CASE REPORT

Pancytopenia in an adult patient with thiamine-responsive megaloblastic anaemia

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SUMMARY

Thiamine-responsive megaloblastic anaemia (TRMA) is a syndrome associated with megaloblastic anaemia, diabetes mellitus and sensorineural deafness, due to mutations in the *SLC19A2* gene, which codes for a thiamine carrier protein. Oral thiamine supplementation is the main treatment. We report the case of a 25-year-old woman known for TRMA, who presented with pancytopenia (haemoglobin 7.6 g/dL, leucocytes 2.9×10^9 /L, thrombocytes 6×10^9 /L) revealed by dyspnoea. Investigations excluded coagulopathy, a recent viral infection, vitamin and iron deficiencies, and a malignant process. We later found out that thiamine treatment had been discontinued 5 weeks before, due to prescription error. Parenteral thiamine administration resulted in the recovery of haematopoiesis within 3 weeks. Pancytopenia is uncommon in patients with TRMA. Pre-existing medullary impairment caused by the patient's daily antipsychotic medications or the natural course of the syndrome may explain the severity of the laboratory findings in our patient.

BACKGROUND

Thiamine-responsive megaloblastic anaemia (TRMA, or Rogers syndrome) is a rare autosomal recessive disease characterised by three main components: megaloblastic anaemia, diabetes mellitus and sensorineural deafness.¹ Other findings include bicytopenia (anaemia associated with mild leucopenia or thrombocytopenia), retinal degeneration, optic nerve atrophy, congenital cardiac malformations with conduction defects and/or dysrhythmias, cardiomyopathy and cerebrovascular accidents.^{2–4} These features typically develop in infancy but occasionally later in adolescence. First described in 1969 by Rogers *et al.*,⁵ the syndrome has been identified in more than 40 families so far, mainly among consanguineous marriages and isolated communities.¹ It is caused by various mutations in the *SLC19A2* gene, located on the long arm of chromosome 1.^{6–10} This gene codes for a high-affinity thiamine transporter (THTR-1), which is the main thiamine transporter in haematopoietic stem cells, pancreatic beta cells and inner ear cells.¹¹ Treatment is based on thiamine supplementation. Long-term supplementation usually reverses anaemia and may delay development of diabetes, but it cannot alleviate already existing hearing defects. Most cases of TRMA have been reported in children population, with anaemia or bicytopenia. We present a case of pancytopenia in an adult with known TRMA.

CASE PRESENTATION

A 25-year-old woman was transferred from a psychiatric ward to the department of internal medicine of a Swiss university hospital because of progressively worsening dyspnoea. She had been hospitalised for more than a year because of recurrent psychotic episodes. She did not report any other symptom.

She was born in Switzerland to non-consanguineous Turkish parents. At the age of 14 months, newly diagnosed isolated megaloblastic anaemia (thrombocyte and leucocyte counts were normal), insulin-dependent diabetes mellitus, severe bilateral sensorineural hearing loss and bilateral pigmentation retinopathy led to a suspicion of TRMA. Thiamine treatment (100 mg daily) led to normoglycaemia and normalisation of haemoglobin levels. It also allowed for temporary discontinuation of insulin treatment.

During childhood and puberty, our patient developed psychotic and depressive manifestations associated with personality disorders, which required initiation of antipsychotic treatment. Permanent insulin treatment became necessary because of elevated fasting glucose levels.

Diagnosis of TRMA was confirmed at the age of 24 by sequencing of the *SLC19A2* gene, which revealed a homozygous mutation.

On admission to our department, antipsychotic medications were (total daily dose): lithium (1320 mg), sertraline (100 mg), amisulpride (800 mg) and levomepromazine (150 mg). There had been no change in dosages in the last 6 months. Oral thiamine supplementation (100 mg daily) had been administered since childhood. Our patient required daily insulin treatment. She smoked two packs of cigarettes per day, did not drink alcohol or take drugs.

Further information from the usual psychiatrist revealed that thiamine treatment had been discontinued 5 weeks prior to admission because of a prescription error.

INVESTIGATIONS

Body temperature and physical examination, as well as ECG and chest radiograph, were normal. An abdominal ultrasound excluded hepatomegaly and splenomegaly.

Blood tests revealed pancytopenia (haemoglobin 8.2 g/dL, mean corpuscular volume (MCV) 92 fL, haematocrit 23%, reticulocytes 3.2×10^9 /L (1%), thrombocytes 6×10^9 /L, leucocytes 2.9×10^9 /L).

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Figure 1 Evolution of reticulocyte, thrombocyte and haemoglobin counts over time. Thiamine supplementation was stopped from 16th December to 23rd January included. Haemoglobin level is expressed in gram per litre (g/L). Reticulocyte, thrombocyte counts are expressed in giga per litre (G/L).

with neutrophils $1.44 \times 10^9/L$) and negative C reactive protein. Peripheral blood smear showed anisocytosis with a predominance of macrocytic cells and no haemolytic findings or atypical cells.

Serum ferritin level was $289 \mu g/L$, folate concentration 45.4 nmol/L , and vitamin B_{12} 264 pmol/L . There was no coagulopathy (D-dimer, prothrombin time, partial thromboplastin time and fibrinogen values were normal). Serology tests for Epstein-Barr virus, cytomegalovirus, parvovirus B19, HIV, hepatitis A, B and C viruses were negative for recent infections. PCR analyses performed on nasal swab samples were negative for influenza A, influenza B and respiratory syncytial viruses. Fasting serum glucose levels were elevated (between 8 and 11.5 mmol/L), as well as the HbA1c level (8.7%). Pregnancy test was negative.

TREATMENT

A single platelet concentrate was transfused on admission. Parenteral thiamine supplementation (300 mg three times a day during the first 3 days) was started on day 1, followed by oral supplementation (300 mg one time a day).

OUTCOME AND FOLLOW-UP

Within 7 days of thiamine supplementation, reticulocytes rose to 80% ($223 \times 10^9/L$), haemoglobin level to 9.6 g/dL , leucocytes to $7.6 \times 10^9/L$ and platelets to $219 \times 10^9/L$.

Probably caused by the rapid onset of anaemia, dyspnoea disappeared once anaemia was partially corrected. The insulin requirements did not change. The patient was discharged on day 7 and oral thiamine supplementation (300 mg daily) was continued. Three weeks after initiation of treatment, the blood cell counts returned to normal values.

Early laboratory findings are summarised in figures 1 and 2.

DISCUSSION

Our initial hypotheses on the aetiology of pancytopenia included the unexpected discontinuation of thiamine supplementation, vitamin and iron deficiencies, an acute viral infection, a side effect of the antipsychotic treatments and a myelodysplastic syndrome.

We attribute the aetiology of our patient's pancytopenia to the unexpected discontinuation of thiamine supplementation for the following reasons:

Figure 2 Evolution of leucocyte count over time. Thiamine supplementation was stopped from 16 December to 23 January included. Leucocyte count is expressed in giga per litre (G/L).

- Other causes of pancytopenia were eliminated or highly unlikely.
 - Blood tests on admission ruled out coagulopathy, vitamin and iron deficiencies.
 - Serology screenings for the commonly implicated viruses in pancytopenia were negative for recent infections. Although pancytopenia caused by other viruses has been described (rubella, influenza, parainfluenza, measles and mumps),¹² this seemed highly unlikely as the patient did not have any symptom in the weeks before admission. A recent bacterial infection was ruled out by the absence of fever and symptoms, as well as a negative C reactive protein value.
 - Among the patient's daily medications, levomepromazine and amisulpride are known to cause agranulocytosis, and sertraline can induce leucopenia and thrombocytopenia. However, the patient had had these treatments for several years without any change in dosage in the 6 months prior to admission. Lithium is not known to cause anaemia or pancytopenia. Moreover, these treatments were continued without dosage modifications in our department, and this did not prevent the recovery of haematopoiesis. The probability pancytopenia was induced by antipsychotic treatments was therefore very low.
 - An abdominal ultrasound excluded hepatomegaly and splenomegaly. Peripheral blood smear did not show signs consistent with myelodysplastic changes. Because of rapid haematopoiesis recovery after thiamine supplementation, a myelodysplastic syndrome was very unlikely. Therefore, bone marrow examination was not realised.
- Complete recovery of haematopoiesis was obtained within 3 weeks once thiamine supplementation was reintroduced. The leucocyte count, initially mildly low, increased 2.6-fold. The timeframe of 3 weeks is consistent with other case reports, which usually describe a normalisation of haemoglobin and platelet counts within 2–4 weeks after the beginning of thiamine supplementation.^{5 13 14}

TRMA is a rare syndrome, with less than 80 reported cases.⁸ To our knowledge, this case is the only one described in Switzerland. Our patient's medical history and initial presentation were similar to other case reports: Turkish origin, classic triad of manifestations (megaloblastic anaemia, diabetes mellitus and sensorineural deafness), diagnosis made during childhood. Although most cases have been reported in consanguineous families of Middle and Far Eastern origins,¹³ our patient did not have a family history of consanguinity.

Our patient presented with levels of anaemia and MCV similar to those found in previous publications. Bone marrow examination usually reveals megaloblastic changes or sideroblastic changes (erythroblasts containing iron-filled mitochondria).¹⁴ Megloblastic anaemia can be explained by the role of thiamine in DNA metabolism while sideroblastic anaemia is caused by the role of thiamine in haem synthesis.^{15 16}

While anaemia is a cardinal feature in TRMA, thrombocytopenia and leucopenia are less often observed, probably because of different needs of the respective haematopoietic progenitor cells to intracellular thiamine. When present, they are generally mild, except in one case report (platelets $16 \times 10^9/L$).¹⁴ Pancytopenia is uncommon, with very few described cases.¹³

Why our patient's haematopoietic manifestations were initially so severe (pancytopenia with profound thrombocytopenia) is unclear. One hypothesis is a state of pre-existing relative medullary impairment due to the antipsychotic medications, which may cause haematopoiesis to be more sensitive to thiamine

deficiency. Another hypothesis is that the natural course of the syndrome in adults is associated with more severe haematopoietic manifestations in case of thiamine deficiency. The majority of patients with TRMA in the literature are toddlers and children, with information lacking on the severity and evolution of the syndrome in older patients. Whether impairment of bone marrow function increases over time (as in myelodysplastic syndromes) is unknown.

Cellular uptake of thiamine from blood follows two main paths. At physiological thiamine concentrations, transport proceeds through saturable, high-affinity low-performance transporters (to which THTR-1, encoded by the *SLC19A2* gene, belongs)⁶; at high concentrations, thiamine passively diffuses through cell membrane.^{7 11}

In patients with TRMA, mutations in the *SLC19A2* gene impair the function of the THTR-1 transporter. THTR-1 is the main thiamine transporter in haematopoietic cells, pancreatic beta cells and cochlear cells.¹¹ In these cells, the saturable, active uptake mechanism is defective, while the other pathway is present. Thus, at physiological concentrations, thiamine is not normally transported. Cells lacking thiamine suffer from changes in their metabolism, impairment of DNA/RNA synthesis and undergo apoptosis.¹⁵ This is why mutations in the *SLC19A2* gene cause the triad of manifestations of the syndrome: megaloblastic anaemia, diabetes mellitus and sensorineural deafness. In the other organs, thiamine is transported into the cells through another high-affinity thiamine transporter, THTR-2, which remains functional.¹¹

These pathophysiological explanations have two practical implications: (1) measurement of thiamine level in the blood is not necessary, as it does not correlate with its availability in the cells. (2) Daily thiamine supplementation leads to higher blood thiamine concentration, which enables intensified thiamine transport through the alternative pathway.⁷

In our patient, pancytopenia appeared 5 weeks after the discontinuation of thiamine supplementation, probably because of depletion of thiamine reserves. It is possible that long-term daily supplementation resulted in large thiamine reserves. As thiamine has an estimated half-life of 10–20 days,¹⁷ 5 weeks after thiamine discontinuation, thiamine concentration probably decreased to a level too low to allow its passive diffusion through cell membrane.

Sequencing of the *SLC19A2* gene in May 2017 revealed homozygosity for the c.1147_48delGT (p.Val383Glyfs2*) mutation, resulting in a frameshift and truncated protein. This mutation was previously reported in three publications.^{18–20}

Our scheme of thiamine supplementation (parenteral 300 mg three times a day during the first 3 days followed by an oral supplementation of 300 mg daily) is based on our hospital protocol for Wernicke encephalopathy. We hypothesised that high-dose, rapid parenteral thiamine administration would induce prompt haematopoietic regeneration. Besides, intravenous thiamine administration is safe, simple, inexpensive and effective, with no known overdose toxicity.²¹ Most publications report 50–100 mg of daily oral thiamine supplementation to be sufficient to correct anaemia.^{7 13 22}

In patients with TRMA, insulin secretion is primarily defective.²² Autoantibodies typical of type 1 diabetes are negative. Our patient had transient insulin dependence until puberty, when permanent insulin use became necessary. There was no change in insulin requirements after the reintroduction of thiamine supplementation. This suggests a progression of pancreatic endocrine insufficiency over time and shows that currently, there is no pancreatic endocrine response to thiamine supplementation.

This is consistent with previous publications which reported patients with TRMA usually become insulin dependent over time.^{22 23}

Finally, neuropsychiatric manifestations related to thiamine deficiency are well known in patients with alcoholic abuse and nutrient deficits but not in patients with TRMA. To our knowledge, only two other patients with TRMA and psychotic symptoms have been reported.²⁴ Our patient's psychotic and depressive symptoms did not change, either with thiamine depletion or supplementation. This observation raises the question of a causal association between TRMA and psychiatric manifestations and needs further investigations.

Learning points

- ▶ Thiamine-responsive megaloblastic anaemia (TRMA) is a rare genetic syndrome characterised by megaloblastic anaemia, non-type 1 diabetes mellitus and sensorineural deafness, mostly found in consanguineous families of Middle and Far Eastern origins.
- ▶ Thiamine metabolism is disrupted because of impairment of thiamine absorption, mainly in haematopoietic cells, pancreatic beta cells and cochlear cells.
- ▶ Lifelong daily oral thiamine supplementation (50–100 mg daily) is necessary to counterbalance the impaired transporter function by enhancing thiamine passive diffusion.
- ▶ Adult patients may present more severe haematological manifestations (pancytopenia with profound thrombocytopenia) in case of thiamine deficiency.

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REFERENCES

- 1 Oishi K, Diaz GA. Thiamine-Responsive Megaloblastic Anemia Syndrome. In: Adam MP, Ardinger HH, Pagon RA, eds. *GeneReviews® [Internet]*. Seattle (WA: University of Washington Seattle, 2003:1993–2018.
- 2 Viana MB, Carvalho RI. Thiamine-responsive megaloblastic anemia, sensorineural deafness, and diabetes mellitus: A new syndrome? *J Pediatr* 1978;93:235–8.
- 3 Mandel H, Berant M, Hazani A, et al. Thiamine-dependent beriberi in the "thiamine-responsive anemia syndrome". *N Engl J Med* 1984;311:836–8.
- 4 Meire FM, Lemmens K, Lemmens K, et al. Thiamine-responsive megaloblastic anemia syndrome (TRMA) with cone-rod dystrophy. *Ophthalmic Genet* 2000;21:243–50.
- 5 Porter FS, Rogers LE, Sidbury JB. Thiamine-responsive megaloblastic anemia. *J Pediatr* 1969;74:494–504.
- 6 Dutta B, Huang W, Molero M, et al. Cloning of the human thiamine transporter, a member of the folate transporter family. *J Biol Chem* 1999;274:31925–9.
- 7 Ozdemir MA, Akcakus M, Kurtoglu S, et al. TRMA syndrome (thiamine-responsive megaloblastic anemia): a case report and review of the literature. *Pediatr Diabetes* 2002;3:205–9.
- 8 Mikstiene V, Songailiene J, Byckova J, et al. Thiamine responsive megaloblastic anemia syndrome: A novel homozygous *SLC19A2* gene mutation identified. *Am J Med Genet A* 2015;167:1605–9.
- 9 Diaz GA, Banikazemi M, Oishi K, et al. Mutations in a new gene encoding a thiamine transporter cause thiamine-responsive megaloblastic anaemia syndrome. *Nat Genet* 1999;22:309–12.
- 10 Ricketts CJ, Minton JA, Samuel J, et al. Thiamine-responsive megaloblastic anaemia syndrome: long-term follow-up and mutation analysis of seven families. *Acta Paediatr* 2006;95:99–104.
- 11 Habeb AM, Flanagan SE, Zulali MA, et al. Pharmacogenomics in diabetes: outcomes of thiamine therapy in TRMA syndrome. *Diabetologia* 2018;61.
- 12 Hiraiwa K, Obara K, Sato A. Mumps virus-associated hemophagocytic syndrome. *Emerg Infect Dis* 2005;11:343a.
- 13 Pichler H, Zeithofer P, Dworzak MN, et al. Thiamine-responsive megaloblastic anemia (TRMA) in an Austrian boy with compound heterozygous *SLC19A2* mutations. *Eur J Pediatr* 2012;171:1711–5.
- 14 Bay A, Keskin M, Hizli S, et al. Thiamine-responsive megaloblastic anemia syndrome. *Int J Hematol* 2010;92:524–6.
- 15 Boros LG, Steinkamp MP, Fleming JC, et al. Defective RNA ribose synthesis in fibroblasts from patients with thiamine-responsive megaloblastic anemia (TRMA). *Blood* 2003;102:3556–61.
- 16 Abboud MR, Alexander D, Najjar SS. Diabetes mellitus, thiamine-dependent megaloblastic anemia, and sensorineural deafness associated with deficient alpha-ketoglutarate dehydrogenase activity. *J Pediatr* 1985;107:537–41.
- 17 Institute of Medicine. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*. Washington (DC: National Academies Press (US), 1998.
- 18 Fleming JC, Tartaglioni E, Steinkamp MP, et al. The gene mutated in thiamine-responsive anaemia with diabetes and deafness (TRMA) encodes a functional thiamine transporter. *Nat Genet* 1999;22:305–8.
- 19 Aycan Z, Baş VN, Cetinkaya S, et al. Thiamine-responsive megaloblastic anemia syndrome with atrial standstill: a case report. *J Pediatr Hematol Oncol* 2011;33:144–7.
- 20 Pomahačová R, Zamboryová J, Sýkora J, et al. First 2 cases with thiamine-responsive megaloblastic anemia in the Czech Republic, a rare form of monogenic diabetes mellitus: a novel mutation in the thiamine transporter *SLC19A2* gene-intron 1 mutation c.204+2T>G. *Pediatr Diabetes* 2017;18:844–7.
- 21 Wrenn KD, Murphy F, Slovis CM. A toxicity study of parenteral thiamine hydrochloride. *Ann Emerg Med* 1989;18:867–70.
- 22 Katipoğlu N, Karapinar TH, Demir K, et al. Infantile-onset thiamine responsive megaloblastic anemia syndrome with *SLC19A2* mutation: a case report. *Arch Argent Pediatr* 2017;115:e153–6.
- 23 Valerio G, Franzese A, Poggi V, et al. Long-term follow-up of diabetes in two patients with thiamine-responsive megaloblastic anemia syndrome. *Diabetes Care* 1998;21:38–41.
- 24 Wood MC, Tsiouris JA, Velinov M. Recurrent psychiatric manifestations in thiamine-responsive megaloblastic anemia syndrome due to a novel mutation c.63_71 delACCGCTC in the gene *SLC19A2*. *Psychiatry Clin Neurosci* 2014;68:487.

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