Thiamine-responsive Megaloblastic Anemia

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Thiamine-responsive megaloblastic anemia

An 11-year-old Caucasian girl is presented who had a megaloblastic anemia responsive only to thiamine. Other abnormalities included diabetes mellitus, aminoaciduria, and sensorineural deafness. Initially the anemia, refractory to vitamin B_{12} and folic acid therapy, responded to administration of a multiple vitamin preparation. Vitamin supplementation was withdrawn followed by a recurrence of anemia 3½ months later. The implicated vitamins were then administered sequentially. A reticulocytosis followed administration of thiamine. Anemia again recurred 4 months after cessation of vitamin supplementation. On this occasion the anemia was corrected by the oral administration of 20 mg. thiamine daily. Thiamine blood levels and activities of 3 thiamine-dependent enzymes of the patient's blood cells were normal, excluding a generalized defect of thiamine metabolism. The patient therefore appeared to have a thiamine-dependent megaloblastic anemia. This represents the first demonstration of a role for this vitamin in DNA metabolism.

Lon E. Rogers, M.D., F. Stanley Porter, M.D.,* and

James B. Sidbury, Jr., M.D.

DURHAM, N. C.

Rogers et al, J Pediatr 1969

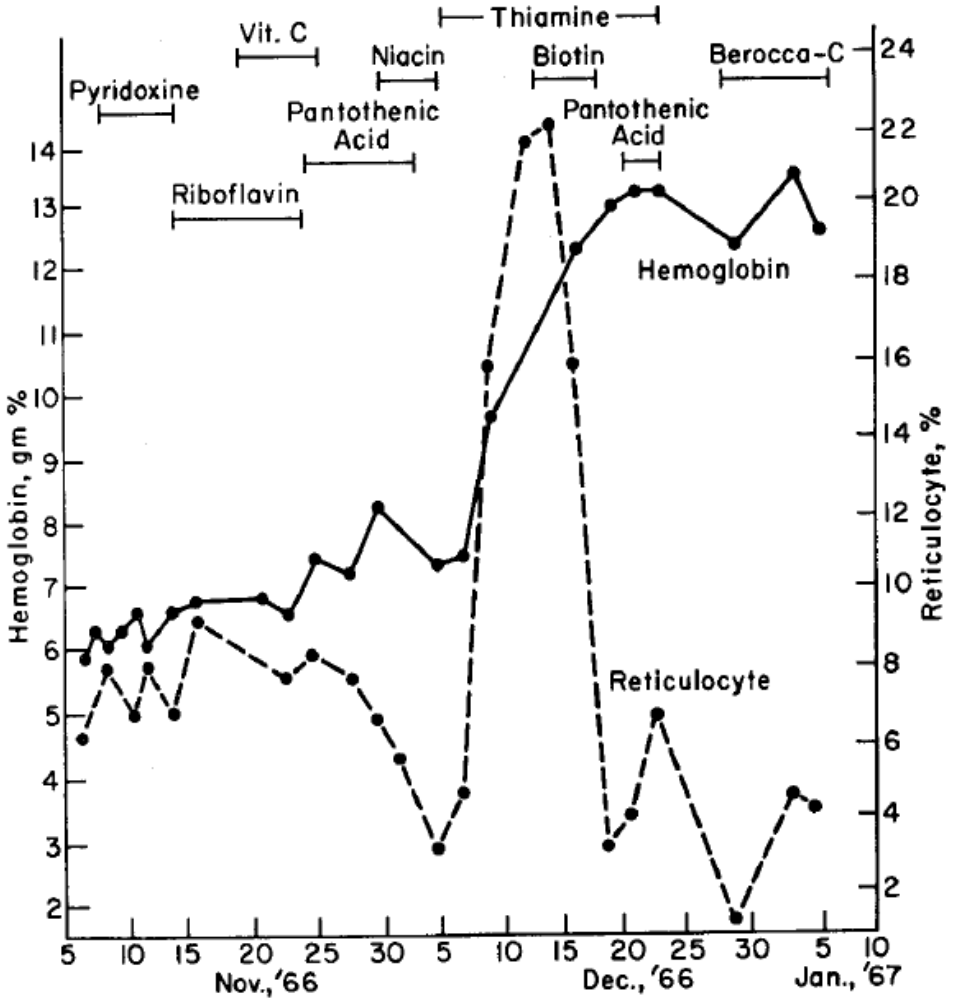


Fig. 4. Reticulocytosis and rise of hemoglobin following administration of thiamine. Lack of response to pyridoxine, riboflavin, vitamin C, niacin, and pantothenic acid is shown. The daily dosages and dates of administration of the vitamins are as follows: pyridoxine 25 mg., Nov. 8-13, 1966; riboflavin 30 mg., Nov. 14-22; ascorbic acid 50 mg., Nov. 19-23; pantothenic acid 250 mg., Nov. 24–Dec. 2; niacin 50 mg., Nov. 30–Dec. 4; thiamine 50 mg., Dec. 5-16; thiamine 25 mg., Dec. 17-22; biotin 10 mg., Dec. 12-16; pantothenic acid 63 mg., Dec. 20-22; Berocca-C 2 ml., Dec. 28-31; Berocca-C 1 ml., Jan. 1-5, 1967. All vitamins were given intramuscularly except biotin and riboflavin, which were taken orally.

Thiamine-responsive Megaloblastic Anemia (TRMA) (Rogers Syndrome, OMIM #249270)

- Bislang ca. 80 Patienten beschrieben, viele aus konsanguinen Familien (Bias?)
- Vererbung: a.r.
- Meist klassische Symptomtrias, vereinzelt aber heterogene Klinik!
- Manifestationsalter unterschiedlich

Table I. Other clinical findings in patients with TRMA

Other clinical findings in patients with TRMA	Cases (references of previous reports)
Visual impairments	
Retinal dystrophy and optic nerve atrophy	(Ref 10-14)
Maculopathy	Patient 3 (Ref 10)
Cone-rod dystrophy	Patient 4a (Ref 15)
Dystrophic pigmentary epithelium	Patient 5
Others	
Astigmatism	Patient 1 (Ref 10)
Vision loss (cause unknown)	Patient 1 and 2
Nystagmus	Patient 2 and 4a
Cardiac defects	
Atrial septal defect	Patient 3 (Ref 16,17)
Ventricular septal defect	(Ref 7,16,17)
Arrhythmia/Conduction abnormalities	(Ref 11,18-21)
Neurologic impairments	
Seizures	Patient 1,6 (Ref 20)
Developmental delay	Patient 1
Stroke	Patient 3 (Ref 18,22)
Ataxia	(Ref 23)
Others	
Short stature	Patient 1,2,4a (Ref 10,11,29,30)
GE reflux, vocal cord nodules	Patient 1
Cryptorchidism	Patient 1
Situs inversus	(Ref 20)
Immune thyroiditis	(Ref 24)

Bergmann AK et al., J Pediatr 2009

Thiamine-responsive Megaloblastic Anemia (TRMA) (Rogers Syndrome, OMIM #249270)

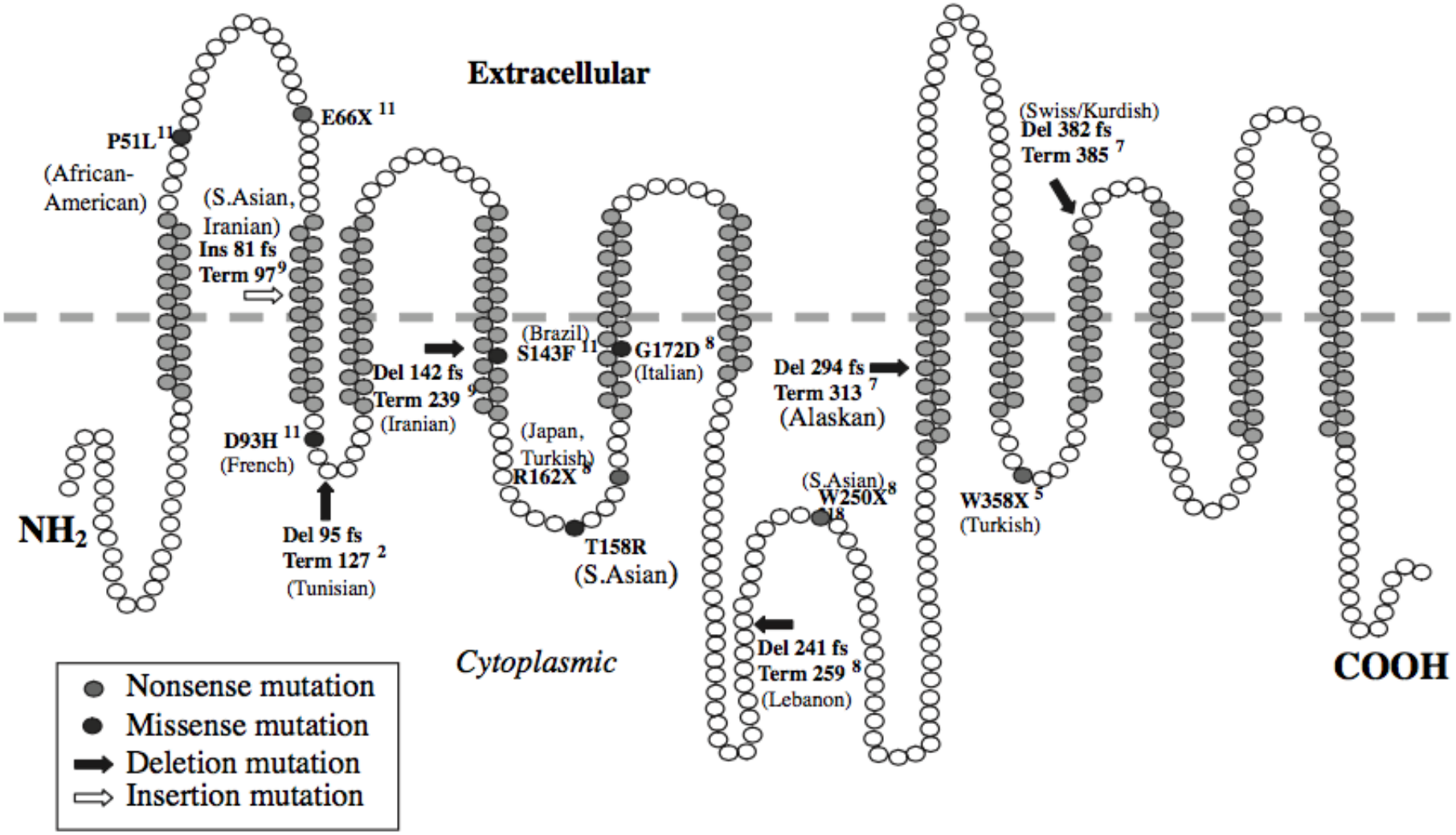
- Rare disorder of impaired vitamin B1/thiamine uptake

- Mutations in the solute carrier family 19 member 2 *(SLC19A2)* gene on chromosome 1q23.3

- Impaired function of the encoded thiamine transporter (THTR-1)

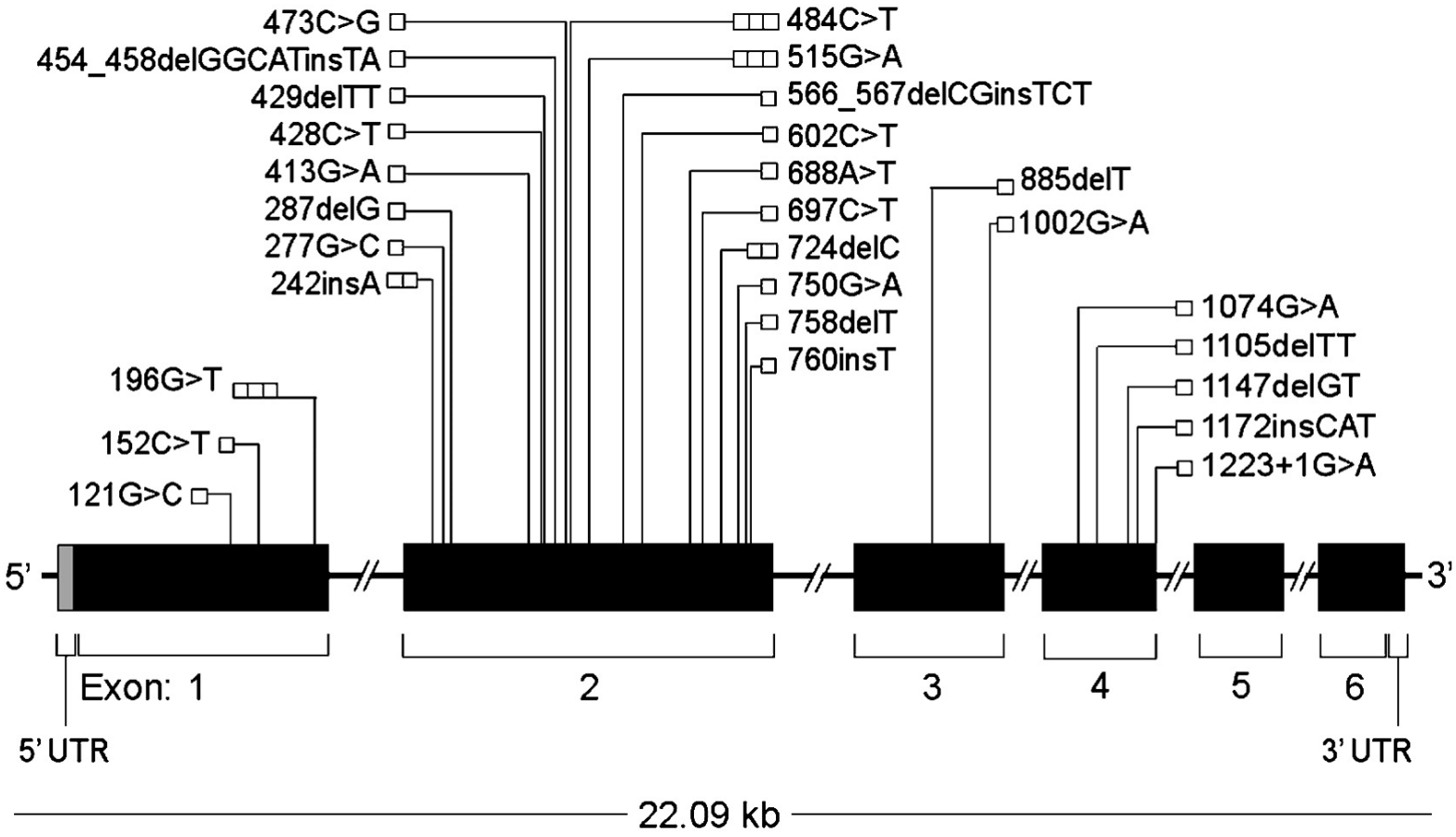
Fleming JC et al., Nature Genetics 1999
Labay V et al., Nature Genetics 1999
Neufeld EJ et al., Am J Hum Genet 1997

Struktur des Thiamintransporters THRT-1



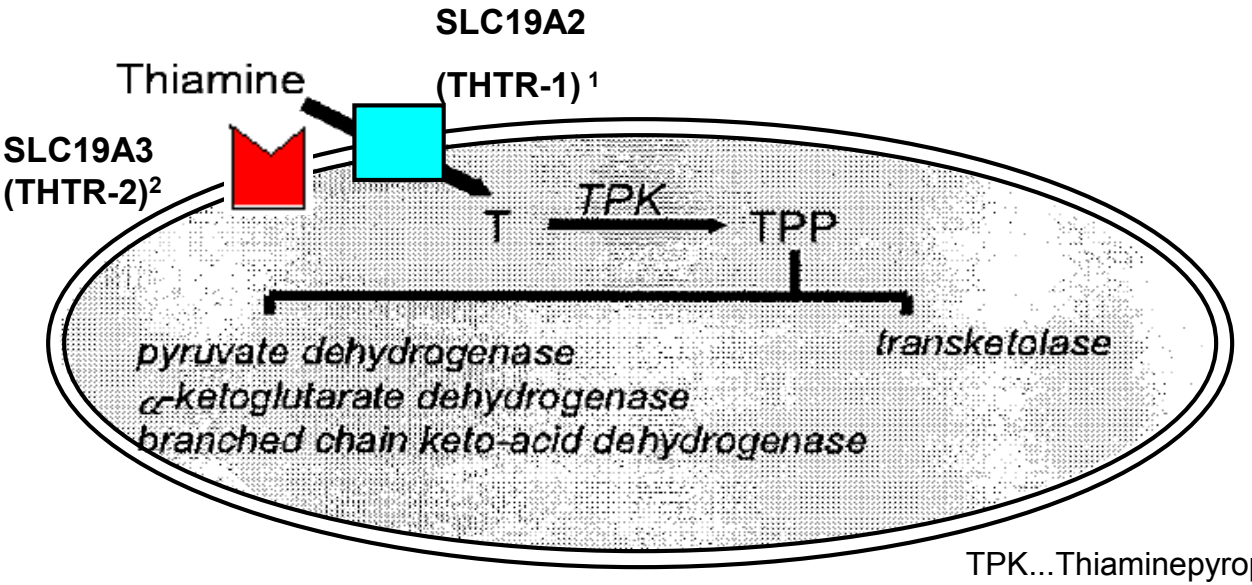
Ricketts CJ et al., Acta Pediatrica 2005

TRMA – Mutations in SLC19A2



Bergmann AK et al., J Pediatrics 2009

Thiamine homeostasis and metabolism



TPK...Thiaminepyrophosphokinase
TPP....Thiaminepyrophosphate

Thiamine homeostasis:

Active intestinal uptake of thiamine is maintained via THTR-2 (encoded by *SLC19A3*)[2], as vitamin B1 plasma levels in TRMA patients (with defective THRT-1) are normal. Passive cellular uptake is possible at higher extracellular concentrations.

[1]THTR-1 is the only thiamine transporter in erythroid precursors, pancreatic islet cells and inner hair cells.

Neufeld EJ et al., Blood Cells Mol Dis 2001 (modif.)
Reidling JC et al., Gastroenterology 2009

Consequences of intracellular thiamine deficiency

- Reduced de novo synthesis of nucleic acids via pentose phosphate shunt and defective heme biosynthesis:
  → megaloblastic changes, sideroblasts

(Boros LG et al.; Blood 2003)

- Impaired synthesis und secretion of insulin:
  → diabetes

(Mee L et al.; Am J Physiol Gastrointest Liver Physiol 2009)

- Selective inner hair cell loss in *SLc19a2*-deficient mice:
  → mechanism of sensorineural deafness in humans?

(Liberman MC et al.; J Assoc Res Otolaryngol 2006)

TRMA - Diagnostik

- Verdachtsdiagnose aus der klinischen Symptomatik (Trias)
- Ausschluss infektiöser Ursachen einer Anämie:

  Parvovirus B19, CMV, EBV, HHV6,…
- Ausschluss anderer nutritiver Anämien:

  Vitamin B12, Folsäure,…
- Ausschluss eines immun-mediierten Diabetes mellitus:

  Antikörper gegen Inselzellstrukturen (GADA, IAA, ICA)

  oGTT

  ev. Insulinbestimmung, C-Peptid
- Knochenmarkmorphologie:

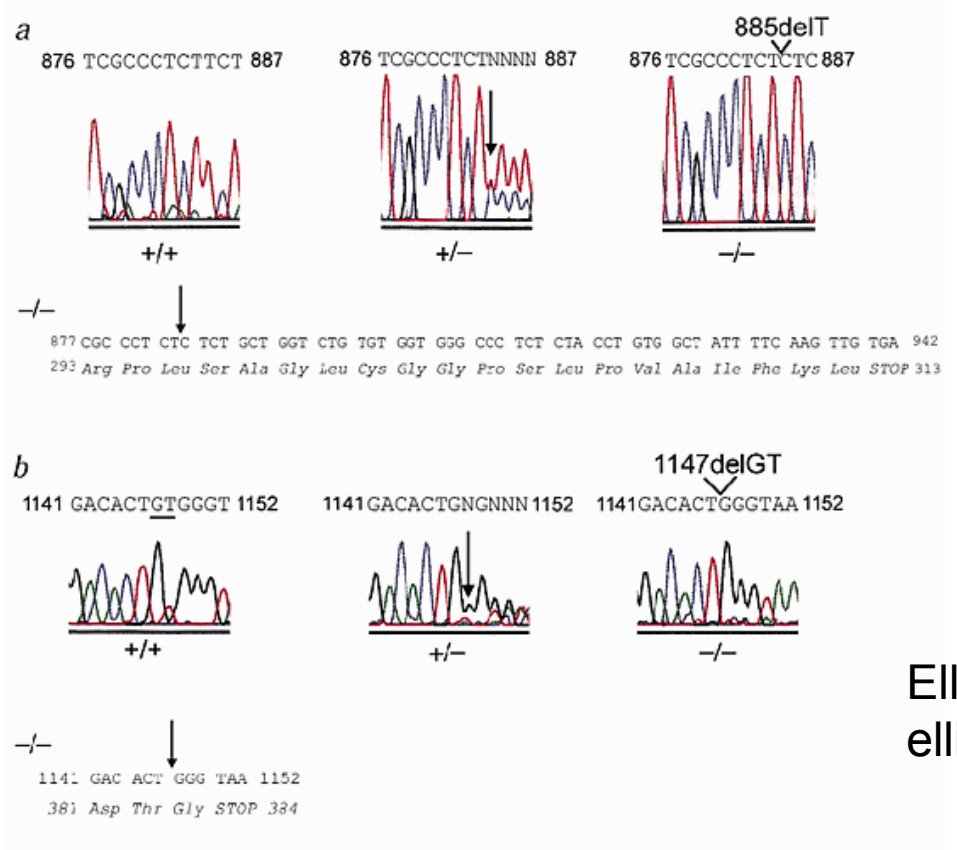
  Ringsideroblasten + megaloblastäre Erythropoiese
- Audiometrie zur Verifizierung einer Hörstörung

TRMA - Diagnosesicherung

- Therapieversuch mit Thiamin in pharmakologischer Dosis:

  25-75mg/d, Steigerung bis 300mg/d möglich

- Sequenzanalyse des *SLC19A2*-Gens (Mutationsnachweis):



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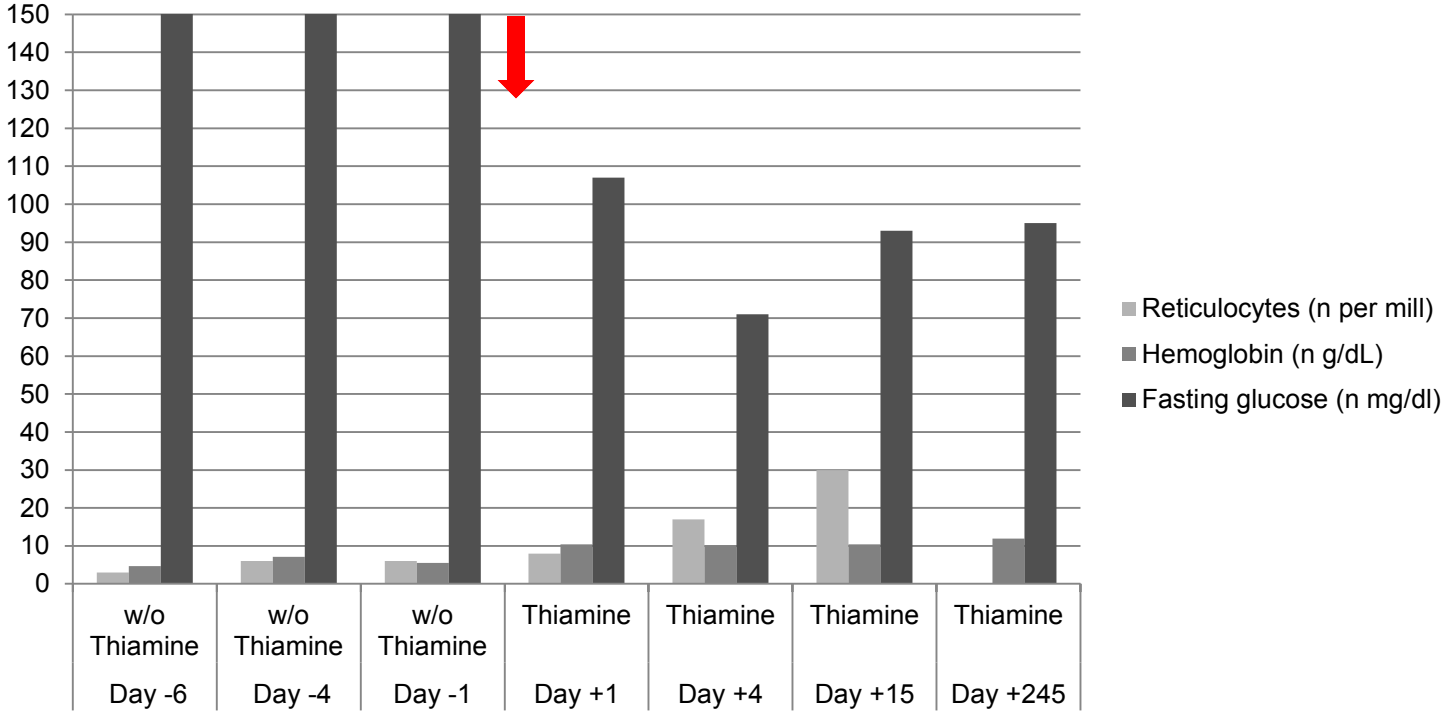
TRMA und Thiaminsubstitution

- Meist promptes Ansprechen der Anämie auf Thiamin
- Variable Besserung einer diabetischen Stoffwechsellage
- Bestehende Hörstörungen bleiben unbeeinflusst



Verschiedene Mutationen in *SLC19A2* – unterschiedliche Verläufe?

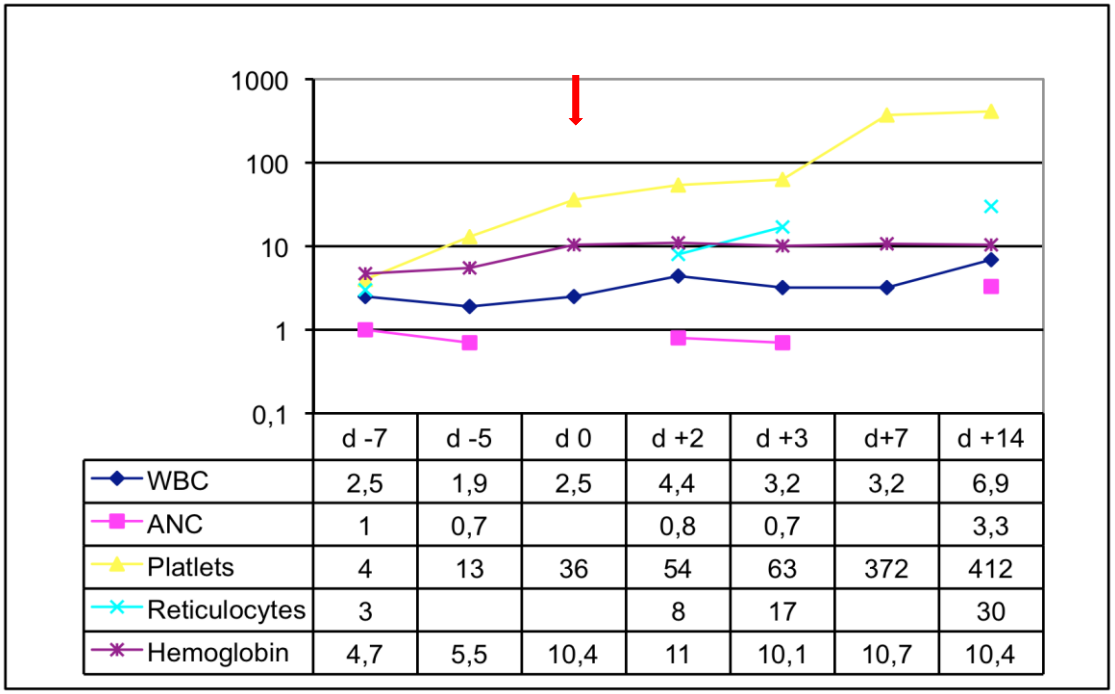
- Unregelmäßige Genotyp-Phenotyp Korrelation
- Schwerere Verlaufsformen eher bei homozygoten Trägern
- Compound-heterozygote Individuen (noch) unterrepräsentiert bzw. noch zu wenige diagnostiziert? Leichtere Verläufe?

Klinisches Beispiel:

Panzytopenie (schwere TZ-Penie, normozytärer Anämie, Leukopenie)
akzidentelle Glucosurie / Diabetes
normales Hörvermögen

Mutationen:
c.484C>T (p.R162X) in exon 2
c.1001G>A (p.G334D) in exon 3

Pichler et al, Eur J Pediatr 2012



	d -7	d -5	d 0	d +2	d +3	d+7	d +14
WBC	2,5	1,9	2,5	4,4	3,2	3,2	6,9
ANC	1	0,7		0,8	0,7		3,3
Platlets	4	13	36	54	63	372	412
Reticulocytes	3			8	17		30
Hemoglobin	4,7	5,5	10,4	11	10,1	10,7	10,4

TRMA - Differentialdiagnose

- **Vitamin B12-, Folsäuremangel**
- **Myelodysplastische Syndrome**
- **Wolfram Syndrom (DIDMOAD) / WFS-like disorders**
  (Mutationen in *WFS1* (Wolframin), impaired calcium homeostasis)
  Diabetes **i**nsipidus, **d**iabetes **m**ellitus, **o**ptical **a**trophy, **d**eafness, dementia, ataxia,...
- **Mitochondriopathien:**
  Pearson Syndrom (Ringsideroblasten, exokrine Pankreasdysfunktion)
  Kearns-Sayre Syndrom (mitochondr. DNA Deletionssyndrom)

TRMA – Therapie

- Thiamindosis 25-75mg/d, Steigerung bis zu 300mg/d möglich

  (Long term follow up: Borgna-Pignatti, J Pediatr 2009)

- Nebenwirkungen einer Thiamin-Supplementierung:

  - Thiamin besitzt eine große therapeutische Breite!
  - vereinzelt anaphyaktische Reaktionen nach parenteraler Gabe bei Wernicke Enzephalopathie

  (Van Haecke, Am J Emerg Med 1995; Juel, BMJ Case Report 2013)

  - keine relevanten Nebenwirkungen bei TRMA bisher berichtet
  - Langzeiterfahrungen bei chron. Herzinsuffizienz/Niereninsuffizienz

  (Metaanalyse von DiNicolantonio JJ, Congest Heart Fail 2013)

TRMA – Fazit/Zusammenfassung

- Sehr seltene Erkrankung
- Bei megaloblastären Veränderungen und normalen Vitamin B12- oder Folsäurespiegeln daran denken, insbesondere bei zusätzlicher Symptomatik (Diabetes oder Hörstörung)
- Frühzeitige Sequenzanalyse bei Patienten mit zumindest 2 Symptomen der klassischen Trias empfehlenswert
- Unter Thiaminsupplementierung rasches Ansprechen der Anämie und des Diabetes zu erwarten; Hörstörungen nicht beeinflussbar
- Leichtere Verläufe bei compound-heterozygoten Patienten?