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Bilateral severe proliferative retinopathy, macular oedema, and lack of macrocytosis in an adolescent male with thiamine-responsive megaloblastic anaemia

Thiamine-Responsive Megaloblastic Anaemia (Rogers Syndrome)

- Very rare autosomal recessive disorder
- Mutations in the ***SLC19A2*** gene which encodes for ***Thiamine transporter 1 (THT1) protein***
- Presentation: ***Sensorineural hearing loss, Megaloblastic anaemia and Non-immune diabetes mellitus***
- Ocular manifestations: optic atrophy and cone-rod retinal dystrophy

Purpose of this case report

1. To present a case report of an adolescent male with TRMA, who developed severe proliferative retinopathy within three months of diabetes diagnosis (extremely rare) and discuss the possible contribution of intracellular thiamine deficiency as an etiological mechanism
2. To highlight that TRMA can sometimes present with "normocytic" rather than macrocytic anaemia.

Case report

- British-Pakistani adolescent boy presented with acute mastoiditis and new diagnosis of diabetic ketoacidosis at 14 years of age
- Weight - 48 kg (25th–50th percentile)
- Height - 161 cm (25th percentile)
- Body mass index - 18.5 kg/m^2
  (HbA1c=147 mmol/mol. Anti-GAD and anti-IA2 antibodies negative)
  Dx: Diabetes mellitus, ? Type-1
  Tx: Basal-bolus Insulin therapy
- **Past Medical History:**
  - Bilateral sensorineural hearing loss at 2 years of age
- **Family History:**
  - Consanguinity - his parents are 1st cousins
  - 2nd generation immigrants from Mirpur region of Kashmir
  - No family history of diabetes or deafness.

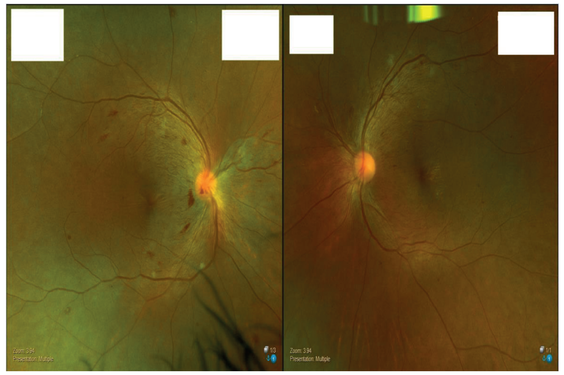
Further investigations/management

3 months after presentation with DKA:

- **First diabetic retinal screening:**
  - No visual symptoms
  - Visual acuity - 6/18 in the right eye and 6/12 in the left eye
  - No evidence of optic atrophy or retinal dystrophy
- **But..**
  - **Bilateral severe proliferative retinopathy**
  - **Clinically significant macular oedema**

Further investigations/management

Figure 1: Fundus photographs depicting neovascularisation, papillitis, pre-retinal haemorrhages and cotton-wool spots in the right eye (left picture) and papillitis in the left eye (right picture).



- **At the same time, he was also**
  - Admitted acutely with breathing difficulty and
  - Severe normocytic anaemia, thrombocytopaenia and reticulocytopenia

Investigation	Patient's results
Haemoglobin	40 g/L
RBC Count	1.49 * 10^12/L
Mean corpuscular volume	**79.9 fL**
Platelets	42 * 10^ 9/L
WCC	4.1 * 10^9/L
Reticulocyte Count	4 * 10^9/L

Further blood tests

- **Peripheral smear:** Marked poikilocytosis with fragments, target cells and tear drop cells
- Comprehensive haematological investigations failed to determine the cause of pancytopenia
- **Bone marrow examination:** Erythroid dysplasia and numerous ring sideroblasts
- At this point, a literature search for deafness, diabetes and ring sideroblasts led to the suspicion of **TRMA as a possible diagnosis**
- Red-cell thiamine level: 60 nmol/L (67-200)

Post Dx of TRMA

- **Started on high-dose thiamine therapy (50 mg/day)**
- Genetic testing: homozygous for a pathogenic SLC19A2 nonsense variant NM_006996.2:c.196G>T p. (Glu66Ter) and both his parents are heterozygous for the same mutation
- ECHO (to detect cardiac defects or rhythm disturbances): structurally normal heart.

Outcome and follow up

- Improvement since starting thiamine therapy:
- **Anaemia:**
  - Hb, RBC and PLT normalised within 3 weeks of starting thiamine.
  - To date, he has remained transfusion independent
- **Retinopathy:**
  - Worsening retinopathy within 2 months of initial retinal screening required indirect laser pan-retinal photocoagulation
  - Macular oedema: regressed spontaneously in both the eyes
  - Retinal neovascularisation: regressed completely
  - Visual acuity: stable thereafter (6/12 in both eyes)
- **Diabetes** much better controlled (HbA1c < 48 mmol/mol), but continues to require insulin
- **Blood pressure** and urinary Albumin to Creatinine Ratio: within normal limits
- He has been on Thiamine therapy for nearly 18 months and will require to continue for life.
- Presently, he is in secondary school, has an Education, Health, and Care Plan in view of his hearing difficulty.
- He has not developed any neurological manifestations (e.g. stroke, seizures) as reported in some cases of TRMA

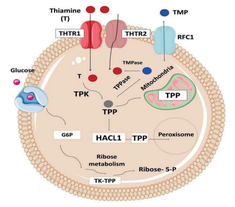
Thiamine-Responsive Megaloblastic Anaemia

Disorder of the bone marrow:

- Ineffective hematopoiesis
- Ringed sideroblasts fail to enter blood circulation due to their larger size reduction in number of RBCs

Thiamine and glucose metabolism

- **Thiamine** acts as a coenzyme for enzymes which play a **fundamental role** in intracellular **glucose metabolism** (Transketolase, pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase complexes)
- In TRMA, hyperglycaemia -> relative thiamine-deficient state and accumulation of highly reactive metabolites -> formation of advanced glycosylation end products



The role of thiamine transporters, THTR-1 in glucose metabolism. (THTR-1: Thiamine transporter 1, THTR-2: Thiamine transporter 2, RFC1: Reduced folate carrier 1, TMP: Thiamine monophosphate, TMPase: Thiamine monophosphatase, HACL1: 2-Hydroxyacyl-CoA Lyase 1, TPP: Thiamine pyrophosphate, TPPase: Thiamine pyrophosphatase, TK-TPP: Transketolase-Thiamine pyrophosphate, TPK: Thiamine pyrophosphokinase, TDP: Thiamine diphosphate). Clin. Pract. 2011; 65 (6) 633-716

SLC19A2 gene mutations and THTR-1

- ***SLC19A2*** = Gene responsible for TRMA
- On **chromosome 1q** and codes for the high-affinity **thiamine transporter protein, THTR-1**
- At least 17 **mutations** in the SLC19A2 gene lead to the production of an abnormally short, **nonfunctional thiamine transporter** causing TRMA

THTR1 and THTR2 proteins

- THTR1: high-affinity thiamine transporter protein (encoded by SLC19A2 gene)
  - The sole thiamine transporter expressed in bone marrow, in a subset of cochlear cells and in pancreatic beta cells,
  - This explains the clinical triad that defines TRMA
- THTR2: low-affinity thiamine transport (encoded by SLC19A3 gene)
  - Widely expressed in all human tissues
  - Plays an important role in the management of TRMA

Management of TRMA

- Pharmacological doses of thiamine lead to the utilisation of passive low-affinity thiamine transport through THTR2 protein
- High-dose thiamine treatment -> anaemia is corrected and insulin treatment can either be stopped or significantly reduced
- Sensorineural deafness has not been found to improve with thiamine therapy (may be due to irreversible damage to the inner ear cells soon after birth)

Learning Points

- Although puberty and early worsening of retinopathy reported with the initiation of intensive insulin therapy could have been the contributing factors, severe proliferative retinopathy requiring pan-retinal photocoagulation in just 3 months after the diagnosis of diabetes is exceptionally rare
- In this case, it may have resulted from combined effect of intracellular thiamine deficiency and severe hyperglycaemia
- **Intracellular thiamine deficiency** may lead to accelerated development of diabetic retinopathy in patients with TRMA as well as in patients with all other types of diabetes mellitus
- Children with TRMA may benefit from **regular retinal screening** starting at a younger age than that recommended for type-1 and type-2 diabetes.
- **This case report emphasises the need for further well-designed controlled studies to determine the beneficial role of thiamine in primary and secondary prevention of diabetic retinopathy**
- TRMA should be considered while evaluating a child with non-immune-mediated diabetes and anaemia
- **Anaemia may be either normocytic or macrocytic at presentation**

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Diabetes and insulin
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P2-118