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 (THTR1) 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 new diagnosis of diabetic ketoacidosis at 14 years of age
2. To summarise the clinical picture and possible management options

Case report
- British-Pakistani adolescent boy presented with acute malaise and new diagnosis of diabetic ketoacidosis at 14 years of age
- Weight - 48 kg (20th–50th percentile)
- Height - 161 cm (25th percentile)
- Body mass index - 18.5 kg/m²
- (hbA1c=147 mmol/mol. Anti-GAD and anti-IgA antibodies negative)
- Diabetes mellitus, Type-1
- 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

- At the same time, he was also:
  - Admitted acutely with breathing difficulty and
  - Severe non-normocytic anaemia, thrombocytopenia and reticulocytopenia

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)

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-keto glutarate dehydrogenase complexes)
- In TRMA, hyperglycaemia → relative thiamine-deficient state and accumulation of highly reactive metabolites → formation of advanced glycosylation and products

Investigation Patient’s results
- Haemoglobin 40 g/L
- RBC Count 1.89 * 10¹²/L
- Mean corpuscular volume 79 fl
- Platelets 62 * 10⁹/L
- WCC 7.6 * 10⁹/L
- Reticulocyte Count 4 * 10⁹/L

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 photoocoagulation
    - 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

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 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 photoocoagulation 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
- Intraocular 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

Reference