SEVERE B12 DEFICIENCY MIMICKING TTP

Dr Siobhan Cross, Children's Haematology Oncology Centre, Christchurch Hospital

Canterbury District Health Board
Te Poari Hauora ō Waitaha

INTRODUCTION

Thrombotic thrombocytopaenic purpura (TTP) is a medical emergency with a high mortality rate if not promptly treated. We present a case of a 10 month old infant with severe anaemia and thrombocytopaenia with schistocytes on the blood film suggesting TTP. The patient was transferred to ICU but second review of the blood film and bone marrow along with the patient's history suggested megaloblastic anaemia due to cobalamin (vitamin B12) deficiency, was a more likely diagnosis.

CASE

A 10 month old female presented to her general practitioner with a 2 week history of listlessness and decreased feeding. She was the youngest of 3 children of non-consanguineous parents and was exclusively breastfed. She has been previously well and was growing well. On examination there was marked pallor without hepatosplenomegaly or lymphadenopathy. An urgent full blood count (FBC) showed:
Hb 37g/L (105 – 136), **MCV 89 fL** (69 – 84), **WCC 4.4 x 10^9/L** (6.4 – 17), **Neuts 0.29 x 10^9/L** (0.9 – 5.9), **Platelets 31 x 10^9/L** (150 – 575)
Reticulocytes 28 x 10^9/L 20 – 100)
The specimen was grossly lipaemic while the blood film showed microspherocytes, significant fragmentation and nucleated red blood cells (RBC) (**Figure 1a**).

On further history she was unimmunised due to parental choice and had been well until approximately 1 month prior when her milestones had slowed and then regressed. Her mother followed a strict vegan diet and the patient had not yet started solid food. On admission she was mildly febrile at 38.1c but exam findings were otherwise as above.
Other bloods showed:
Triglycerides of 9.5 (H); High iron studies (transferrin saturation 100%); Bilirubin 56 umol/L (2-20); Renal function normal
Coags: **INR 3.8**, **APTT 48, Fibrinogen 1.4**

A provisional diagnosis TTP was made based on the blood count and film appearances. Other conditions such as disseminated intravascular coagulation (DIC) or haemophagocytic lymphohisteocytosis (HLH) were considered less likely given the near normal fibrinogen and ferritin of only 300ug/L. A bone marrow aspirate to exclude malignancy or aplasia was also performed.

She was treated in the ICU where received 15ml/kg RBC as well as platelets and fresh frozen plasma. The next morning further review of blood film and bone marrow showed a megaloblastic bone marrow (**Figure 2)** while the red cell fragments were rounded rather than shcistocytic (**Figure 1a**). Her **Vitamin B12 <61 pmol/L** (130 – 650)
While later that day her ADAMTS-13 activity 66% (>50) was found to be normal excluding TTP.

On further history it was found that the patient did not receive vitamin K at birth and the maternal diet was low in fat and vitamin K.

The patient was treated with IM B12 replacement as well as folate supplementation to prevent folate deficiency from excess utilisation. She also received Vitamin K IV and, after further testing showed Vitamin A, D and E deficiency, these were also replaced.

B12 therapy lead to rapid improvement in the blood parameters (**Figure 3**) and no further blood transfusions were required. By 3 weeks post diagnosis she had lowered iron stores and required iron supplementation. She was discharged 4 weeks after admission. Neurological assessment showed ongoing hypotonia and developmental delay and a CT scan showed cerebral parenchymal volume loss.

She is now 1 year post presentation with normal blood results and improving although still delayed development. She remains under paediatric outpatient follow up

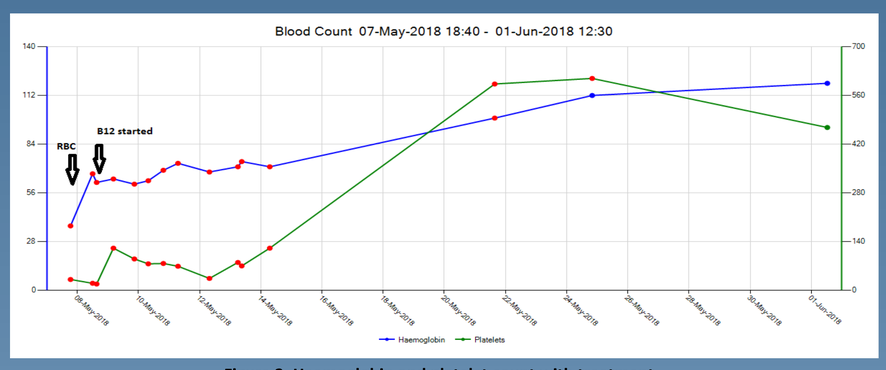

Figure 3. Haemoglobin and platelet count with treatment

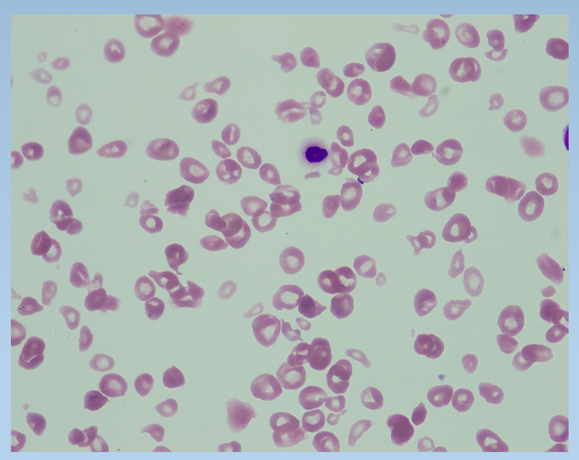

Figure 1a. Patient's blood film showing NRBC microspherocytes and fragmentation

Figure 1b. Classic picture of vitamin B12 deficiency

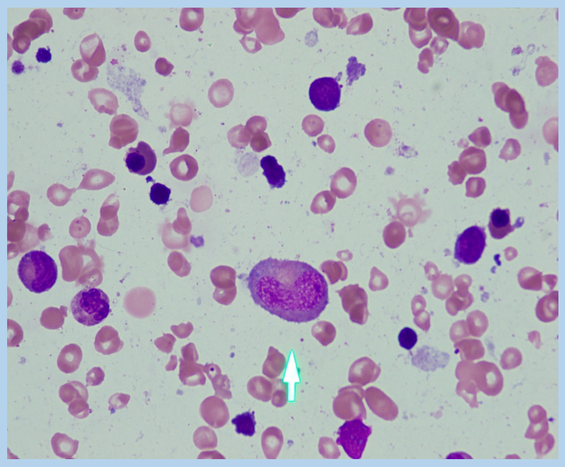

Figure 2. Patient's bone marrow showing megaloblastic dyserythropoesis and a giant metamyelocyte

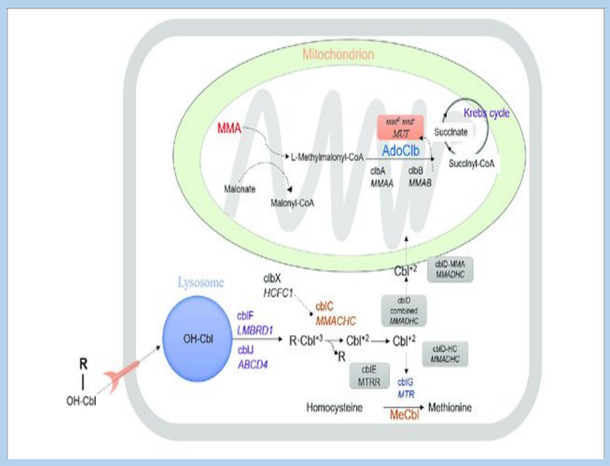

Figure 4. Cobalamin metabolic pathway

DISCUSSION

Pancytopaenia is an uncommon presentation in infants and in first world countries usually represents acute leukaemia or aplastic anaemia. In third world countries or countries where vegetarian diets are more common megaloblastic anaemia due to B12 deficiency is the most common cause[1] and may present with severe thrombocytopaenia as well as the classic macrocytic anaemia. Other causes of bi-cytopaenia or pancytopaenia include microangiopathies such as HLH or haemolytic uraemic syndrome (HUS), DIC, TTP, viral infections or overwhelming sepsis.

In our patient acute leukaemia and aplastic anaemia were excluded due to bone marrow findings, HLH was unlikely given the ferritin of only 300 and while DIC and overwhelming sepsis were theoretical possibilities there were no clinical indicators or precipitators for these conditions. Viral infections were unlikely given the severity of the pancytopaenia leaving TTP and B12 deficiency.

TTP classically presents with an altered mental state, bi-cytopaenia of platelets and RBC and schistocytes (RBC fragments) on the blood film. TTP is a deficiency of ADAMTS-13 metalloprotease enzyme[2]. The enzyme acts on high molecular weight von Willebrand factor (VWF) multimers to cleave them in to shorter molecules. Deficiency leads to a lack of clearance of VWF and excessive platelet aggregation, leading to a mixed picture of thrombosis and consumptive coagulopathy of platelets, along with shearing damage to RBC. Neutropaenia is not a common feature of TTP. In TTP the coagulation profile is usually near normal and the fibrinogen is often raised.

ADAMTS-13 deficiency can be congenital, due to mutations in the gene that encodes the enzyme or an acquired autoimmune phenomenon. Plasma exchange, ideally using cryosupernatant which is deficient in VWF, and other therapies such as Rituximab are used in acquired TTP while congenital TTP is treated with regular fresh frozen plasma infusion to replace the ADAMTS-13. The day after admission our patient had an ADAMTS-13 level reported which was normal, excluding this condition.

Severe B12 deficiency is rare in New Zealand but there are reported cases with significant morbidity and mortality. In 2002 in New Zealand parents were found guilty of manslaughter for refusing B12 treatment for their 6 month old infant who subsequently died. In 2018 an Australian couple were prosecuted for putting their 20 month on a vegan diet that left her malnourished with B12 deficiency and Ricketts, while in Belgium a couple have been found guilty of manslaughter for the death of their 7 month old child, again from B12 deficiency.

Cobalamin or vitamin B12 is an essential co-factor in the conversion of homocysteine into methionine which is required for DNA methylation (**Figure 4**). It is also a co-factor in the conversion of l-methylmalonyl CoA to succinyl CoA which is part of the process where energy is extracted from proteins and fats. Succinyl CoA is also needed for haemoglobin production. Deficiency leads not only to bone marrow hypofunction but because the DNA methylation of all body cells is affected, other effects include peripheral neuropathy and neurological defects, which in infants can include long term developmental delay.

The classic blood film of B12 deficiency is oval macrocytosis with hypersegmented neutrophils (**Figure 1b**) however the blood film appearances of severe B12 deficiency are more pronounced and bizarre that those of mild to moderate deficiency as the ineffective erythropoiesis leads to the appearances of RBC fragmentation and anisopoikilocytosis. Due to this and the severe thrombocytopaenia that is not found in more mild B12 deficiencies the process can be mistaken for TTP[3,4]. In our case the condition was partially masked by the fact that the MCV was only mildly elevated. This was due to the fact that the RBC fragments and microspherocytes had artificially lowered the total MCV and there was a wide MCV distribution width[5].

Unsupplemented vegan diets are not recommended for children due to the risk of multiple dietary deficiencies. Our case was the youngest of three children. The older two had moved on to a mixed solid and breast milk diet at between 5 and 7 months with some B12 but our patient had not shown interest in solids or become overly hungry while breast feeding and so had remained exclusively breastfed. At the time of her admission she was deficient in B12 and several fat soluble vitamins.

Our patient's blood count recovered well after B12 supplementation. Folate was also added as in severe B12 deficiency if there is sudden replacement of B12 the body folate stores can be used up rapidly leading to severe folate deficiency and similar problems. Her neurological recovery is more guarded and while she is currently improving she remains developmentally behind her peers. Long term neurological outcomes after B12 deficiency in infancy are not well studied and most reports are of small case series[6]. Therefore it is unclear if there will be long term neurological sequalae.

CONCLUSION

B12 deficiency is a severe but correctable problem. Severe B12 deficiency may have marked blood film changes that may mimic TTP and macrocytosis may not be apparent on the reported RBC indices. A high index of suspicion is required, especially as other results may be altered by co-existing dietary deficiencies such as iron, vitamin K etc.

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