A novel missense variant, p.(Thr405Arg), in the *SLC19A2* gene in an infant with thiamine responsive megaloblastic anemia syndrome presenting with anemia and diabetes but with normal hearing

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BACKGROUND

Thiamine responsive megaloblastic anemia syndrome (TRMA) is characterized by the clinical triad of megaloblastic anemia, non-immune diabetes mellitus and sensorineural deafness. It is a very rare autosomal recessive disease with an increased frequency in consanguineous marriages and isolated communities. The syndrome is due to intracellular thiamine deficiency which is the result of a defective high affinity low performance thiamine transporter protein (THTR1) encoded by the *SLC19A2* gene. Treatment with pharmacological doses of thiamine leads to an increase in intracellular thiamine concentrations, resolution of anemia and better glycemic control, but apparently does not affect hearing loss. To date approximately 50 different mutations in 80 patients have been described.

PATIENTS AND METHODS

We present a 4 months old boy born to non-consanguineous parents who presented with failure to thrive, profound anemia (Hgb 58, Hct 0.170, MCV 92.4 fL), diabetes mellitus (blood glucose 24.4 mmol/L, HbA1c 7.1%) and preserved hearing. After initial red blood cell transfusion and insulin treatment (0.66 IU/kg/day) a diagnosis of TRMA syndrome was suspected and the patient was started empirically on oral thiamine (100 mg/day). Insulin treatment could be stopped on the second day of thiamine treatment and his hemoglobin level improved (Table 1). Weight gain was registered during follow-up visits (Figure 1).

RESULTS

Analysis of all coding regions and exon/intron boundaries of the *SLC19A2* gene (NM_006996.2) by Sanger sequencing was performed and revealed that our patient is a compound heterozygote for a nonsense, c.373C>T; p.(Gln125Ter), and a novel missense variant, c.1214C>G; p.(Thr405Arg), in the *SLC19A2* gene. Both variants are predicted to be pathogenic and this result confirms the TRMA diagnosis

CONCLUSION

Patients with TRMA rarely present with neonatal diabetes mellitus, while preserved hearing is exceptional in those patients. Due to later presentation, minority of patients started thiamine treatment at the age of 4 months or earlier, and this could be crucial for the preservation of hearing, or at least for postponing hearing loss. However, it is possible that compound heterozygotes may have less severe phenotype regarding hearing loss but further data is needed. Follow- up is needed to evaluate effect of novel gene variant and therapy on hearing in our patient.

Table 1. Laboratory findings and therapy before and during thiamine therapy.

	Before thiamine therapy	Thiamine 100 mg/day			
		7 days	21 days	3 mo	6mo
Hgb **MCV**	91 88.9	95 88.7	96 87.5	98 87.0	99 85.2
Lactate	3.2	1.24			
HbA1c	7.1%			4.9%	5.3%
Insulin (dose)	detemir 2 x 2 i.j. (0.66 IU/kg/d)	no insulin	no insulin	no insulin	no insulin

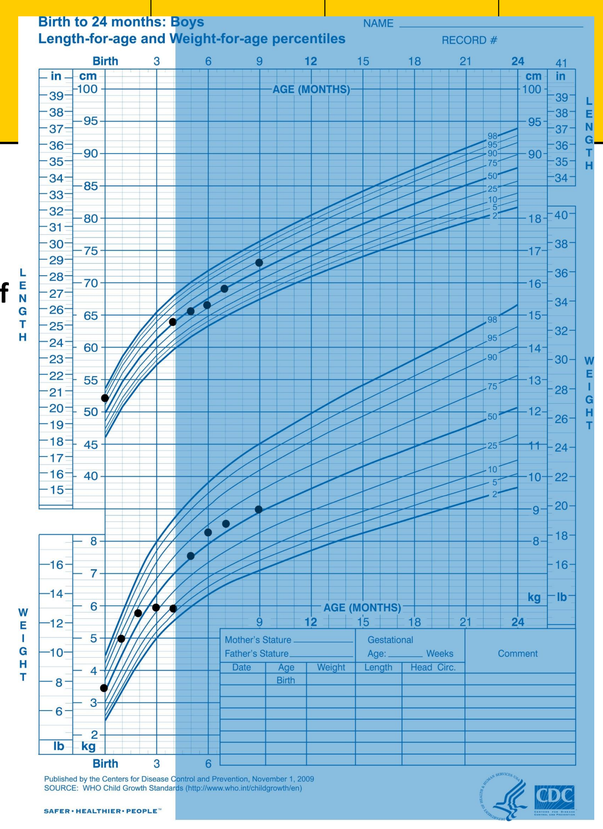

Figure 1. Patient's somatrogram showing weight gain after beginning of thiamine therapy (colored blue).

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