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Case 16-2013: A 12-Year-Old Girl with Irritability, Hypersomnia, and Somatic Symptoms

Suzanne L. Bender, M.D., Nicole A. Sherry, M.D., and Ricard Masia, M.D., Ph.D.

Departments of Psychiatry (S.L.B.), Pediatrics (N.A.S.), and Pathology (R.M.), Massachusetts General Hospital; and the Departments of Psychiatry (S.L.B.), Pediatrics (N.A.S.), and Pathology (R.M.), Harvard Medical School — both in Boston.

PRESENTATION OF CASE

Dr. Elizabeth G. Pinsky (Psychiatry): A 12-year-old girl was seen in the outpatient psychiatry clinic of this hospital because of severe irritability, hypersomnia, and multiple somatic symptoms.

The patient had celiac disease but had been otherwise well until approximately 8 months earlier, when she became increasingly irritable and reported daily stomachaches, tingling and pain in her arms and legs, dizziness, anorexia, and severe fatigue; she also became increasingly somnolent, sleeping up to 13 hours per night. She had frequent angry outbursts directed at her mother and sister, and acted out physically on occasion. She became increasingly isolated from her friends and lost interest in activities. Her performance in school deteriorated, and she failed mathematics. Approximately 4.5 months before this presentation, red-cell indexes and results of thyroid-function tests were normal, and testing for heterophile antibody was negative; other test results are shown in Table 1. She was referred to the outpatient gastroenterology, neurology, and psychiatry clinics of this hospital.

The patient was born to a 39-year-old mother by cesarean section because of maternal preeclampsia, and her childhood development was normal. A diagnosis of celiac disease had been made at the age of 8 years, when she presented with abdominal pain and constipation; elevated levels of tissue transglutaminase antibody (70 U per milliliter) and endomysial antibody (80 U per milliliter) were detected, and examination of a biopsy specimen of the duodenum showed changes consistent with celiac disease. She adhered to a gluten-free diet and had been otherwise well. She had a history of anxiety and depression; she had no response to a trial of sertraline but did have a response to both escitalopram, begun 2 years before this evaluation, and 7 months of cognitive behavioral therapy. Sixteen months before this evaluation, the first of three episodes of severe vomiting requiring intravenous hydration occurred; subsequent episodes occurred 6 months and 4 months before this evaluation, each preceded by fever and viral symptoms. There was no associated headache, and neurologic evaluation including an electroencephalogram was reportedly normal.

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The patient's mother noted that the patient had a long history of daydreaming. She had not begun to menstruate. She had no history of head injury, loss of consciousness, urinary symptoms, hospitalizations, or surgery. Her only medication was 10 mg daily of escitalopram. She had no known allergies. She lived with her parents and younger sister. Her mother had thyroid disease; maternal and paternal aunts, a paternal uncle, and her paternal grandmother had celiac disease; a paternal uncle had bipolar disorder; and other relatives had anxiety, depression, or attention deficit–hyperactivity disorder (ADHD). There was no family history of cystic fibrosis, inflammatory bowel disease, liver disease, pancreatitis, or diabetes mellitus.

On examination, the patient was slim and appeared exhausted, without apparent physical distress. The blood pressure was 83/52 mm Hg, the pulse 102 beats per minute, the head circumference 53.2 cm, the weight 35.4 kg, and the height 149.9 cm, with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 15.8 (12th percentile for age). The skin was freckled, with multiple dark nevi and slight hyperpigmentation in the axillae. Results of cranial-nerve testing and funduscopic examination were normal. Strength was full throughout. Reflexes were brisk, and plantar responses were flexor. Clonus (2 to 3 beats, unsustained) on the right foot occurred, but the finding was not easily repeated. The patient initially rocked on her feet during tandem gait but later skipped and jumped without difficulty. Results of sensory examination and Romberg testing were normal. When talking with the psychiatrist, the patient focused primarily on her pain and fatigue. She appeared withdrawn and disengaged, with a sad and apathetic affect. Her speech was sparse, slow, and soft at times, and eye contact and spontaneous movements were limited. Her three wishes were to have a cell phone so she could call her mother when she became nervous while waiting for her mother to pick her up at school, to have different friends, and to have school be different. There was no delusional content, suicidal ideation, or hallucinations. In the waiting area, she fell asleep, awakening to gentle shaking but not to voice. Magnetic resonance imaging (MRI) of the head was normal. Diagnoses of major depressive disorder and generalized anxiety disorder were made.

Weekly therapy sessions were begun. During the next 3 weeks, the administration of escitalopram was changed to bedtime; the administration of bupropion was begun and gradually increased to 75 mg daily. The patient continued to have worsening dizziness, lightheadedness, headaches, stomachaches, and musculoskeletal pain. She had two episodes of vomiting at school, with nonbloody, nonbilious emesis and dry heaves, and her oral intake decreased.

On repeat examination in the psychiatry clinic 6 weeks after the initial evaluation, the patient appeared listless and pallid. Her weight was 34.0 kg. She was referred to her pediatrician for further evaluation. On examination at the pediatrician's office 5 days later, the weight was 32.9 kg. Blood levels of platelets, glucose, total protein, albumin, total and direct bilirubin, alanine aminotransferase, and C-reactive protein were normal; other test results are shown in Table 1. Bupropion was stopped, and she was referred to the emergency department of another hospital.

On examination, the blood pressure was 87/45 mm Hg, the pulse 92 beats per minute with the patient in a supine position and 124 beats per minute while she was standing, the tympanic temperature 36.4°C, and the weight 33.5 kg. The remainder of the examination was normal. An electrocardiogram reportedly showed sinus rhythm at 100 beats per minute, with a normal axis, a prolonged QT interval corrected for heart rate of 505 msec, a T-wave inversion in lead III, and biphasic T waves in lead V₃. Test results are shown in Table 1. The patient was admitted to the other hospital.

Additional diagnostic tests were performed.

DIFFERENTIAL DIAGNOSIS

Dr. Suzanne L. Bender: I am aware of the diagnosis in this case. This 12-year-old girl with celiac disease adhered to her gluten-free diet. She reported many somatic symptoms and had hypersomnia but appeared in no physical distress. No medical illness had been found by her pediatrician, gastroenterologist, or neurologist. She was irritable, with frequent angry outbursts at home, and had academic difficulty at school. She was referred to child psychiatry for evaluation. Because some medical conditions take time to become apparent, a multidisciplinary team was established to coordinate ongoing diagnosis and treatment in this child with somatic symptoms that had no clear cause but that impaired daily functioning.

SOMATIC SYMPTOMS

Emotional distress may be affecting this patient's bodily function. This is well-described in irritable bowel syndrome as the "brain-gut axis." Psychosocial influences affect gut motility and may increase visceral sensitivity. A change in gut motility and visceral sensitivity may in turn increase anxiety and depression in some patients.¹⁻³ There is an ongoing conversation between the brain and the body. When I talk to families in my clinic about this mind-body interaction, I explain that this is why we have a neck. In addition, some children may have difficulty distinguishing emotional pain from physical pain. All they know is that they don't feel well, and then this is translated, in their minds, into feeling sick. Emotional distress expressed as somatic symptoms is a new type of referred pain — pain that is referred from brain to body.

Pediatric patients with somatization are likely to have psychopathological symptoms, family dysfunction, and poor performance and attendance at school.⁴ Children with abdominal pain who have a negative medical workup may have been exposed to a traumatic event and may have underlying anxiety.⁵ In addition, the mothers of such children often have higher rates of anxiety, depression, and various physical ailments, as compared with a control population.^{5,6}

It is notable that one of this patient's three wishes was not a wish to feel physically better. Her wishes "to have different friends" and "to have school be different" signal that these areas in her life are causing distress and perhaps her experience of pain.

IRRITABLE MOOD

Evaluation of pediatric irritable mood includes an assessment of a child's functioning at home and at school. This patient's frequent fights with her mother and sister and concerns about her peer group could both cause and result in her current irritability. Although this patient had anxiety, her symptoms could not be explained by anxiety alone. Persons with anxiety usually present with sleeplessness or restlessness, and not with hypersomnia and psychomotor retardation.

Academic struggles may also decrease self-esteem and emotional resiliency. This patient's grades dropped, she failed mathematics, and she expressed concern about school. A consideration in this case is attention-deficit disorder, inattentive type. Young girls with this disorder who do not have behavioral issues are often first diagnosed during middle school, when organizational challenges increase. The results of neuropsychological testing could show whether this child has a nonverbal learning disorder, defined on a test such as the Wechsler Intelligence Scale for Children, fourth edition, as a verbal comprehension score that is much greater than the perceptual reasoning score. Difficulties with organization, social skills, and academics, specifically mathematics, are often seen in children with this disorder.⁷

This patient's irritability could be due to a medical condition.⁸ Anemia, thyroid dysfunction, mononucleosis, and disorders involving calcium metabolism are associated with depressive symptoms; these disorders have already been considered in this case and do not seem to explain her symptoms. She has celiac disease, and adolescents with celiac disease have a higher lifetime prevalence of major depressive disorders before diagnosis and before adoption of a gluten-free diet than do matched controls.⁹ Celiac disease with malabsorption may cause vitamin B₁₂ and folate deficiencies, both of which are associated with mood disorders.^{10,11} An additional screening blood chemical profile would be useful for identifying abnormal liver and renal function and abnormal levels of electrolytes, vitamins, and glucose, which may be associated with mood symptoms (Tables 2 and 3).¹¹ Irritability may be due to the effects of a substance (e.g., a drug of abuse, a medication, or a toxin).⁸ Although surreptitious substance abuse could account for all this patient's symptoms, it would be highly unlikely in a well-supervised child whose only medication is escitalopram.

DEPRESSION

On a review of this patient's symptoms, she meets all the criteria for a major depressive episode (i.e., for more than 2 weeks, she has had persistent irritable mood and five or more of the following neurovegetative symptoms: low energy, decreased appetite, hypersomnia, diminished interest in daily activities, psychomotor retardation, and decreased concentration). She reported no sadness, feelings of worthlessness, or suicidal ideation, but children often have trouble recognizing and reporting their emotional state. Alexithymia (the inability to express one's feelings) does not rule out depression. Child psychiatrists base their diagnoses on observation and on reports from parents, as well as on the child's self-report. Prepubertal patients with depression commonly present with somatic symptoms, irritability, or social withdrawal, whereas adolescents are more likely to have hypersomnia

or psychomotor retardation. This patient, straddling the worlds of childhood and adolescence, had all these symptoms.⁸

This patient did not have a recent loss or trauma to account for her symptoms. It was possible that she was in the depressive phase of an emerging pediatric bipolar disorder, since she had some risk factors, including an early onset of depression, atypical depression with hypersomnia, and an extensive family history of mood disorders. However, the absence of adverse effects (e.g., agitation) associated with her use of escitalopram argues against a current diagnosis of bipolar illness.¹²⁻¹⁵

The patient had several risk factors for major depressive disorder, including a family history of depression,¹⁶ the presence of another nonaffective psychiatric disorder predating the depression (anxiety), female sex (after puberty), and multiple major life stressors (including a physical illness, family conflict, and poor performance in school). The more risk factors a patient has, the more likely it is that depression will develop.^{17,18}

While I continued to collect laboratory data, I made a preliminary diagnosis in this patient of treatment-resistant major depressive disorder. More information would clarify the potential diagnosis of attention-deficit disorder, inattentive type.

MANAGEMENT OF CHILDHOOD DEPRESSION

Both medications and psychotherapy are used to treat childhood depression. Many different psychotherapies (e.g., psychodynamic psychotherapy, family therapy, interpersonal psychotherapy, and cognitive behavioral therapy) are thought to be effective in the treatment of pediatric depression.¹⁹⁻²² Cognitive behavioral therapy and relaxation techniques have been useful in the treatment of chronic pain.²³

Only two selective serotonin-reuptake inhibitors (SSRIs) are approved by the Food and Drug Administration (FDA) — fluoxetine for the treatment of children 8 years of age or older, and escitalopram for the treatment of children 12 years of age or older. The FDA issued a black-box warning in 2004 that some children, adolescents, and young adults may have an increased risk of suicidal thoughts or behavior while taking antidepressants.²⁴ One meta-analysis showed that the increased risk in suicidal thoughts was between 1% and 3%.²⁵ Another meta-analysis concluded that the clinical benefits associated with the use of antidepressants in children with depression outweighed the risks.²⁶

In patients who have not previously received treatment, evidence supports the use of fluoxetine combined with cognitive behavioral therapy for the safest and fastest clinical response.^{27,28} This patient's depression continued despite psychotherapy and two trials of an SSRI. Although venlafaxine has been studied as an alternative antidepressant agent for adolescents with treatment-resistant depression, it has a higher incidence of side effects, including suicidality, over the long term than do SSRIs.²⁹⁻³¹

Studies of treatment-resistant depression in adults provide guidance for medications for this child with treatment-resistant depression. Augmenting an antidepressant with either bupropion or sustained-release bupropion results in a 30% increase in the remission rate; therefore, it is a reasonable next step for this child, who had treatment-resistant major

depressive disorder and no response to two trials of an SSRI.^{20,32,33} Bupropion works through noradrenergic and dopaminergic mechanisms and affects different neurotransmitters from those affected by SSRIs. If the administration of bupropion were added, this patient could continue on escitalopram to treat her anxiety. Bupropion is also used to treat attentional disorders and may help reduce the patient's reported daydreaming.³⁴ I have found bupropion to be very effective in the treatment of disengaged adolescents with somatic symptoms who have not responded to an SSRI.

The clinical approach to major depressive disorder and multiple somatic symptoms in this treatment-resistant child needs to be inclusive and comprehensive. Further laboratory studies are warranted to screen for a medical condition that is fueling the mood disorder (Table 3). I recommended weekly cognitive behavioral therapy (for problem-solving and cognitive restructuring), the practice of relaxation techniques (to help with chronic pain),²³ and the use of a psychodynamic approach for identifying and discussing the patient's feelings about her friends, family, and school. Escitalopram and bupropion were administered. I recommended evaluation for possible attention-deficit disorder, as well as neuropsychological testing to identify any learning disorders.

Despite these approaches, the patient's somatic symptoms worsened, and she began to lose weight and appear ill. She was urgently referred back to her pediatrician.

DR. SUZANNE L. BENDER'S DIAGNOSIS

Major depressive disorder and high suspicion for a concurrent medical illness.

PATHOLOGICAL DISCUSSION

Dr. Ricard Masia: The patient had undergone upper gastrointestinal endoscopy at 8 years of age. Diffuse mildly scalloped mucosa was found in the second part of the duodenum. Biopsy specimens showed duodenal mucosa with subtotal villous atrophy and crypt hyperplasia (Fig. 1A). The number of intraepithelial lymphocytes was markedly increased, with more than 40 intraepithelial lymphocytes per 100 enterocytes, and there was associated enterocyte injury (Fig. 1B). In the context of the patient's symptoms and positive anti-tissue transglutaminase antibody test, these findings were consistent with duodenal involvement by celiac disease. According to the Marsh–Oberhuber classification, the histologic findings correspond to a type 3b lesion (subtotal villous atrophy, crypt hyperplasia, and >40 intraepithelial lymphocytes per 100 enterocytes).³⁵

The diagnostic tests performed at the other hospital included a plasma cortisol test, which involved three specimens drawn at baseline and during a cosyntropin stimulation test, all measuring less than 0.3 μg per deciliter (8.3 nmol per liter; reference range, 5.0 to 25.0 μg per deciliter [138.0 to 689.8 nmol per liter]). The plasma corticotropin level was 2069 pg per milliliter (456 pmol per liter; reference range, 46 pg per milliliter [10 pmol per liter]), the anti-21-hydroxylase antibody level 684.2 U per milliliter (reference range, 1.0), and the plasma renin activity 5633 ng per deciliter per hour (reference range, 50 to 330). These results indicate adrenal insufficiency.

Data are limited regarding the pathological findings in patients with both celiac disease and Addison's disease; therefore, it is difficult to assess whether findings on examination of small-bowel-biopsy specimens can help identify patients with celiac disease who are at increased risk for the development of Addison's disease. However, case series involving patients with Addison's disease have identified some patients with previously known or undiagnosed celiac disease. Although most patients with celiac disease and Addison's disease had destructive lesions (Marsh–Oberhuber type 3) on duodenal biopsy, some patients had a histologically normal mucosa.³⁶⁻³⁹ These data suggest that there is no reliable correlation between biopsy findings and the risk of the development of Addison's disease.

DISCUSSION OF MANAGEMENT

Dr. Nicole A. Sherry: The undetectable plasma cortisol levels, elevated plasma corticotropin level, elevated plasma renin activity, and elevated 21-hydroxylase antibody level are diagnostic of autoimmune primary adrenal failure. This results in a loss of adrenal glucocorticoid, mineralocorticoid, and androgen production because of destruction of the adrenal cortex by autoreactive T cells. As a result of the loss of negative feedback of cortisol on the hypothalamus and pituitary, corticotropin levels rise dramatically and levels of thyrotropin can rise mildly. Because of the loss of the effects of mineralocorticoids on salt and water balance, there is decreased renal perfusion pressure, which drives the production of plasma renin activity.

Through the lens of an endocrinologist, this patient's signs and symptoms match the textbook description of adrenal insufficiency, just as they matched the textbook picture of major depressive disorder when interpreted by her psychiatrist. Specifically, the patient had chronic weakness, fatigue, anorexia, nausea, vomiting, abdominal pain, dizziness, and muscle and joint pains. She had weight loss, hyperpigmentation, hypotension, hyponatremia, hyperkalemia, hypercalcemia, anemia, and eosinophilia. Even more striking, she had had episodes of acute adrenal crises with profound deterioration during intercurrent viral illnesses over the preceding year and a half that had required three hospitalizations.

The diagnosis of Addison's disease is often missed for some time, as it was in this case. In one study, only 47% of the cases were diagnosed within 1 year after initial symptoms and more than 20% were diagnosed more than 5 years after initial symptoms.⁴⁰ Thirty percent of the patients had seen five physicians before the diagnosis of Addison's disease was made. More than 80% had had a previous incorrect diagnosis, 50% of which were psychiatric disorders and 31% of which were gastrointestinal diseases.

In this case, there is an important clue to the diagnosis. This patient had a personal history of celiac disease and a family history of both celiac disease and autoimmune thyroid disease. This constellation of diseases is highly suggestive of the autoimmune polyglandular syndrome type 2 and should alert the clinician that the patient is at high risk for other autoimmune disorders, including autoimmune adrenal insufficiency, thyroid disease, and celiac disease.⁴¹

After the diagnosis of Addison's disease was made, the patient was treated with hydrocortisone (9 mg per square meter of body-surface area divided into three doses daily)

and fludrocortisone (0.1 mg daily). Although the somatic symptoms resolved, she continued to have psychiatric symptoms. It has been recognized that for patients with adrenal insufficiency who adhere to current treatment regimens, the quality of life can be impaired,⁴² with a perception of reduced general health and vitality and increased fatigue as compared with population norms. Patients with autoimmune polyendocrine syndromes have lower scores in these measures on subjective health-assessment questionnaires than do those with adrenal insufficiency in isolation.^{43,44}

The administration of adrenal androgens that have not been traditionally replaced may improve the quality of life. Several short-term studies have shown that the administration of dehydroepiandrosterone improves psychological health,^{45,46} but the results are mixed, and longer-term studies have not shown as pronounced an effect.^{43,47}

Dr. Pinsky: The patient was discharged from the other hospital taking only escitalopram and glucocorticoid-replacement and mineralocorticoid-replacement therapy. The nausea, vomiting, pain, and weakness diminished rapidly, and her appetite quickly improved; her mother reported that the patient ate two candy bars on the way home from the hospital. Fatigue persisted but was improved. The hope was that her symptoms had all been related to underlying adrenal insufficiency and that she might eventually be able to discontinue escitalopram.

After approximately 3 months of glucocorticoid-replacement therapy, the patient continued to be socially withdrawn and anxious, was still sleeping 12 to 14 hours a day, and struggled with inattention and academic faltering. Neuropsychiatric testing was performed and was suggestive of ADHD, although assessment of attention was confounded by depressed mood and anxiety, as well as her recent medical illness. The administration of bupropion was resumed. After several weeks, symptoms of withdrawal, anxiety, energy, and attention improved. At the end of the academic year, the patient was the champion of the science fair.

Dr. Sherry: Although the focus of current treatment studies has been finding a better physiological match of hormonal replacement to help with psychiatric symptoms, this patient's symptoms were successfully treated with a combination of traditional hormonal replacement and psychopharmacologic approaches.

Dr. Nancy Lee Harris (Pathology): Are there any comments or questions?

Dr. Joshua Roffman (Psychiatry): In retrospect, were there any red flags in the patient's presentation that suggested a medical component to her symptoms that we should look for when evaluating depression in children?

Dr. Bender: At first, this patient looked tired but otherwise physically well and she had a negative medical workup. Many patients with a similar presentation get better with psychiatric treatment. Some medical diagnoses become clear as symptoms evolve over time, which is why ongoing coordinated care between psychiatry and pediatrics is so critical for patients with somatic symptoms. A key moment was when the patient, who had appeared well, started to look sick. Dr. Pinsky recognized that her condition had changed and referred her for additional evaluation.

A Physician: Were her parents angry that it took 16 months for a diagnosis to be made?

The Patient's Father: For a very long time, our daughter has had continuing mental and physical problems. It was difficult and traumatic, but we're very thankful for all the doctors who eventually made the diagnosis and brought her to where she is today.

Dr. Harris: I think it's instructive to learn of the usual delay in the diagnosis of Addison's disease. There are so many possible causes of all these symptoms that Addison's disease is not on the top of anyone's differential diagnosis.

Dr. Harland Winter (Pediatric Gastroenterology): Was the axillary hyperpigmentation a potential clue to adrenal insufficiency?

Dr. Sherry: Yes, hyperpigmentation in Addison's disease is due to an increase in melanocyte-stimulating hormone. The axillae are a typical location for hyperpigmentation, which is most often diffuse.

Dr. Robin M. Jones (Neurology): The patient was referred to me from gastroenterology because of recurrent nausea and vomiting, which had been attributed to the cyclic vomiting syndrome at an outside institution. An electroencephalogram was reportedly normal. Because of the axillary freckling, I entertained the diagnosis of neurofibromatosis 1. I referred her for an ophthalmologic examination to look for Lisch nodules and ordered a brain MRI to rule out an intracranial process that might account for the nausea and vomiting.

Dr. Sherry: Addison's disease can be associated with other skin findings, such as more generalized hyperpigmentation, especially in sun-exposed areas, whereas neurofibromatosis can be associated with café au lait lesions. In this patient with no other skin findings, a distinction between Addison's disease and neurofibromatosis could not be made on the basis of axillary freckling alone.

ANATOMICAL DIAGNOSIS

Celiac disease, Addison's disease, and major depressive disorder.

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Figure 1. Duodenal-Biopsy Specimen (Hematoxylin and Eosin)

The duodenal mucosa shows subtotal villous atrophy and crypt hyperplasia (Panel A). The number of intraepithelial lymphocytes is markedly increased (Panel B, arrows).

Table 1

Laboratory Data.*

Variable	Reference Range, Other Hospital [†]	4.5 Mo before Evaluation, Pediatrician's Office	6 Wk after Evaluation, Pediatrician's Office	On Admission, Other Hospital
Blood				
Hematocrit (%)	32.1–38.7	35.3 (ref 35.0–45.0)	40.9 (ref 34–40)	40.3
Hemoglobin (g/dl)	11.3–13.4	11.9 (ref 11.5–15.5)	13.7 (ref 11.0–16.0)	13.8
White-cell count (per mm ³)	5520–9290	3600 (ref 4500–13,500)	5260 (ref 4000–10,800)	5070
Differential count (%)				
Neutrophils	46–76	39.1	45.0 (ref 30.0–85.0)	39
Lymphocytes	8–39	45.9	44.7 (ref 15.0–55.0)	45
Monocytes	4–7	9.9	6.7 (ref 0–10.0)	7
Eosinophils	1–3	4.5	3.4 (ref 0–5.0)	6
Basophils	0–1	0.6	0.2 (ref 0–2.0)	1
Atypical lymphocytes	0–4			2
Erythrocyte sedimentation rate (mm/hr)	0–20	3	7	8
Heterophile	Negative	Negative	Negative	
Free thyroxine (ng/dl)	0.80–1.90	0.9 (ref 0.9–1.4)		1.25
Thyrotropin (μU/ml)	0.700–5.700	3.43	9.64	6.820
Sodium (mmol/liter)	135–148		133 (ref 137–145)	126
Potassium (mmol/liter)	3.20–4.50		5.2 (ref 3.5–5.1)	5.55
Chloride (mmol/liter)	99–111		93 (ref 98–107)	94
Carbon dioxide (mmol/liter)	22–30		26.0 (ref 22.0–30.0)	23
Urea nitrogen (mg/dl)	5–18		22 (ref 7–17)	18
Creatinine (mg/dl)	0.3–1.0		0.6 (ref 0.5–1.0)	0.5
Calcium (mg/dl)			10.6 (ref 8.3–10.3)	
Alkaline phosphatase (U/liter)	60–335		235 (ref 38–126)	209
Aspartate aminotransferase (U/liter)	2–40		63 (ref 15–46)	58 (hemolyzed specimen)
Creatine kinase (U/liter)	4–150			476
Urine				
Sodium (mmol/liter)				119
Creatinine (mg/dl)				67.4

* Ref denotes reference range at the pediatrician's office. To convert the values for free thyroxine to picomoles per liter, multiply by 12.87. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for calcium to millimoles per liter, multiply by 0.250.

[†] Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges shown are obtained from the laboratories at the other hospital.

Table 2

Differential Diagnosis of Irritable Mood in Children.*

General medical condition	Neurologic	Metrizamide
Autoimmune	Brain tumor	Metronidazole
Celiac disease	Multiple sclerosis	Nalidixic acid
Polyarteritis nodosa	Stroke	Narcotics
Rheumatoid arthritis	Temporal lobe epilepsy	Nifedipine
Systemic lupus erythematosus	Nutritional	Nonsteroidal antiinflammatory drug
Cardiovascular	Vitamin B ₁₂ deficiency	Norfloxacin
Cardiac tumors	Folate deficiency	Oral contraceptive pill
Congestive heart failure	Medication use	Oseltamivir phosphate
Hypertensive encephalopathy	Acyclovir	Phenylephrine
Anemia	Anabolic steroids	Prazosin
Endocrine	Anticonvulsants	Procaine derivatives: penicillin G procaine, lidocaine, procainamide
Diabetes mellitus	Carbamazepine	
Hyperadrenalism	Phenytoin	Thyroid hormones
Hypoadrenalism	Primidone	Trimethoprim–sulfamethoxazole
Hyperparathyroidism	Asparaginase	Exposure to substances
Hypoparathyroidism	Baclofen	Alcohol-use disorders
Hypopituitarism	Barbiturates	Amphetamine-use disorders
Hypothyroidism	Benzodiazepines	Carbon monoxide
Hyperthyroidism	Beta-blockers	Cocaine-use disorders including withdrawal
Infectious	Bromides	Heavy metals
Hepatitis	Bromocriptine	Methylsulfonylmethane
Human immunodeficiency virus	Clonidine	Opioid use
Influenza	Glucocorticoid	Bereavement
Lyme disease	Cycloserine	Trauma
Mononucleosis	Dapsone	Acute stress disorder
Metabolic	Digitalis	Posttraumatic stress disorder
Acid–base problems	Diltiazem	Other mood disorders
Hypokalemia	Disopyramide	Major depressive disorder
Hypernatremia	Ethionamide	Bipolar I disorder
Hyponatremia	Halothane (postoperatively)	Bipolar II disorder
Renal failure	Histamine H ₂ –receptor antagonists	Bipolar disorder, not otherwise specified
Neoplastic	Interferon alfa	Cyclothymic disorder
Occult cancer	Isoniazid	Dysthymic disorder
	Isotretinoin	Adjustment disorder with depressed mood
	Mefloquine	Depressive disorder, not otherwise specified
	Metoclopramid	

* The table is modified from Geringer et al.¹¹

Table 3

Screening Laboratory Evaluation of Irritability in a Child with Somatic Symptoms.*

Complete blood count with differential count
Complete blood chemical panel including calcium
Blood and urine toxicologic analysis
Vitamin B ₁₂
Folate
Heterophile antibody test
Thyrotropin
Other tests to consider
Cerebrospinal fluid analysis
Electroencephalogram
Neuroimaging

* The table is modified from Geringer et al.¹¹