Clinical case

Diabetic acido-ketosis revealing thiamine-responsive megaloblastic anemia

Cétoacidose diabétique révélatrice d’une anémie mégaloblastique sensible à la thiamine

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Available online 18 November 2009

Résumé

Le syndrome d’anémie mégaloblastique thiamine dépendante est une affection autosomique récessive rare qui associe un diabète sucré, une anémie mégaloblastique et une surdité. Nous rapportons les observations de deux nourrissons, âgés, respectivement, de quatre et de cinq mois, hospitalisés pour acido-cétose diabétique. Les examens complémentaires ont montré une anémie mégaloblastique et une thrombopénie. Les taux sériques de la thiamine étaient normaux. Les explorations neurosensorielles ont mis en évidence une surdité de perception bilatérale et une atteinte oculaire. L’évolution sous thiamine orale a été marquée par la correction des anomalies hématologiques et la diminution des doses d’insuline. Aucun effet n’a été noté sur l’atteinte neurosensorielle.

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Mots clés : Diabète sucré ; Thiamine ; Anémie mégaloblastique ; Surdité

Abstract

Thiamine-responsive megaloblastic anemia (TRMA) is a rare autosomal recessive disorder characterized by megaloblastic anemia, diabetes mellitus and progressive sensorineural deafness. We report the cases of two infants, aged 4 and 5 months, hospitalized for diabetic ketoacidosis requiring insulin therapy. Laboratory tests revealed megaloblastic anemia, thrombocytopenia and normal thiamine level. Neurosensorial investigations showed bilateral deafness and ophthalmic involvement. Treatment with oral thiamine normalized hematological disorders and controlled diabetes; however, thiamine therapy had no impact on neurosensorial disorders.

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Keywords: Diabetes mellitus; Thiamine; Megaloblastic anemia; Deafness

1. Introduction

Thiamine-responsive megaloblastic anemia (TRMA), or Roger’s syndrome, is a rare disease defined by the occurrence of megaloblastic anemia, diabetes mellitus, sensorineural deafness and variable response to thiamine treatment [1,2]. TRMA is an early-onset autosomal recessive disorder, caused by an inactivation of thiamine transporter gene. It is a very rare cause of diabetes mellitus among children [1–3].

In this report, we present two pediatric cases of TRMA revealed by a diabetic ketoacidosis and describe the salutary outcome of treatment with thiamine.

2. Case 1

The first patient was a 4-month-old boy noticed to be lethargic during his 4-month and dyspneic later. Physical examination revealed cutaneous and mucous pallor, tachypnea, acidotic breath and stage-two dehydratation. Urine examination showed 4+ glucosuria and 3+ acetonuria. Laboratory findings showed glycemia at 24 mmol/L, serum bicarbonate at 11 mmol/L and serum pH at 7.12. The complete blood cell count showed severe anemia with a hemoglobin level of 1.8 g/dl and a mean cell volume of 99 μL. Reticulocyte count was 0.35 × 10⁹/L, white blood cell count was 10 × 10⁹/L, platelet count was 39 × 10⁹/L. Diabetes was controlled by insulin therapy. Bone marrow puncture noted megaloblastosis, sparse megakaryocytes and ringed sideroblasts. Hemoglobin electrophoresis was normal. An inborn error of metabolism, such as an organic aciduria, was suspected despite the absence of an acute neurological disorder. Urine...
blood cell count showed hemoglobin at 4.5 g/dl with a mean cell volume 19 mmol/L and serum bicarbonate was 14 mmol/L. Complete blood count revealed cutaneous and mucous pallor, acidotic breath, horizontal nystagmus, and optic atrophy. Thiamine blood level was normal. Diagnosis of TRMA was made and oral thiamine at the dose of 100 mg per day was started. The hematological disorders disappeared within 14 days. Daily insulin requirement fell to two units within 3 months of treatment. No hearing improvement was noted.

Four years after diagnosis, the patient received 125 mg of oral thiamine daily. His hemoglobin level was 12 g/dl, and he required two to three insulin units per day. His neurosensorial disorders persisted. A homozygous mutation at position 515 in the SLC19A2 gene was found.

3. Case 2

A female child, sibling to the first patient, was hospitalized at the age of 5 months for diabetic ketoacidosis. She has been diagnosed with anemia at 1 month of age. Physical examination revealed cutaneous and mucous pallor, acidic breath, horizontal nystagmus, 3× acetonuria and 3× glucosuria. Glycemia was 19 mmol/L and serum bicarbonate was 14 mmol/L. Complete blood cell count showed hemoglobin at 4.5 g/dl with a mean cell volume of 95 μm³. Platelet count was 120 × 10⁹/L, reticulocyte count was 14 × 10⁹/L, white blood cell count was 9.3 × 10⁹/L. Bone marrow puncture showed megaloblastosis with sideroblasts. Neurosensorial investigations showed optic atrophy and bilateral perception deafness. Mitochondrial cytopathy tests, urine and blood amino acid chromatography, and urine organic acid chromatography were normal. Cardiac ultrasonography was normal. The patient received insulin therapy. The combination of diabetes mellitus with associated megaloblastic anemia and neurosensorial disorders led to the diagnosis of TRMA. Oral treatment based on thiamine (125 mg/day) led to improvement of the hematological disorders within 12 days and enabled discontinuation of insulin therapy within 3 months. The patient remained with normal glycemia and normal glycosylated hemoglobin levels throughout the following 12-month period, without insulin therapy.

Three years after diagnosis, she received 150 mg oral thiamine and two to three insulin units daily. Total blood count was normal; however, no improvement of the neurosensorial disorders was noted.

4. Discussion

TRMA is a rare cause of diabetes mellitus among children, cases reported in fewer than 30 families [4,5]. The main causes of diabetes mellitus in children are listed in Table 1. In addition to the cardinal triad of anemia, deafness and diabetes, other manifestations including optic atrophy, cardiomyopathy and stroke-like episodes have been described [2,4,5]. The two cases reported here included auditory and ophthalmic involvement.

The combination of megaloblastic changes and ringed sideroblasts in TRMA, as noted in the two cases described, is particular to anemia arising from metabolic or nutritional causes. This combination is most suggestive of myelodysplastic syndromes, where sideroblasts and megaloblastosis are frequently observed [6].

Thiamine is a precursor of thiamine pyrophosphate, a cofactor of several enzymes involved in glycolysis and energy production in mitochondria [7]. Cumulative cell loss via apoptosis explains why clinical manifestations are not apparent in early infancy [1,4].

TRMA results from a mutation of the SLC19A2 gene, situated on chromosome 1q 23.3, which codes for a high-affinity thiamine transporter [1,3,4].

In a recent study, northern-blot analysis combined with PCR of cDNAs from various tissues revealed expression of the gene in all tissues tested, including pancreas, placenta, heart, brain, liver, skeletal muscle, retina, bone marrow and fibroblasts. A higher mRNA expression in skeletal muscle, heart and placenta, was observed [1].

SLC19A2 is present in intestinal tissue. There could be at least two transporters and passive diffusion of thiamine has not been excluded. A second transporter could account for the fact that TRMA patients have normal plasma thiamine levels, as in these two cases, and do not show evidence of acute thiamine deficiency [8].

Thiamine administration rapidly corrects the hematological disorders; however, it is inefficient in preventing the progression of neurosensorial deafness [2,5,9]. Diabetes response to thiamine therapy is variable. In the majority of cases reported, this response was either absent or partial. Diabetes imbalance is generally unavoidable at the onset of puberty with requirement of oral glucose-lowering agents or reinstitution of insulin therapy [5,10]. Bappal et al. recommend high thiamine doses exceeding 200 mg per day before declaring thiamine inefficiency in controlling diabetes in TRMA patients. High oral thiamine doses may decrease insulin requirement by 30% in patients with TRMA [5,9]. There have been few follow-up studies of TRMA into adulthood. Ricketts et al. followed up 13 patients for a median 9 years (2–30 years). All patients had

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### Table 1

<table>
<thead>
<tr>
<th>Type of diabetes</th>
<th>Frequency in childhood</th>
</tr>
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<tbody>
<tr>
<td>Diabetes type 1</td>
<td>Incidence: 3.6–43.9/100000 (Europe) [13]</td>
</tr>
<tr>
<td>Diabetes type 2</td>
<td>Prevalence: 0.25–1.3/1000 (&lt;15 years) [14,15]</td>
</tr>
<tr>
<td>Others rare causes</td>
<td>Diabetes mellitus with TRMA syndrome: ≈30 families [4,5]</td>
</tr>
<tr>
<td></td>
<td>Diabetes associated with neurodegenerative disorders (Wolfman’s syndrome, ataxia-telangiectasia, Down’s syndrome, Alström syndrome, Bardet-Biedl syndrome, Prader-Willi syndrome, mitochondrial disorders, Kearns-Sayre syndrome...) [16]</td>
</tr>
</tbody>
</table>

TRMA: thiamine-responsive megaloblastic anemia.
diabetes mellitus, neurosensorial deafness and variable anemia during the first 5 years of life. The anemia and diabetes responded to oral thiamine. During puberty, thiamine supplements became ineffective and almost all patients required insulin therapy [11,12].

Our patients showed a typical course with rapid improvement of hematological disorders and partial response to insulin but no changes in neurosensorial deafness. Diabetes was well controlled with low insulin doses in both cases.

5. Conclusion

In conclusion, in children with diabetes mellitus, TRMA syndrome should be suspected especially when diabetes is associated with megaloblastic anemia and/or neurosensorial deficits. Despite normal blood thiamine levels, a therapeutic trial of high-dose oral thiamine therapy should be initiated. It can lead to improvement of anemia and eliminate the need for insulin therapy. Thiamine, however, is insufficient to improve neurosensorial disorders.

References