Outbreak of Life-Threatening Thiamine Deficiency in Infants in Israel Caused by a Defective Soy-Based Formula

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ABSTRACT. Objective. Between October and November 2003, several infants with encephalopathy were hospitalized in pediatric intensive care units in Israel. Two died of cardiomyopathy. Analysis of the accumulated data showed that all had been fed the same brand of soy-based formula (Remedia Super Soya 1), specifically manufactured for the Israeli market. The source was identified on November 6, 2003, when a 5.5-month-old infant was admitted to Sourasky Medical Center with upbeat nystagmus, ophthalmoplegia, and vomiting. Wernicke’s encephalopathy was suspected, and treatment with supplementary thiamine was started. His condition improved within hours. Detailed history revealed that the infant was being fed the same formula, raising suspicions that it was deficient in thiamine. The formula was tested by the Israeli public health authorities, and the thiamine level was found to be undetectable (<0.5 μg/g). The product was pulled from the shelves, and the public was alerted. Thiamine deficiency in infants is very rare in developed countries. The aim of this study was to report the epidemiology of the outbreak and to describe the diagnosis, clinical course, and outcome of 9 affected infants in our care.

Methods. After the index case, an additional 8 infants were identified in our centers by medical history, physical examination, and laboratory testing. The group consisted of 6 male and 3 female infants aged 2 to 12 months. All were assessed with the erythrocyte transketolase activity assay, wherein the extent of thiamine deficiency is expressed in percentage stimulation compared with baseline (thiamine pyrophosphate effect [TPPE]). Normal values range from 0% to 15%; a value of 15% to 25% indicates thiamine deficiency, and >25% indicates severe deficiency. Blood lactate levels (normal: 0.5–2 mmol/L) were measured in 6 infants, cerebrospinal fluid lactate in 2 (normal: 0.5–2 mmol/L), and blood pyruvate in 4 (normal: 0.03–0.08 mmol/L). The diagnostic criteria for thiamine deficiency were abnormal transketolase activity and/or unexplained lactic acidosis. Treatment consisted of intramuscular thiamine 50 mg/day for 14 days combined with a switch to another infant formula.

Results. Early symptoms were nonspecific and included mainly vomiting (n = 8), lethargy (n = 7), irritability (n = 5), abdominal distension (n = 4), diarrhea (n = 4), respiratory symptoms (n = 4), developmental delay (n = 3), and failure to thrive (n = 2). Infection was found in all cases. Six infants were admitted with fever. One patient had clinical dysentery and group C Salmonella sepsis; the others had mild infection: acute gastroenteritis (n = 2); upper respiratory infection (n = 2); bronchopneumonia, acute bronchitis, and viral infection (n = 1 each). Two infants were treated with antibiotics. Three infants had neurologic symptoms of ophthalmoplegia with bilateral abduction deficit with or without upbeat nystagmus. All 3 had blood lactic acidosis, and 2 had high cerebrospinal fluid lactate levels. Patient 1, our index case, was hospitalized for upbeat nystagmus and ophthalmoplegia, in addition to daily vomiting episodes since 4 months of age and weight loss of 0.5 kg. Findings on brain computed tomography were normal. Blood lactate levels were high, and TPPE was 37.8%. Brain magnetic resonance imaging (MRI) revealed no abnormalities.

Patient 2, who presented at 5 months with lethargy, vomiting, grunting, and abdominal tenderness, was found to have intussusception on abdominal ultrasound and underwent 2 attempts at reduction with air enema several hours apart. However, the lethargy failed to resolve and ophthalmoplegia appeared the next day, leading to suspicions of Wernicke’s encephalopathy. Laboratory tests showed severe thiamine deficiency (TPPE 31.2%). In patients 1 and 2, treatment led to complete resolution of symptoms. The third infant, a 5-month-old girl, was admitted on October 10, 2003, well before the outbreak was recognized, with vomiting, fever, and ophthalmoplegia. Her condition deteriorated to seizures, apnea, and coma. Brain MRI showed a bilateral symmetrical hyperintense signal in the basal ganglia, mamillary bodies, and periaqueductal gray matter. Suspecting a metabolic disease, vitamins were added to the intravenous solution, including thiamine 250 mg twice a day. Clinical improvement was noted 1 day later. TPPE assay performed after treatment with thiamine was started was still abnormal (17.6%). Her formula was substituted after 4 weeks, after the announcement about the thiamine deficiency. Although the MRI findings improved 5 weeks later, the infant had sequelae of ophthalmoplegia.

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PEDiATRICS (ISSN 0031 4005). Copyright © 2005 by the American Academy of Pediatrics.
and motor abnormalities and is currently receiving physiotherapy. All 3 patients with neurologic manifestations were fed exclusively with the soy-based formula for 2 to 3.5 months, whereas the others had received solid food supplements. Longer administration of the formula (ie, chronic thiamine deficiency) was associated with failure to thrive. For example, one 12-month-old girl who received the defective formula for 8 months presented with refusal to eat, vomiting, failure to thrive (75th to <5th percentile), hypotonia, weakness, and motor delay. Extensive workup was negative for malabsorption and immunodeficiency. On admission, the patient had Salmonella gastroenteritis and sepsis and was treated with antibiotics. After thiamine deficiency was diagnosed, she received large doses of thiamine (50 mg/day) for 2 weeks. Like the other 5 infants without neurologic involvement, her clinical signs and symptoms disappeared completely within 2 to 3 weeks of treatment, and TPPE levels normalized within 1 to 7 days. There were no side effects. As part of its investigation, the Israel Ministry of Health screened 156 infants who were fed the soy-based formula for thiamine deficiency. However, by that time, most were already being fed alternative formulas and had begun oral thiamine treatment. Abnormal TPPE results (>15%) were noted in 8 infants, 3 male and 5 female, all >1 year old, who were receiving solid food supplements. Although their parents failed to notice any symptoms, irritability, lethargy, vomiting, anorexia, failure to thrive, and developmental delay were documented by the examining physicians. None had signs of neurologic involvement. Treatment consisted of oral thiamine supplements for 2 weeks.

Conclusions. Clinician awareness of the possibility of thiamine deficiency even in well-nourished infants is important for early recognition and prevention of irreversible brain damage. Therapy with large doses of thiamine should be initiated at the earliest suspicion of vitamin depletion, even before laboratory evidence is available and before neurologic or cardiologic symptoms appear. Pediatrics 2005;115:e233–e238. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1255; thiamine, Wernicke's encephalopathy, infant, formula, vitamin.

Infantile thiamine deficiency is a very rare condition in developed countries today. It occurs mainly in breastfed infants of mothers who have inadequate intake of thiamine and is hardly seen in formula-fed infants with no underlying disease or malnutrition state.1–3 Thiamine is an essential vitamin for brain development in infants,4,5 and its deficiency can be expressed by nervous system (dry beriberi, or Wernicke-Korsakoff syndrome) or cardiovascular (wet beriberi) manifestations and even lead to death (Shoshin beriberi, Wernicke's encephalopathy).6–10 In November 2003, thiamine deficiency was diagnosed in 20 infants in Israel, a highly Westernized country with state-of-the-art medical care. The aim of the present study was to describe the epidemiology of this outbreak and the symptoms, diagnosis, course, and outcome of 9 of the infants who were hospitalized in our centers. In addition, the findings of a screen of a series of nonsymptomatic infants are provided. These data are important to alert physicians to the possibility of thiamine deficiency even in well-nourished populations and to highlight the specific manifestations in young infants.

Between October and November 2003, several infants with encephalopathy were hospitalized in pediatric intensive care units in Israel. The clinical signs reported were constipation, agitation, apathy, vomiting, lack of appetite, and, later, diarrhea, grunting, nystagmus, convulsions, and unconsciousness. Two infants died of cardiomyopathy.11 The news of the first wave of hospitalizations broke on November 7, 2003, and set off what could only be considered a national state of pandemonium, which exerted intense pressure on the treating physicians to find the source(s) of the pathology. Analysis of the data accumulated on the affected children yielded only a single link among them: all had been fed with the same popular and highly reputable international brand of nondairy, soy-based infant formula (Remedia Super Soya 1), specifically designed and manufactured by Humana Milchunion (Germany) for export to the Israeli market and distributed in Israel by the company Remedia. The contents of the formula as printed on the label of the containers met the stringent standards of the Israel Department of Health. There was therefore no apparent reason to suspect the product of being implicated in these events.

On November 6, 2003, a male infant aged 5.5 months was admitted to Sourasky Medical Center with upbeat nystagmus, opthalmoplegia, and vomiting. The tentative diagnosis was Wernicke's encephalopathy. Within hours of treatment with supplementary thiamine, his condition improved. A brief investigation revealed that the infant was being fed the same formula whose name was being flashed across the country. Suspecting the formula to be the source of the nationwide epidemic, we immediately (November 8, 2003) informed the Israel Ministry of Health of our findings. The formula was tested by the Israeli public health authorities (November 9, 2003), and the thiamine level was found to be undetectable (<0.5 μg/g). A call went out to all mothers who were using the formula to bring their infants in for testing and to receive a 14-day oral preparation of multivitamins. The product was pulled from the shelves, and the public was warned against its continued use. Humana reported that they had changed the formula in early 2003, and they publicly confirmed the absence of thiamine in the formula. The Israel Ministry of Health sounded an alert to the World Health Organization, which sent an announcement to its member states on November 21, 2003.12 At the time that the present study was prepared, the issue was still under investigation, and no additional details were available.

METHODS

After the diagnosis of the first case of thiamine deficiency, an additional 8 infants were identified in our centers. A thorough medical history was obtained from the parents, including the type and amount of intake of formula and solid food, and the signs and symptoms on presentation were reviewed. Growth charts using the data obtained since birth were completed in all cases. Physical examination was performed by a pediatrician and a pediatric

ABBREVIATIONS. TPPE, thiamine pyrophosphate effect; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.
neurologist; cardiologic and ophthalmologic examinations were
done when indicated by the clinical findings. Laboratory testing
included erythrocyte transketolase activity assay, wherein the ex-
tent of thiamine deficiency is expressed in percentage stimulation
compared with baseline level (the thiamine pyrophosphate effect
[TPPE]). Normal values range from 0% to 15%; a value of 15% to
25% indicates thiamine deficiency, and >25% indicates severe
deficiency.\textsuperscript{13,14} In addition, blood lactate levels (normal: 0.5–2
mmol/L) were measured in 6 infants, cerebrospinal fluid (CSF)
lactate levels in 2 (normal: 0.5–2 mmol/L), and blood pyruvate
levels in 4 (normal: 0.03–0.08 mmol/L). The diagnosis of thiamine
deficiency was defined as the presence of abnormal transketolase
activity (TPPE >15%) and/or unexplained lactic acidosis (>2.0
mmol/L).\textsuperscript{15}

Treatment consisted of intramuscular thiamine 50 mg/day for
14 days combined with a switch to another infant formula. Sup-
portive treatment was given as determined by the attending phy-
sician.

RESULTS

All 9 infants met the laboratory criteria for thia-
mine deficiency (TPPE 13.8–37.8 mmol/L), exclud-
ing patient 8 for whom the level was low because of
a technical error. The group included 6 male and 3
female infants aged 2.5 to 12 months. There was no
ethnic predominance. Clinical and dietary character-
stics are shown in Table 1. Early symptoms were
nonspecific. Almost all of the patients presented with
vomiting and other gastrointestinal symptoms, such
as diarrhea, anorexia, abdominal distension, weight
loss, failure to thrive, and dehydration. Other symp-
toms included respiratory (cough and dyspnea) and
behavioral (lethargy or irritability) symptoms. De-
velopmental delay, mainly motoric, was reported in
3 infants (Table 2).

Infection was the precipitating factor in all cases.
Six of the 9 infants were admitted with fever. One
patient (patient 3) had clinical dysentery and group C Salmonella
sepsis; the others had mild infection: acute gastroenteritis in 2, upper respiratory infection in 2, bronchopneumonia in 1, acute bronchitis in 1,
and viral infection in 1. Two infants (patients 3 and 4)
were treated with antibiotics.

Three of the younger infants (all <6 months old;
patients 1, 2, and 9) displayed clear neurologic symp-
toms of ophthalmoplegia with bilateral abduction
deficit with or without upbeat nystagmus (Fig 1). All
3 had blood lactic acidosis, and 2 had high lactate
levels in the CSF.

Patient 1, the first of our patients in whom Wer-
nicke’s encephalopathy was suspected, was hospital-
ized for upbeat nystagmus and ophthalmoplegia af-
after domperidone administration. History revealed
daily vomiting episodes since 4 months of age and
weight loss of 0.5 kg in the preceding month. He was
treated with budesonide and salbutamol for sus-
pected bronchitis with no improvement. Normal
findings on brain computerized tomography and
high blood lactate level led to a tentative diagnosis
of Wernicke’s encephalopathy. Testing revealed a TPPE
of 37.8%. Brain magnetic resonance imaging (MRI)
scan was normal.

Patient 2, who presented with lethargy, vomiting,
grunting, and abdominal tenderness, was found to
have intussusception on abdominal ultrasound and
underwent 2 attempts at reduction with air enema
several hours apart. However, the lethargy failed to

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, mo</th>
<th>Gender</th>
<th>Main Clinical Symptoms</th>
<th>Duration, mo/Daily Amount, mL of Soy-Formula Feeding</th>
<th>Blood Lactate, mmol/L</th>
<th>CSF Lactate, mmol/L</th>
<th>TPPE, %</th>
<th>Blood Pyruvate, mmol/L</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>5.5</td>
<td>M</td>
<td>Vomiting, weight loss, lethargy, restlessness, respiratory delay, ophthalmoplegia, dysagia</td>
<td>3.5</td>
<td>4.4</td>
<td>2.4</td>
<td>31.2</td>
<td>24.4</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>M</td>
<td>Vomiting, lethargy, intussuction, ophthalmoplegia, dysagia</td>
<td>3.5</td>
<td>4.4</td>
<td>2.4</td>
<td>31.2</td>
<td>24.4</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>F</td>
<td>Vomiting, lethargy, intussuction, ophthalmoplegia, dysagia</td>
<td>3.5</td>
<td>4.4</td>
<td>2.4</td>
<td>31.2</td>
<td>24.4</td>
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<td>4</td>
<td>10</td>
<td>M</td>
<td>Vomiting, lethargy, intussuction, ophthalmoplegia, dysagia</td>
<td>3.5</td>
<td>4.4</td>
<td>2.4</td>
<td>31.2</td>
<td>24.4</td>
</tr>
<tr>
<td>5</td>
<td>8.5</td>
<td>M</td>
<td>Vomiting, lethargy, intussuction, ophthalmoplegia, dysagia</td>
<td>3.5</td>
<td>4.4</td>
<td>2.4</td>
<td>31.2</td>
<td>24.4</td>
</tr>
<tr>
<td>6</td>
<td>5.5</td>
<td>M</td>
<td>Restlessness, vomiting, intussuction, ophthalmoplegia, dysagia</td>
<td>3.5</td>
<td>4.4</td>
<td>2.4</td>
<td>31.2</td>
<td>24.4</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>M</td>
<td>Restlessness, vomiting, intussuction, ophthalmoplegia, dysagia</td>
<td>3.5</td>
<td>4.4</td>
<td>2.4</td>
<td>31.2</td>
<td>24.4</td>
</tr>
<tr>
<td>8</td>
<td>2.5</td>
<td>F</td>
<td>Vomiting, lethargy, intussuction, ophthalmoplegia, dysagia</td>
<td>3.5</td>
<td>4.4</td>
<td>2.4</td>
<td>31.2</td>
<td>24.4</td>
</tr>
<tr>
<td>9</td>
<td>2.5</td>
<td>M</td>
<td>Vomiting, lethargy, intussuction, ophthalmoplegia, dysagia</td>
<td>3.5</td>
<td>4.4</td>
<td>2.4</td>
<td>31.2</td>
<td>24.4</td>
</tr>
</tbody>
</table>

FTT indicates failure to thrive; M, male; F, female; —, samples not taken. Normal ranges: TPPE <15%; blood lactate 0.5–2 mmol/L; CSF lactate 0.5–2 mmol/L; blood pyruvate 0.03–0.08 mmol/L.
resolve and ophthalmoplegia appeared the next day (Fig 1), leading to suspicions of Wernicke’s encephalopathy. Laboratory tests in this case, too, showed severe thiamine deficiency (TPPE 31.2%).

Patient 9 was admitted to Assaf Harofeh Medical Center on October 10, 2003, well before the outbreak was recognized, with vomiting, fever, and ophthalmoplegia. She rapidly deteriorated to abdominal distension and episodes of apnea followed by prolonged seizures treated with diphenylhydantoin. She lost consciousness and required ventilation. MRI showed a bilateral symmetric hyperintense signal in the basal ganglia, mamillary bodies, and periaqueductal gray matter (Fig 2 A). A metabolic disease was suspected, and vitamins were added to the intravenous solution, including thiamine 250 mg twice a day. Clinical improvement was noted 1 day later, and an improvement in the radiologic picture was noted 5 weeks later (Fig 2 B). Although the assay in this case was performed after treatment was started, thiamine levels were still low (TPPE 17.6%). After the announcement about the deficient soy-based formula, her formula was substituted.

The diagnosis was also difficult in the patients without neurologic signs. Patient 3, who received the defective formula for a relatively long period (8 months), presented with refusal to eat, vomiting, failure to thrive (75th to <5th percentile), hypotonia, weakness, and motor delay. Extensive workup was negative for malabsorption, celiac disease, and immunodeficiency. On admission, the patient had diarrhea and dehydration, and stool culture was positive for Salmonella infection. Patient 4, who presented with fever, cough, lethargy, and refusal to eat, had a history of bronchopneumonia treated by azithromycin and inhalation of budesonide and salbutamol. In patient 7, although the only symptom was irritability, the TPPE was a very high 26.5%. Patient 8, who was admitted for vomiting, lethargy, and low-grade fever, was tested for thiamine deficiency only after treatment was started owing to a technical error. The result was 0.6% (compatible with treatment) and 7.5% 3 days later.

Patients 5 and 6 were screened for thiamine deficiency on November 9, 2003. Patient 5 presented with vomiting episodes of >5 months’ duration, accompanied by behavioral changes, refusal to eat, and

<table>
<thead>
<tr>
<th>Symptom</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precipitating infection</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8</td>
</tr>
<tr>
<td>Lethargy</td>
<td>7</td>
</tr>
<tr>
<td>Restlessness</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>4</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>3</td>
</tr>
<tr>
<td>Ophthalmoplegia</td>
<td>3</td>
</tr>
<tr>
<td>FTT</td>
<td>2</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>1</td>
</tr>
<tr>
<td>Intussusception</td>
<td>1</td>
</tr>
</tbody>
</table>

Fig 1. Ophthalmoplegia with abduction deficit in patient 2.

Fig 2. A, MRI scan of patient 9 showing bilateral symmetric hyperintense signal in the periaqueductal gray matter. B, Improved findings after treatment.

TABLE 2. Clinical Symptoms in the 9 Patients
failure to thrive. History included hospitalization for upper respiratory infection treated with intravenous electrolyte and fluid administration and inhalation of budesonide and salbutamol. However, the lethargy and vomiting persisted. His psychomotor development was delayed, and he was referred to our child development center for evaluation. Patient 6 had had irritability and vomiting since 3 months of age that improved at 4 months of age when cereal that contained half the recommended daily allowance of thiamine for his age was added to the formula.

All 3 patients with neurologic manifestations were fed exclusively with the soy-based formula, as was the youngest patient in the group (patient 8). The others had received solid food or cereal supplements (Table 1).

### Outcome

In the 6 infants without neurologic involvement, the clinical signs and symptoms disappeared completely within 2 to 3 weeks of treatment, and TPPE levels at discharge were within normal range (0–7.5%). The normalization of TPPE was very rapid, occurring 1 to 7 days after treatment.

Patient 8, who was fed exclusively with the soy formula, had a normal TPPE result, probably because she started thiamine treatment a few hours before blood was taken. She has some motor delay.

The neurologic signs and symptoms resolved completely after treatment in 2 of the 3 affected infants. The ophthalmoplegia (patients 1 and 2) resolved after 2 weeks, and the nystagmus (patient 1) resolved after 2 months. The growth and psychomotor development normalized in patients 1 and 2. Patient 9, who presented before the outbreak was identified, had residual ophthalmoplegia and abnormal motor development. She is currently receiving physiotherapy.

### Subclinical Cases

As part of its investigation, the Israel Ministry of Health conducted screening studies for thiamine deficiency in 156 infants who were fed the soy-based formula. However, most of the infants were already being fed alternative formulas and had begun oral thiamine treatment by the time of the study, as the story broke on a Friday evening and testing was begun only Sunday, because of the Sabbath. Nevertheless, abnormal assay results (TPPE >15%) were noted in 8 cases. The clinical and dietary characteristics of these children are presented in Table 3. All were >1 year old; 3 were male, and 5 were female; ethnicity was variable. All were receiving solid food products that contained thiamine in addition to formula. Normal development was documented in all patients, and none had signs of neurologic involvement. Although these children were considered asymptomatic by their parents, we noted some symptoms that might have been attributable to the thiamine deficiency (Table 3), namely, irritability, lethargy, vomiting, anorexia, failure to thrive, and developmental delay. Treatment consisted of oral thiamine supplements for 2 weeks.

### DISCUSSION

Thiamine deficiency is very rare in developed countries, yet beriberi is a classic and important epidemic disease that has affected whole countries, populations, and historical events. It still occurs in small numbers in unusual situations, such as in total parenteral nutrition–dependent patients during a multivitamin shortage.\(^{15}\) We describe an outbreak of thiamine deficiency in infants in Israel caused by a defective soy-based infant formula. The formula was consumed by an estimated 1% to 3% of infants who were <1 year old (1500–5000 infants; Israel Ministry of Health, unpublished data). The relatively small number of infants affected (20 total) can probably be explained by the fact that the defective formula had been introduced gradually to the market only a few months before the outbreak.

The early clinical symptoms in our patients (n = 9) were nonspecific and included gastrointestinal manifestations (vomiting, anorexia, diarrhea, and abdominal distension), neurologic symptoms (lethargy, irritability, and developmental delay), and respiratory symptoms. Most of the parents linked the symptoms to concomitant infections, teething, or food intolerance. Longer administration of the thiamine-depleted formula (ie, chronic thiamine deficiency) was associated with failure to thrive (patients 3 and 5). As shown by the series of subclinical cases, infants who were >1 year old were less vulnerable, even in the presence of an abnormally high TPPE (Table 3).

### TABLE 3. Subclinical Cases of Thiamine Deficiency

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, mo</th>
<th>Gender</th>
<th>TPPE*, %</th>
<th>Duration of Soy-Formula Feeding, mo</th>
<th>Age at Introduction of Solid Food Supplement, mo</th>
<th>Clinical Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>M</td>
<td>18.4</td>
<td>4–17</td>
<td>6</td>
<td>Recurrent infections, lethargy, diarrhea</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>F</td>
<td>16.4</td>
<td>0–2, 3–5.5</td>
<td>4</td>
<td>FIT (p25 to p5)</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>F</td>
<td>28.8</td>
<td>6–18</td>
<td>6</td>
<td>FIT (p50 to p25), recurrent infections, anorexia, vomiting, irritability</td>
</tr>
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<td>4</td>
<td>17</td>
<td>M</td>
<td>15.8</td>
<td>7–17</td>
<td>7</td>
<td>FIT (p25 to p5)</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>F</td>
<td>26.7</td>
<td>2.5–16</td>
<td>6</td>
<td>Diarrhea, vomiting</td>
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<tr>
<td>6</td>
<td>14</td>
<td>M</td>
<td>17.7</td>
<td>9–14</td>
<td>6</td>
<td>Hypotonia, motor delay</td>
</tr>
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<td>7</td>
<td>13</td>
<td>F</td>
<td>15.1</td>
<td>1–12</td>
<td>6</td>
<td>None</td>
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<td>8</td>
<td>7</td>
<td>F</td>
<td>20.3</td>
<td>1–7</td>
<td>6</td>
<td>Intussusception (at 3.5 mo) irritability, motor delay</td>
</tr>
</tbody>
</table>

FITT indicates failure to thrive; M, male; F, female.

* Normal range: TPPE <15%.
Conspicuous neurologic signs were upbeat nystagmus and ophthalmoplegia, indicating brainstem involvement. The severity of the thiamine deficiency was related to the severity of the symptoms, mainly the neurologic ones. In all cases, the appearance of symptoms of thiamine deficiency was accompanied by fever or viral or bacterial infection. The clinical picture in our patients is somewhat different from classical beriberi and Wernicke-Korsakoff syndrome in that cardiopathy, peripheral neuropathy, and ataxia were absent.

Even when suspected, thiamine deficiency is difficult to diagnose. The assay for stimulation of erythrocyte transketolase activity is technically demanding and expensive and not available in every laboratory. It is, however, very sensitive to the effects of treatment, with results normalizing (mostly around 0%) within a few hours. Blood pyruvate and lactate measurements, although nonspecific, are helpful, as thiamine is a co-factor of the pyruvate dehydrogenase enzyme. This may explain the similarities between thiamine deficiency and Leigh’s disease, one of the most important mitochondrial diseases of infancy. However, it is important to differentiate the two, because thiamine deficiency is treatable. In our group, abnormal pyruvate and lactic acid results were associated with severe disease, mainly accompanied by neurologic symptoms. The search for morphologic evidence of central nervous system compromise is usually done by MRI, but the results may be normal if encephalopathy is not prominent, as in our first case. When abnormal, findings are highly specific (Fig 2 A) and may improve with treatment (Fig 2 B). The definitive diagnostic evidence is a favorable response to thiamine treatment, as shown in patient 1.

The administration of dextrose and other carbohydrates in this setting can be hazardous, because glucose oxidation is a thiamine-intensive process that may drive the last reserves of circulating vitamin B1 toward the intracellular compartment, thereby aggravating the neurologic damage. We cannot exclude the possibility that this contributed to the deterioration in the condition of patient 9.

Early diagnosis and treatment of thiamine deficiency are crucial to prevent residual loss. Therapy should be initiated at the very earliest suspicion of vitamin depletion, even before laboratory evidence is available and before neurologic or cardiologic symptoms appear. Late interventions entail the risk of irreversible damage. In our group, the neurologic manifestations resolved when the patients were treated early (patients 1 and 2). However, in patient 9, treatment was started after 3 days. Although she improved clinically and radiologically, some ophthalmoplegia and motor abnormalities persisted. There is no established treatment protocol for infantile thiamine deficiency. We treated our patients with large doses of thiamine (50 mg/day) for 2 weeks, and each had a quick response with no side effects.

This study shows that thiamine deficiency in infants is not exclusive to developing countries. Clinical awareness and aggressive vitamin replenishment are currently the safest approach to prevent acute symptoms and long-term sequelae.

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REFERENCES

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