercaptotriglycylglycine; DTPA, diethylenetriamine pentaacetic acid; ACE, angiotensin-converting enzyme.

Renal hypoperfusion causes hypertension through activation of the renin angiotensin system.¹ Chronic and acute causes of renovascular hypertension in children are well-described, as is cardiomyopathy related to severe or long-standing hypertension.² The most common cause of neonatal renovascular hypertension is related to umbilical artery catheter placement.³ Modern imaging techniques can establish the presence of renovascular lesions, particularly those resulting in high-grade occlusion. We report 3 full-term neonates, 2 with congestive heart failure (CHF), never treated with indwelling umbilical artery catheters, who developed life-threatening renovascular hypertension in the first week of life.

CASE REPORTS

Case 1

A 5-day-old white boy was admitted to the intensive care unit because of severe CHF and metabolic acidosis after 2 days of initially mild but progressive diaphoresis and difficulty in feeding. After an uneventful term pregnancy, this 4.74-kg infant had un-

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dergone spontaneous vaginal delivery and had required only usual care.

Dobutamine was administered. An echocardiogram showed very poor systolic function (shortening fraction: 8%; normal, >35%) and no structural abnormalities. Although perfusion and overall status improved, the blood pressure rose to 130/72 mm Hg. Hypertension persisted despite maximal doses of nitroglycerin. Renal ultrasonography showed kidneys of normal size (Fig 1). However, a technetium 99 (^{99m}Tc)-mercaptotriglycylglycine (MAG₃) renal scan showed a paucity of flow to the right kidney and normal flow to the left kidney (Fig 2).

Captopril therapy was initiated and the infant's blood pressure rapidly normalized (70–80/40–50 mm Hg). Mechanical ventilation and inotropic agents were discontinued and the infant was discharged on the 10th day of life. Follow-up has shown progressive atrophy of the right kidney with nearly complete loss of function as assessed by renal scans, and compensatory left kidney hypertrophy. By 6 months of age, myocardial function had returned to normal and captopril was discontinued without recurrent hypertension. Development at 3 years of age was normal.

Case 2

A 5-day-old Asian girl presented with respiratory distress, hypotension, and acidosis. The 3.4-kg product of an uneventful term pregnancy, the infant had been delivered vaginally without assisted extraction. A large cephalohematoma was noted, but the infant was otherwise well until presentation.

The infant was placed on a mechanical ventilator and inotropic agents were administered. The infant's overall status improved but the blood pressure increased (114–123/69–87 mm Hg) despite weaning of inotropic agents. Echocardiography showed a dilated and poorly contracting left ventricle (shortening fraction: 15%) but no important structural abnormalities. Renal ultrasonography showed a left kidney of 4.9 cm greatest dimension and a right kidney of 3.9 cm with increased echogenicity of the pyramids; biphasic blood flow was found bilaterally. A ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA) scan showed no blood flow to the right kidney. Peripheral renin activity at that time was 54 001 ng/dL/hour (normal range: 235-3700).

Digoxin and captopril therapy was initiated on day of life 6 with immediate resolution of hypertension. The infant rapidly was weaned from mechanical ventilation. Heart size as assessed by chest radiograph normalized and the patient was discharged on the ninth day of life. By 3 months of age cardiac function was normal (shortening fraction 34%) and digoxin was discontinued. Hypertension remained controlled with captopril and the infant was developing normally.

Case 3

An 8-day-old white girl was referred for evaluation of severe hypertension 2 days after discharge from the nursery. The product of an uncomplicated pregnancy and delivery, the infant underwent no special procedures. Hypertension was noted at 13 hours of life. At that time, hydralazine therapy was initiated and blood pressures reportedly normalized. Abdominal ultrasound, echocardiogram, head computed tomography, and sepsis evaluation showed no abnormalities. Hydralazine was discontinued on the fourth day of life, and after 2 subsequent days of stable blood

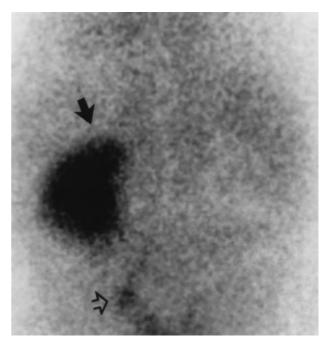


Fig 2. Representative image of 99m Tc-labeled MAG₃ renal scan with furosemide wash out. The left kidney (arrow) and ureter (open arrow) were well-visualized but no functional renal mass was present on the right.

pressure measurements, the infant was discharged from the nursery.

The infant was admitted to Children's Medical Center at 8 days of age with a blood pressure of 159/123 mm Hg. The infant weighed 2.23 kg, was in no distress, and showed no evidence of CHF. Renin activity was 6150 ng/dL/hour (normal range: 235-3700) and aldosterone was 551 ng/dL (normal range: 5–175). Sonography showed normal kidneys measuring 4.2 cm on the right and 4.3 cm on the left. A ^{99m}Tc glucoheptonate scan revealed marked asymmetry with the right accounting for 18% and the left for 82% of function. The infant was subsequently treated with captopril and hydralazine and hypertension resolved.

Follow-up sonography showed the severe atrophy of the right kidney without uptake on renal scans. There was compensatory left renal hypertrophy. Antihypertensive therapy was eventually discontinued, but mild hypertension recurred. At age 4 years the development and overall health of the child was excellent although she continued to be treated with captopril. An elective right nephrectomy was performed and the hypertension resolved completely, without additional treatment.

DISCUSSION

We describe 3 neonates who never had indwelling umbilical artery catheters but yet had renovascular

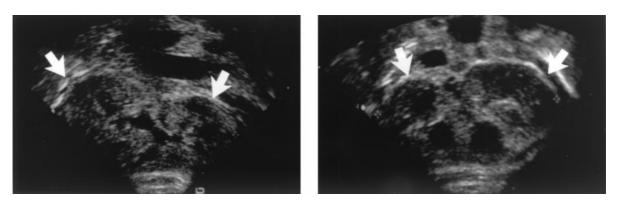


Fig 1. Ultrasonography of right and left kidneys (arrows) showing sizes 5.0 cm and 5.7 cm, respectively.

lesions and presented with malignant hypertension. In 2, near-fatal CHF developed and the third received early antihypertensive therapy, which may have prevented that outcome. Each of the infants rapidly responded to angiotension-converting enzyme (ACE) inhibitor therapy and have since shown normal development. Similar treatment of an infant with catheter-related renal artery thrombosis and malignant hypertension also reversed severe myocardial dysfunction.⁴

Cases 1 and 2 demonstrate that severe hypertension in the first week of life can present with cardiomyopathy. The blood pressures in each case were significantly higher than the 90% for a term neonate (76/68 in boys and 87/68 in girls).⁵ The acuity of the cardiogenic shock in cases 1 and 2 and the severity of hypertension in case 3 following relatively asymptomatic periods leads us to the conclusion that these infants suffered perinatal ischemic renal insults or infarctions. Presumably, early fetal ischemic events would have significantly impaired renal growth. Indeed, long-term follow-up of cases 1 and 3 has demonstrated severe atrophy of the affected kidneys. It is important to note that functional renal scans like the ones used in these cases clearly demonstrated persistent unilateral hypoperfusion that cannot be demonstrated by ultrasonography. Correspondingly, the plasma renin activity was high in the 2 infants in whom it was measured, markedly so in case 2.

Review of the literature produced case reports of 7 neonates who developed heart failure in the first week of life secondary to renovascular hypertension not related to umbilical artery catheter placement.^{6–11} Death occurred in 2, hypertension was cured by unilateral nephrectomy in 4 cases^{6,7,9,10} and by captopril therapy in 1 case.¹¹ Although exceedingly rare in general, congenital renal artery stenosis was the most common cause found during pathologic examination. It is notable that despite stenosis, the kidney was of normal weight in 1,⁶ decreased weight in another,⁸ and was sonographically normal in the third.⁹

Several other mechanisms, also very rare, may cause perinatal, isolated, and unilateral renovascular lesions. Renovascular embolism from a thrombosing ductus arteriosum or ductus diverticulum has been postulated but this etiology more characteristically results in multiorgan ischemic lesions from wide-spread emboli.^{11–14} Thrombosis in situ was demonstrated in 2 infants described by Woodard et al.¹⁰

It is worthwhile to consider how neonates with hypertension secondary to congenital renal artery stenosis can demonstrate normal kidney growth and development. Fetal renal blood flow equals 2 to 4% of the cardiac output and may be mostly trophic since glomerular filtration is low and the placenta plays the major role in metabolic clearance.¹⁵ Following birth, renal blood flow increases as renal vascular

resistance decreases and systemic blood pressure rises.¹⁵ Hypothetically, if renal vascular resistance fails to decrease appropriately to meet increased perfusion requirements, renin-mediated hypertension followed by ischemia could occur.

This report presents 3 cases of life-threatening neonatal hypertension secondary to isolated unilateral perinatal ischemic renal insults despite the absence of umbilical artery catheters. In each case, medical treatment allowed rapid recovery. Malignant hypertension should be considered a cause of CHF in neonates. Renal arteriography, a procedure with potential morbidity in neonates, was not necessary to make the diagnosis in these cases. Functional renal scans with ultrasonography can be diagnostic of renovascular lesions. In such cases, ACE inhibition is an effective treatment for CHF and hypertension.

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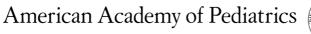
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