Thiamine transporter-2 deficiency is a recessive disease caused by mutations in the SLC19A3 gene. Patients manifest acute episodes of encephalopathy, symmetric lesions in the cortex, basal ganglia, thalamus or periaqueductal gray matter, and a dramatic response to biotin or thiamine. We report a 30-day-old patient with mutations in the SLC19A3 gene who presented with acute encephalopathy and increased level of lactate in the blood (8.6 mmol/L) and cerebrospinal fluid (7.12 mmol/L), a high excretion of α-ketoglutarate in the urine, and increased concentrations of the branched-chain amino acids leucine and isoleucine in the plasma. MRI detected bilateral and symmetric cortico-subcortical lesions involving the perirolandic area, bilateral putamina, and medial thalami. Some lesions showed low apparent diffusion coefficient values suggesting an acute evolution; others had high values likely to be subacute or chronic, most likely related to the perinatal period. After treatment with thiamine and biotin, irritability and opisthotonus disappeared, and the patient recovered consciousness. Biochemical disturbances also disappeared within 48 hours. After discontinuing biotin, the patient remained stable for 6 months on thiamine supplementation (20 mg/kg/day). After treatment with thiamine and biotin, irritability and opisthotonus disappeared, and the patient recovered consciousness. Biochemical disturbances also disappeared within 48 hours. After discontinuing biotin, the patient remained stable for 6 months on thiamine supplementation (20 mg/kg/day). The examination revealed subtle signs of neurologic sequelae, and MRI showed necrotic changes and volume loss in some affected areas. Our observations suggest that patients with thiamine transporter 2 deficiency may be vulnerable to metabolic decompensation during the perinatal period, when energy demands are high. Thiamine defects should be excluded in newborns and infants with lactic acidosis because prognosis largely depends on the time from diagnosis to thiamine supplementation. Pediatrics 2013;131:e1670–e1675
Thiamine transporter 2 (hTHTR2) deficiency is an inherited autosomal recessive disease due to mutations in the SLC19A3 gene. Three clinical variants have been related to the defect: biotin-responsive basal ganglia disease, Wernicke-like encephalopathy, and atypical infantile spasms with progressive cerebral atrophy and basal ganglia lesions. Despite the great variation among these phenotypes, they share relevant clinical features: (1) most affected children present with acute and recurrent episodes of encephalopathy that are sometimes triggered by febrile illnesses, vaccination, or trauma; (2) brain lesions are symmetrically distributed in the cerebral cortex, basal ganglia, thalami, or periaqueductal gray matter; and (3) children show a dramatic clinical improvement when biotin or thiamine is administered early in relation to the onset of symptoms.

Our aim was to report a 30-day-old infant with acute encephalopathy and lactic acidosis due to hTHTR2 deficiency.

Thiamine and biotin supplementation resulted in an excellent clinical and biochemical outcome.

**CASE REPORT**

This 1-month-old male infant was referred to our center because of a 3-day history of poor feeding, vomiting, and irritability. He was the first son of healthy consanguineous parents from Morocco. After a monitored and uneventful pregnancy, the patient was delivered at 38 weeks by emergent cesarean delivery due to suspicion of fetal distress. His Apgar scores were 8/9; his birth weight was 2530 g (5th percentile), and his head circumference was 33 cm (20th percentile). The umbilical cord blood acid-base status was normal.

The examination at 1 month of life showed a nondysmorphic child with normal vital signs; his weight was 3.570 kg (6th percentile), and his head circumference was 36.5 cm (20th percentile). There were no clinical or biological signs of infection. He appeared lethargic and had intermittent opisthotonus, jitteriness in the upper limbs, hyper-reflexia and clonus in the 4 limbs, decreased palmar and plantar grasp reflexes, and an exaggerated Moro reflex. A biochemical analysis showed mild metabolic acidosis (venous pH: 7.30, pCO2: 37 mm Hg, base excess: -6.4) and high lactate levels in blood (8.6 mmol/L; reference values [RV]: 0.7–2.4) and cerebrospinal fluid (7.1 mmol/L; RV: 1.1–2.2). Viral and bacterial tests were negative.

Plasma amino acids showed increased concentrations of alanine (637 μmol/L; RV: 167–439 μmol/L), leucine (182 μmol/L; RV: 79–150 μmol/L), isoleucine (97 μmol/L; RV: 40–90 μmol/L) and alloisoleucine (3.1 μmol/L; RV: 0; Fig 1); urine organic acid analysis disclosed a high excretion of lactate (3537 mmol/mol creatinine; RV: <270 mmol/mol creatinine) and α-ketoglutarate (1157 mmol/mol creatinine; RV: 20–340 mmol/mol creatinine).

**FIGURE 1**

These illustrations show the plasma concentrations of alanine and the branched-chain amino acids valine, leucine, and isoleucine in our patient at onset (first point) and on follow-up with thiamine administration (last 2 points). Leucine, isoleucine and alanine normalized after thiamine administration.
Biotinidase activity was within normal limits. A cranial ultrasound detected basal ganglia hyperechogenicity combined with patchy hyperechoic cortical/subcortical lesions, resembling a hypoxic-ischemic encephalopathy pattern (images not shown). MRI 24 hours after hospitalization showed bilateral and symmetric cortico-subcortical lesions involving the perirolandic area, bilateral putamina, and medial thalami. Some brain lesions showed low apparent diffusion coefficient (ADC) values, suggesting an acute process. Others had high ADC values that were likely to be due to subacute or chronic processes (Fig 2A–E). Magnetic resonance spectroscopy demonstrated a mild lactate peak. A video EEG recorded occasional bilateral parietal spikes, but clinical seizures were not evident in the patient. Background trace was within normal parameters. The echocardiogram was normal.

OUTCOME AND DIAGNOSIS

With the suspicion of mitochondrial encephalopathy based on analytical findings and MRI features, a combination of thiamine (100 mg/day), biotin (10 mg/day), and carnitine (300 mg/day) was started. There was a dramatic clinical and biochemical improvement in the hours after initiation of therapy: irritability and feeding difficulties ceased within 24 hours of treatment; later, opisthotonus disappeared, and the patient recovered consciousness. After 48 hours, blood lactate levels decreased from 8.6 mmol/L to 2.6 mmol/L, the acid-base status normalized, and the levels of urine organic acids normalized (lactate 33 mmol/mol creatinine and α-ketoglutarate 110 mmol/mol creatinine). One month later, plasma amino acid values were normal (alanine 309 μmol/L; leucine 84 μmol/L; isoleucine 48 μmol/L; alloisoleucine undetectable, Fig 1). The patient was discharged after 6 days of hospitalization with a normal physical examination, except for a mild increase in muscle tone in the lower limbs.

The patient’s excellent response to the combination of thiamine and biotin led to our suspicion that he had an hTHTR2 deficiency. Molecular analysis of the SLC19A3 gene indicated that the child was homozygous for the previously reported pathogenic mutation p.Gly23Val. The parents were both heterozygous for this amino acid substitution.

After confirming the diagnosis through molecular studies, biotin and carnitine were discontinued, and thiamine was maintained at 20 mg/kg/day. At age 6 months, the child remained stable. On examination, he presented with normal ocular pursuit and social interaction. Weight, height, and head circumference were in the 25th percentile. The patient’s axial tone was normal, he had good head control, and he could roll over. Muscle tone was mildly increased in upper limbs; there was some asymmetry of fine motor skills with impaired palmar grasp and thumb adduction of the right hand.

Follow-up MRI at 6 months showed residual hyper T2 fluid-attenuated inversion recovery lesions in the perirolandic area, putamina, and medial thalami (most likely due to gliosis) with associated volume loss in the putamen and perirolandic cortex (representing necrosis; Fig 2F).

DISCUSSION

Thiamine is a vitamin that accumulates in target tissues by transport across the cell membrane using 2 carrier-mediated thiamine transporters: hTHTR1 (encoded by the SLC19A2 gene) and hTHTR2 (encoded by the SLC19A3 gene). Mutations in these genes decrease the average rate of thiamine uptake in living cells and potentially lead to cellular thiamine deficiency. The distributions of hTHTR1 and hTHTR2 are distinct, with hTHTR2 predominantly expressed in the brain.
and hTHTR2 in the body’s tissues may explain the different phenotypes associated with each gene mutation, which are thiamine-responsive megaloblastic anemia and acute and/or recurrent encephalopathy, respectively.\textsuperscript{2-6}

Thiamine-diphosphate, the active vitamer of thiamine, is an essential cofactor of 3 mitochondrial enzymes: pyruvate dehydrogenase complex, \(\alpha\)-ketoglutarate dehydrogenase, and branched-chain \(\alpha\)-keto acid dehydrogenase.\textsuperscript{8,9} These enzymes are involved in the oxidative decarboxylation of pyruvate, \(\alpha\)-ketoglutarate, and branched-chain amino acids, respectively. The biochemical abnormalities detected in our patient, including lactic acidosis, high excretion of \(\alpha\)-ketoglutarate, and increased levels of leucine and isoleucine, could be due to the decreased activity of these thiamine-dependent mitochondrial enzymes (Fig 3). Thus, thiamine administration normalized these activities. Increased \(\alpha\)-ketoglutarate excretion seems to be a relevant biochemical hallmark of thiamine deficiencies because it has also been reported in patients with thiamine pyrophosphokinase deficiency\textsuperscript{10} and mitochondrial thiamine pyrophosphate transporter SLC25A19 deficiency.\textsuperscript{11} In accordance with these observations, experimental models suggest that \(\alpha\)-ketoglutarate dehydrogenase is the most sensitive enzyme to thiamine deficiency.\textsuperscript{8,12}

Branching-chain \(\alpha\)-ketoacid excretion was normal. One explanation would be that the plasma isoleucine and leucine levels were only slightly increased and valine was normal. Consequently, the corresponding ketoacids were not detectable. These data contrast with biochemical abnormalities found in maple syrup urine disease, where a high amount of branched amino acid is associated with ketoacid excretion.

Our patient presented with a new phenotype caused by mutations in the SLC19A3 gene that was characterized by acute encephalopathy and lactic acidosis in the neonatal period. Lactic acid accumulation has not been reported in other patients with thiamine transporter-2 deficiencies except in a 6-year-old girl with acute dystonia who showed a lactate peak on magnetic resonance spectroscopy.\textsuperscript{4}

Neonatal lactic acidosis is a common manifestation of oxidative phosphorylation defects with a high mortality rate and no effective therapy in most cases.\textsuperscript{13} Our clinical observations suggest that patients with hTHTR2 deficiency may be vulnerable to metabolic decompensation during the neonatal period when energy demands are high. In accordance with this hypothesis, severe lactic acidosis has been reported in newborns and infants with secondary thiamine deficiency due to total parenteral nutrition without vitamins\textsuperscript{14} and exclusive soy-based formula diets.\textsuperscript{15} These children showed vomiting, irritability, ophthalmoplegia, and lethargy. One patient also showed symmetric hyperintensities in the basal ganglia, mammillary bodies, and periaqueductal gray matter on MRI.\textsuperscript{15} In all cases, treatment with thiamine resulted in the resolution of lactic acidosis and improved clinical symptoms within a few hours.

In reviewing the previous literature, 4 clinical and radiologic hTHTR2-related phenotypes are described, each with an age-related presentation (Fig 4). The infantile spasm phenotype most likely represents the final evolution of brain injury when treatment is not given at the onset of symptoms.\textsuperscript{6} Moreover, the possibility of an earlier presentation during the intrauterine period cannot be ruled out because the metabolic deficiency is already present. The patient reported here had signs of fetal distress but, unfortunately, we do not have data on lactic acid concentrations at birth. Because some areas of the perirolandic cortex showed high ADC values, we suspect that these lesions had a chronic or subacute origin before the acute clinical presentation. It is possible that the stressful process of delivery was responsible for these lesions at birth but was not enough to trigger a metabolic crisis at that moment.

The perirolandic cortex pattern of involvement in our patient is different from previous reports, suggesting a different metabolic compensation during the neonatal period.
from the diffuse distribution of corti
cal lesions reported in older children with
SLC19A3 mutations. We hypothesize
that the pattern of injury in hTHTR2
deficiency depends largely on the re-
gional variations in glucose metabo-
lism at different ages, with the areas of
higher metabolic demands being those
with selectively greater vulnerability,
as in other brain insults (eg, hypoxia-
ischemia). Thiamine deficiency due to
insufficient cellular thiamine uptake
might impair glucose metabolism
within these structures. The combi-
nation of signal abnormalities affecting
the perirolandic cortex, putamen, and
medial thalami observed in our patient
has also been reported in children with
Wernicke encephalopathy due to
dietary thiamine deficiency, thus
suggesting a common pathologic
mechanism for brain injury in both
acquired (nutritional) and genetic
conditions.

The benefit of biotin treatment in some
patients with hTHTR2 deficiency has
been established in previous studies.
However, the mechanism of action
remains unclear because experimental
cell models have demonstrated that
biotin is not a substrate for hTHTR2. In
our patient, biotin was discontinued
after confirming the diagnosis, and he
remains stable and in good metabolic
control.

The homozygous p.Gly23Val mutation
detected in our patient has already
been described in a 1-year-old child
with progressive loss of psychomotor
milestones, rigidity, and dystonia.1
Neurologic symptoms in this patient
disappeared after biotin administra-
tion. The lack of phenotype consist-
ency in both children points toward
other genetic and environmental fac-
tors modifying the expression of the
disease among individuals with the
same genotype.

In conclusion, this case report expands
the phenotype of mutations in the
SLC19A3 gene to include thiamine
defects in the differential diagnosis of
newborns and infants with lactic aci-
dosis because clinical response to the
combination of thiamin and biotin was
excellent in our patient.

ACKNOWLEDGMENT

We thank Judit Garcia-Villoria for the in-
terpretation of the biochemical data.


Reversible Lactic Acidosis in a Newborn With Thiamine Transporter-2 Deficiency

Belen Perez-Duenas, Mercedes Serrano, Monica Rebollo, Jordi Muchart, Eva Gargallo, Celine Dupuits and Rafael Artuch

*Pediatrics* 2013;131:e1670; originally published online April 15, 2013; DOI: 10.1542/peds.2012-2988

Updated Information & Services
including high resolution figures, can be found at:
/content/131/5/e1670.full.html

References
This article cites 19 articles, 4 of which can be accessed free at:
/content/131/5/e1670.full.html#ref-list-1

Citations
This article has been cited by 6 HighWire-hosted articles:
/content/131/5/e1670.full.html#related-urls

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Fetus/Newborn Infant
/cgi/collection/fetus:newborn_infant_sub
Neonatology
/cgi/collection/neonatology_sub
Neurology
/cgi/collection/neurology_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml
Reversible Lactic Acidosis in a Newborn With Thiamine Transporter-2 Deficiency
Belén Pérez-Dueñas, Mercedes Serrano, Mónica Rebollo, Jordi Muchart, Eva Gargallo, Celine Dupuits and Rafael Artuch
Pediatrics 2013;131;e1670; originally published online April 15, 2013;
DOI: 10.1542/peds.2012-2988

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/131/5/e1670.full.html