Epilepsy in children with infantile thiamine deficiency

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ABSTRACT

Objective: To report the follow-up findings of 7 children with severe epilepsy as a result of thiamine deficiency in infancy caused by a defective soy-based formula.

Methods: The medical records of 7 children aged 5–6 years with thiamine deficiency in infancy who developed epilepsy were reviewed and their clinical data, EEG tracings, and neuroimaging results were recorded. The clinical course and present outcome of these children, now 5 years after exposure to thiamine deficiency, are described.

Results: All infants displayed seizures upon presentation, either tonic, myoclonic, or focal. Six infants had an EEG recording at this stage and all showed slow background. Five of them had no epileptic activity and only 1 displayed focal activity. Following a seizure-free period of 1–9 months, the seizures recurred, and all 7 children displayed either myoclonic or complex partial seizures. Multifocal or generalized spike wave complexes were recorded on the EEGs of all 7 patients, and the tracings of 3 children evolved into hypsarrhythmia. The seizures were refractory to most antiepileptic drugs, and 4 children remain with uncontrolled seizures. All children have mental retardation and motor disabilities as well as symptoms of brainstem dysfunction.

Conclusions: Our findings indicate that severe infantile thiamine deficiency may result in epilepsy.

Glossary

ACTH = adrenocorticotropic hormone.

In 2003, approximately 20 Israeli infants were seriously affected after being fed an international brand of soy-based formula, later found to be deficient in thiamine (vitamin B1).\(^1\)(2) The formula was withdrawn from the shelves and the public warned against its continued use.\(^3\)(4) The manufacturer reported that the formula had been altered in early 2003, and confirmed the absence of thiamine. The outcome of the infants was grave: 2 died of cardiomyopathy,\(^3\) and approximately 10 remain with residual damage: 1 with complete atrioventricular block and permanent pacemaker, and others with ataxia, sensorineural hearing loss, swallowing difficulties, and a wide spectrum of psychomotor retardation. We report here only on those with severe epilepsy.

The major manifestations of thiamine deficiency in humans involve the cardiovascular and nervous systems.\(^5\) Dry beriberi is characterized by sensorimotor neuropathy of the lower extremities and wet beriberi by edema and congestive heart failure. Wernicke-Korsakoff syndrome, most common in the Western world, mainly affects alcoholics and is characterized by confusion, ataxia, ophthalmoplegia, nystagmus, and impaired memory and cognition. It may also be seen in nonalcoholic patients with gastrointestinal diseases and other disorders associated with malnutrition.\(^6\) Symptoms of thiamine deficiency may appear as early as 2 to 3 weeks on a deficient diet, since body storage of thiamine is minimal.\(^5\)
Infantile thiamine deficiency is very rare in developed countries, occurring mainly in breastfed infants of mothers with inadequate thiamine intake.\(^7\)\(^8\) The onset of symptoms in infants is often very rapid and the fatality rate is high.\(^5\) Seizures have been reported upon presentation in children with infantile thiamine deficiency; however, residual epilepsy is extremely rare.\(^9\)

**METHODS** The current study group consists of 7 children, all girls aged 5–6 years, who had infantile thiamine deficiency caused by a defective formula and consequently developed epilepsy. All are being followed up in pediatric neurology clinics and rehabilitation day care facilities in 4 medical centers in Israel. There is no ethnic predominance. Perinatal history was unremarkable; all were born at term: 1 by elective cesarean section and 2 by vacuum extraction. Only 1 of the children had a family history of febrile convulsions (case 6). All medical records were reviewed and clinical data on seizure semiology, frequency, and treatment were compiled using a structured questionnaire. Data on EEG tracings and neuroimaging were recorded. The clinical course and the present outcome of the children, 5 years after exposure to thiamine deficiency, are described. The study was approved by the Institutional Ethics Review Committee.

**Case 1.** This patient, a girl 5 years and 3 months of age, initially breastfed, was switched to the soy-based formula at 3 weeks of age. At 5 months, she presented with vomiting, fever, and ophthalmoplegia. She deteriorated rapidly, developing abdominal distension and apneic episodes, followed by increased tone and rigidity, myoclonic jerks, and coma requiring ventilation. Bacteriologic and virologic studies were negative. Lactic acid was elevated in blood (5.8 mmol/L) and CSF (6.6 mmol/L) (normal range 1.1–2.3 mmol/L). Plasma aminoacids, ammonia, and urine organic acids were normal. EEG upon admission showed background slowing, with occasional bursts of right hemispheric sharp waves. MRI showed bilateral, symmetric, increased T2 signals in the basal ganglia, mammillary bodies, and periqualqductal grey matter. A high lactate peak was detected in the brainstem on magnetic resonance spectroscopy. Suspecting Leigh disease, empiric vitamin cocktail supplementation was initiated (including enteral thiamine 500 mg/day). Clinical improvement was noted the following day. Muscle biopsy revealed normal mitochondrial respiratory chain enzymes and microscopy. On day 7, thiamine deficiency was diagnosed by the thiamine pyrophosphate effect (17.65%, normal values 0–15%).

After being discharged, she continued to have up to 25 daily episodes of myoclonic jerks of the head and upper extremities. EEG showed spikes and slow wave discharges with activation during sleep. After multiple drug failure—phenobarbital, phenytoin, topiramate, valproic acid, and levetiracetam—she was started on a ketogenic diet, with valproic acid. Three weeks later, she was seizure-free and more alert. Repeat EEG showed almost complete normalization. The diet was discontinued after 2 years, at the age of 4. Currently, she is seizure-free with a normal EEG. She walks with aid and has moderate mental retardation, microcephaly, and ophthalmoplegia.

**Case 2.** This 5-year-old girl was switched to the soy-based formula at 2 weeks due to intolerance to milk formula. At 6 weeks, she was noted to have a weak cry, aphonia, and tonic seizures. Only at 14 weeks was she brought to medical attention, with encephalopathy and focal seizures. Her EEG showed diffuse background slowing and later left temporal spikes. MRI demonstrated delayed myelination and a thin corpus callosum. Brainstem auditory evoked response revealed decreased conduction time in the pons. When thiamine deficiency was diagnosed, she was treated with phenobarbital and clonazepam and received IM thiamine, with improvement. In the following month, she began to have multiple daily clusters of myoclonic seizures. EEG reflected multifocal epileptiform activity with secondary generalization. At 6 months, it evolved into modified hypersynchrony that improved with vigabatrin. Currently, on a combination of vigabatrin and phenobarbital, she has only rare seizures, but her EEG demonstrates multifocal epileptiform activity. She has spastic quadriplegia, severe mental retardation, microcephaly, and severe kyphoscoliosis. Due to repeated aspirations and pneumonia, she is ventilated via tracheostomy and fed via gastrostomy.

**Case 3.** This patient, a girl 5 years and 3 months of age, was conceived via in vitro fertilization and fed with the soy-based formula from 10 weeks of age. At 18 weeks, she presented with lethargy and nystagmus. Four days later, she was noted to have left-sided focal seizures. EEG showed background slowing and electrographic seizure in the right frontal region associated with eye deviation. Phenobarbital was initiated with good control of the seizures. CT and MRI demonstrated increased T2 signals in the thalamus, pons, and cortical regions. Lumbar puncture, including serology for viruses and PCR for herpes, and plasma aminoacids, ammonia, and urine organic acids, were all normal. She received plecanaril (an antiviral agent), IV immunoglobulin, and steroids. When thiamine deficiency was diagnosed, she was given thiamine IM. Phenobarbital was discontinued gradually and she remains seizure-free. At 11 months of age, she presented again with focal seizures characterized by daily clusters of eye deviation to the left after awakening. EEG showed bilateral frontal epileptiform activity of spike-wave complexes and polyspikes with secondary generalization. Subsequent EEGs deteriorated to secondary hypsarrhythmia.

At age 3, brain MRI demonstrated atrophy, delayed myelination, and bilateral increased signals in the putamen. Her seizures failed to respond to phenobarbital, vigabatrin, or valproic acid, but did respond to adrenocorticotropic hormone (ACTH) injections. The EEG results improved gradually and 3 months later she had only a mild slow tracing with no epileptiform activity. Currently, on vigabatrin, she is seizure-free. She has moderate mental retardation, strabismus, and left hemiparesis, but is able to walk with support.

**Case 4.** This patient, a girl 5 years and 3 months of age, born by vacuum extraction, received milk formula for 6 weeks, and then she was switched to the soy-based formula due to salmonella infection. At 4 months, she became lethargic and displayed signs of encephalopathy. She deteriorated rapidly, with abnormal breathing, seizures, and loss of consciousness, requiring ventilation. She received phenobarbital and phenytoin. Brain MRI showed increased T2 signals in the brainstem and mammillary bodies. EEG showed slow background with no epileptiform activity. Brainstem auditory evoked response and visual evoked response testing showed abnormal conduction, which later improved. After being diagnosed with thiamine deficiency, the formula was discontinued and she was treated with thiamine. At 7 months, while on phenobarbital maintenance therapy, she presented with complex partial seizures and later with head drops. Modified hypersynchrony was seen on EEG. The seizures stopped with vigabatrin, and her EEG improved. Subsequent EEGs showed multifocal epileptiform activity. Currently, she is...
seizure-free on phenobarbital and vigabatrin. She walks with a walker and has moderate mental retardation, microcephaly, strabismus, hypotonia, and dystonia.

Case 5. This patient, a girl 5 years and 4 months of age, was born by vacuum extraction. She developed normally until the age of 8 months, when she was admitted for vomiting and vertical nystagmus. Brain CT, EEG, abdominal ultrasound, and urine for vanillylmandelic acid were normal. Five days later, she developed lethargy and seizures. She deteriorated rapidly, failed to respond to pain stimuli, and had severe apnea, requiring ventilation. A second EEG showed generalized moderate to severe slowing with no epileptic focus. MRI demonstrated diffuse symmetric abnormalities in the basal ganglia, brainstem, mammillary bodies, and white matter. Brainstem auditory evoked response testing revealed severe abnormality in the lower brainstem function on the left. Lactic acid was elevated in blood (38 mg/dL) and CSF (43.6 mg/dL) (normal 2–20 mg/dL) and she was given multivitamin supplementation and coenzyme Q, with mild improvement. The focal seizures persisted and she was treated with phenobarbital, phenytoin, and, later, topiramate. MRI showed brain atrophy and edema in the caudate and globus pallidum consistent with subacute necrotizing encephalopathy. Muscle biopsy revealed reduced activity of all respiratory chain complexes. Genetic study for mutations of Leigh disease (8993, ATP-6) was negative. Thiamine deficiency was diagnosed 1 month later and she was treated IM with thiamine. Two months later, she was discharged to a rehabilitation center on phenobarbital treatment with a tracheostomy and gastrostomy. At 1 year, EEG displayed background slowing with multifocal epileptic activities which evolved into hypsarrhythmia and she was treated with clonazepam, vigabatrin, and topiramate. She also had dysautonomic symptoms of tachycardia and hypertension, treated with propranolol. She was discharged after 18 months. Currently, she is in a persistent vegetative state, ventilated via tracheostomy, and has breathing difficulties due to paralysis of her left diaphragm. She is on vigabatrin and topiramate and has infrequent seizures during febrile illness. She has spastic quadriplegia, ophthalmoplegia, kyphoscoliosis, and profound mental retardation.

Case 6. This 5-year-old girl was switched to the soy-based formula due to infantile colic at 4 weeks of age. At 8 weeks, she had vomiting and diarrhea and became lethargic. Blood tests were normal except for elevated blood lactate of 2.4 mmol/L (normal range 1.1–2.3 mmol/L). Two days later, she presented with seizures. Brain CT, EEG, and lumbar puncture were normal and she was treated with phenobarbital. Later, there were apneic spells and she was transferred to the pediatric intensive care unit. MRI revealed delayed myelination and brain atrophy. At 10 weeks, she did not display eye-tracking or social smiling and did not respond to pain stimuli. Plasma aminoacids, ammonia, and urine organic acids were normal; urine organic acid revealed gentamicinuria consistent with subacute necrotizing encephalopathy. MRI demonstrated delayed myelinization and brain atrophy. At 10 months, she was given multivitamin supplementation and coenzyme Q, with mild improvement. The focal seizures persisted and she was treated with phenobarbital, phenytoin, and, later, topiramate. MRI showed brain atrophy and edema in the caudate and globus pallidum consistent with subacute necrotizing encephalopathy. Muscle biopsy revealed reduced activity of all respiratory chain complexes. Genetic study for mutations of Leigh disease (8993, ATP-6) was negative. Thiamine deficiency was diagnosed 1 month later and she was treated IM with thiamine. Two months later, she was discharged to a rehabilitation center on phenobarbital treatment with a tracheostomy and gastrostomy. At 1 year, EEG displayed background slowing with multifocal epileptic activities which evolved into hypsarrhythmia and she was treated with clonazepam, vigabatrin, and topiramate. She also had dysautonomic symptoms of tachycardia and hypertension, treated with propranolol. She was discharged after 18 months. Currently, she is in a persistent vegetative state, ventilated via tracheostomy, and has breathing difficulties due to paralysis of her left diaphragm. She is on vigabatrin and topiramate and has infrequent seizures during febrile illness. She has spastic quadriplegia, ophthalmoplegia, kyphoscoliosis, and profound mental retardation.

Case 7. This 6-year-old girl was switched to the soy-based formula due to diarrhea. She developed normally until 9 months, when she became progressively weaker and lethargic with signs of hypotonia. Brain CT, thyroid function tests, plasma aminoacids, and ammonia were normal; urine organic acid revealed general aminoaciduria. At 11 months, she had involuntary movement of the left hand and displayed delayed development and communication. At 14 months, the formula was substituted and she began receiving vitamin supplementation, with improvement. A brainstem auditory evoked response study showed impaired peripheral conduction. MRI at 16 months was normal. At 20 months, she presented with myoclonic jerks of the left hand and EEG showed paroxysmal spike and wave discharge. She was treated with valproic acid and lamotrigine, with improvement. A repeat EEG revealed paroxysmal spikes, polyspikes, and spike-wave discharge. Currently, on valproic acid and lamotrigine treatment, she has only rare seizures. She is able to walk independently, but her walk is unstable. She is communicative but her behavior is characterized by hyperactivity, impulsivity, short attention span, disinhibition, and abnormal judgment. She has moderate mental retardation, hypotonia, and stereotypic movements of her hands.

RESULTS The demographic and clinical characteristics of the study group are given in table 1. All patients displayed abnormal MRI findings except for case 7, in whom the MRI was done 7 months after the acute symptoms. Upon presentation, all infants had episodes of apnea, increased tone, or myoclonic jerks diagnosed as seizures. EEG recording at this stage showed slow background in 6 infants; 5 displayed no epileptic activity and in 1 a focal electrographic seizure was recorded (table 2).

After the initial acute phase caused by the thiamine deficiency, there was a seizure-free period ranging from 1 to 9 months. Later, seizures recurred and were either myoclonic or complex partial; 3 infants had modified hypsarrhythmia on EEG. Antiepileptic treatments included phenobarbital, phenytoin, topiramate, valproic acid, clonazepam, lamotrigine, levetiracetam, vigabatrin, ACTH, prednisone, clobazam, zonigran, and a ketogenic diet. Four children were refractory to all treatments and remain with uncontrolled seizures. Three children are currently seizure-free: 1 responded to treatment with ACTH, 1 to a combination of vigabatrin and phenobarbital, and 1 to a ketogenic diet. All but 1 still display EEG abnormalities and receive antiepileptic drugs (table 2).

The present outcome of these children is grave. All display various degrees of mental retardation: 4 moderate, 2 severe, and 1 profound. All have motor disabilities: 3 are nonwalkers, 3 require aid, and only 1 walks without assistance although her gait
is unstable. Four children remain with hypotonia, 2 with spastic quadriplegia, and 1 with spastic hemiparesis. One child is in a persistent vegetative state. All have various symptoms of brainstem dysfunction (swallowing difficulties, strabismus, ophthalmoplegia, nystagmus), or basal ganglia dysfunction (hypotonia, movement disorder). Four remain with microcephaly.

**DISCUSSION**

We report on the outcome of 7 children who displayed severe epilepsy after being exposed in infancy to a thiamine-deficient formula. All have mental retardation, motor disabilities, and brainstem dysfunction. Data on the long-term effect of children who survived infantile thiamine deficiency are scanty due to the high fatality rate. An association between persistent epilepsy and thiamine deficiency in children has not yet been reported. In one adult study, 16 out of 50 consecutive neurologic patients with thiamine deficiency showed epileptic or epileptiform manifestations. The authors suggested a possible subclinical predisposition for seizures provoked by the thiamine deficiency. There was no such indication in any of our patients.

There are a number of possible pathophysiologic mechanisms by which thiamine deficiency may contribute to seizure activity. Thiamine plays a central role in cerebral metabolism. It serves as a cofactor for several enzymes involved in carbohydrate catabolism, such as pyruvate dehydrogenase complex, a key enzyme in the Krebs cycle. Furthermore, it has an important role in the biosynthesis of neurotransmitters, as well as in the production of reducing equiva-

### Table 1  Demographic and clinical characteristics of the study group

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Current age</th>
<th>Age at formula feeding, mo</th>
<th>Presenting symptoms</th>
<th>MRI</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 y 3 mo</td>
<td>1-5</td>
<td>Vomiting, ophthalmoplegia</td>
<td>Bilateral, symmetric, increased T2 signal in the basal ganglia, mammillary bodies, and periaqueductal gray matter</td>
<td>Walks with aid, moderate mental retardation, microcephaly, hypotonia, ophthalmoplegia</td>
</tr>
<tr>
<td>2</td>
<td>5 y</td>
<td>0.5-3.5</td>
<td>Weak cry, aphonia</td>
<td>Delayed myelination and a thin corpus callosum</td>
<td>Spastic quadriplegia, severe mental retardation, microcephaly, ventilation, severe kyphoscoliosis</td>
</tr>
<tr>
<td>3</td>
<td>5 y 3 mo</td>
<td>2.5-6</td>
<td>Lethargy, nystagmus</td>
<td>Increased T2 signals in the thalamus, pons, and cortical regions</td>
<td>Walks with support, moderate mental retardation, left hemiparesis, strabismus</td>
</tr>
<tr>
<td>4</td>
<td>5 y 3 mo</td>
<td>1.5-4</td>
<td>Lethargy, encephalopathy</td>
<td>Increased T2 signals in the brainstem and mammillary bodies</td>
<td>Walks with a walker, moderate mental retardation, microcephaly, strabismus, hypotonia, dystonia</td>
</tr>
<tr>
<td>5</td>
<td>5 y 4 mo</td>
<td>5-9</td>
<td>Vomiting, vertical nystagmus</td>
<td>Diffuse symmetric abnormalities in the basal ganglia, brainstem, mammillary bodies, and white matter</td>
<td>Persistent vegetative state, spastic quadriplegia, profound mental retardation, paralysis of left diaphragm, ventilation, kyphoscoliosis</td>
</tr>
<tr>
<td>6</td>
<td>5 y</td>
<td>1-3.5</td>
<td>Vomiting, diarrhea, lethargy</td>
<td>Delayed myelination and brain atrophy</td>
<td>Unable to sit or stand, severe mental retardation, vertical nystagmus, hypotonia</td>
</tr>
<tr>
<td>7</td>
<td>6 y</td>
<td>10-14</td>
<td>Weakness, lethargy, hypotonia</td>
<td>Normal (not in the acute stage)</td>
<td>Walks independently unstable, moderate mental retardation, hyperactivity, short attention span, disinhibition, hypotonia, stereotypic movement of hands</td>
</tr>
</tbody>
</table>

### Table 2  Seizure history and EEG abnormalities of the study group

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Initial seizures</th>
<th>EEG at presentation</th>
<th>Seizure-free period, mo</th>
<th>Later seizures</th>
<th>EEG at follow-up</th>
<th>Seizure outcome (current treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tonic, myclonic</td>
<td>Slow background (right &gt; left)</td>
<td>3</td>
<td>Myoclonic</td>
<td>Generalized spike wave</td>
<td>Seizure-free (ketogenic diet)</td>
</tr>
<tr>
<td>2</td>
<td>Tonic</td>
<td>Slow background</td>
<td>1</td>
<td>Myoclonic</td>
<td>Multifocal with secondary generalization</td>
<td>Rare seizures (PB, VGB)</td>
</tr>
<tr>
<td>3</td>
<td>Focal</td>
<td>Slow background</td>
<td>5</td>
<td>Complex partial</td>
<td>Modified hypsarrhythmia</td>
<td>Seizure-free (VGB)</td>
</tr>
<tr>
<td>4</td>
<td>Tonic, myclonic</td>
<td>Slow background</td>
<td>3</td>
<td>Complex partial</td>
<td>Modified hypsarrhythmia, multifocal</td>
<td>Seizure-free (PB, VGB)</td>
</tr>
<tr>
<td>5</td>
<td>Focal</td>
<td>Moderate to severe slowing</td>
<td>3</td>
<td>Focal</td>
<td>Hypsarrhythmia, multifocal</td>
<td>Infrequent seizures (VGB, TPM)</td>
</tr>
<tr>
<td>6</td>
<td>Tonic, myclonic</td>
<td>Mild slowing (right)</td>
<td>7.5</td>
<td>Myoclonic, tonic</td>
<td>Multifocal spike and wave, slowing of the background</td>
<td>Frequent seizures (PB, felbamate, vagal nerve stimulation)</td>
</tr>
<tr>
<td>7</td>
<td>Suspected focal</td>
<td>Not available</td>
<td>9</td>
<td>Myoclonic</td>
<td>Paroxysmal spikes, polyspikes, and spike wave complexes</td>
<td>Rare seizures (VGB, LTG)</td>
</tr>
</tbody>
</table>

PB = phenobarbital; VGB = vigabatrin; TPM = topiramate; LTG = lamotrigine.
lents used in oxidant stress defenses, due to its role as a cofactor in the pentose cycle. Thus, the 3 possible mechanisms for seizures might be the lack of energy production, the lack of inhibitory neurotransmitters in the brain, and possible oxidative stress. Thiamine deficiency results in energy deficiency, similar to mitochondrial disorders, which are known to cause myoclonic seizures (as shown in 4 of our patients). Also, the fact that the first EEGs showed background slowing without epileptic activity supports a metabolic rather than a primary seizure disorder. Another contributing factor is that all the children received IV glucose as part of their treatment. A high-carbohydrate diet is most dangerous in the presence of thiamine deficiency since the metabolic demands for thiamine are increased.

It is important to mention the striking clinical and morphologic similarity between thiamine deficiency and Leigh syndrome. Both are expressed by brainstem and basal ganglia symptoms as well as lactic acidosis. The only histopathologic difference is that in thiamine deficiency, the mammillary bodies are invariably involved, and not the substantia nigra, whereas in Leigh syndrome, the substantia nigra is often involved, while the mammillary bodies rarely are. However, this difference is not absolute. Distinction is essential, since the prognosis differs and in thiamine deficiency depends upon rapid recognition and institution of replacement therapy.

Even though thiamine deficiency involves mainly the thalamic, mammillary, midbrain, and brainstem nuclei, cortical involvement has also been described and confirmed by MRI. This may also be one of the possible mechanisms of the epileptic activity seen in our patients.

Thiamine is an essential vitamin for brain development in infants, and its deficiency provokes neuronal cell loss that persists into adulthood. Animal studies have shown that rat pups develop permanent learning and memory deficits when thiamine deficiency is induced experimentally. We documented severe epilepsy in all the study children after a seizure-free period. This may have been the result of brain insult during a critical period of brain development that led to residual sequelae even after the thiamine restoration.

All the study patients happen to be girls, whereas the 2 deceased infants among the 20, who had been identified and followed, were boys. The recommended daily allowance of thiamine in infants is similar for boys and girls; thus we have no explanation for this phenomenon other than the small sample size.

Although thiamine deficiency was not quantified by blood levels in most patients, these findings are important, because of the unusual event that led to isolated thiamine deficiency in infants otherwise not exposed to malnutrition. Our findings indicate that infantile thiamine deficiency may cause severe epilepsy in children.

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