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COMMENTARY

Vitamin B12 deficiency misdiagnosed as TTP: What can we learn from it?

Bernhard Lämmle[1,2,3] | **Alexander Laemmle**[4,5]

[1]Center for Thrombosis and Hemostasis, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

[2]Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[3]Haemostasis Research Unit, University College London, London, UK

[4]Division of Pediatric Endocrinology, Diabetology and Metabolism, Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[5]University Institute of Clinical Chemistry, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Correspondence
Bernhard Lämmle, Center for Thrombosis and Hemostasis, University Medical Center of the Johannes Gutenberg University, Schützenweg 3, CH 3065 Bolligen, Switzerland.
Email: bernhard.laemmle@uni-mainz.de

The case report by Dwyre et al. shows that vitamin B12 deficiency may be misdiagnosed as acute thrombotic thrombocytopenic purpura. Together with similar observations, this underlines that acquired vitamin B12 deficiency—besides the inherited disorder of intracellular cobalamin metabolism, cbl C disease—should be listed as a separate entity of the thrombotic microangiopathies.

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In their paper of the journal, D.M. Dwyre and colleagues present a case report of substantial clinical relevance.[1] A 22-year-old African American female was hospitalised with abdominal symptoms, thrombocytopenia and Coombs-negative haemolytic anaemia with strongly elevated lactate dehydrogenase (LDH). Based on a clinical diagnosis of thrombotic thrombocytopenic purpura (TTP), she was subjected to a series of daily therapeutic plasma exchanges (TPE) resulting in clinical improvement and normalisation of platelet count and haemolysis. Three months later, she was rehospitalised at another hospital, UC Davis Medical Center, for recurrent symptoms, pancytopenia, haemolysis with anisopoikilocytosis and schistocytes. Assuming a relapsing acute TTP episode, TPEs were resumed and clinical symptoms as well as pancytopenia improved. ADAMTS13 activity in a blood sample obtained before starting TPE was completely normal whereas plasma concentration of vitamin B12 was low and plasma methylmalonic acid was increased.[1] The diagnosis of TTP was revised and a severe vitamin B12 deficiency, presumably due to pernicious anaemia, was diagnosed and treated by repeated intramuscular vitamin B12 applications resulting in long-term correction of the severe megaloblastic anaemia.

There are several learning points for clinical haematologists involved in diagnosis and treatment of thrombotic microangiopathies (TMA) and paediatricians managing inherited and acquired metabolic disorders. These are shortly outlined here.

TMAs comprise pathophysiologically heterogeneous conditions presenting with microangiopathic haemolysis, that is, mechanical erythrocyte fragmentation with schistocytes in the blood smear as a hallmark, consumptive thrombocytopenia and ischaemic organ damage caused by widespread arteriolar and capillary thrombi or microvascular injury.[2,3]

The specific entity among the TMAs labelled as TTP has been pathophysiologically defined during the past 25 years as being caused by a defective Von Willebrand factor multimer size regulation due to a severely deficient activity of the metalloprotease ADAMTS13 (*A Di*sintegrin *a*nd *M*etalloprotease with *T*hrombo*S*pondin type 1 domains, number 13).[3,4] Congenital TTP (cTTP) results from biallelic *ADAMTS13* pathogenic variants, autoimmune TTP (iTTP) from autoantibodies inhibiting and/or clearing plasma ADAMTS13.[4] A rapid and correct diagnosis of cTTP or iTTP must be based on clinical features and measurement of ADAMTS13 activity, anti-ADAMTS13 autoantibodies or functional ADAMTS13 inhibitors.[3,5] In the reported case, the diagnosis at the initial episode was not confirmed by ADAMTS13 assay, but the treating physicians probably assumed that their diagnosis was confirmed by the normalisation of the platelet count after 12 sessions of TPE.[1] When this young patient was readmitted 3 months later with similar symptoms and now pancytopenia, the authors first restarted with daily TPE but rightly questioned the diagnosis. Pancytopenia and the only mild thrombocytopenia are not typical features of TTP, the very high LDH but only spuriously elevated bilirubin and absence of haemoglobinuria, together with hypersegmented neutrophils and basophilic megaloblasts in the blood smear rather evoked a diagnosis of vitamin B12 deficiency which was confirmed by appropriate testing. The normal mean corpuscular volume of the red blood cells was unexpected but could be explained by concomitant alpha-thalassaemia trait. The patient was luckily admitted to a tertiary medical centre and seen by a team of physicians including the senior author of this case report, a haematologist with outstanding knowledge and expertise in vitamin B12 physiology and pathophysiology.[6] In retrospect, the authors suggest that the large volume of plasma, about 20 L, applied during the daily TPE sessions during the initial disease phase provided small amounts of vitamin B12 which may have been responsible for the transient improvement of the platelet count.

Overviews of the various hereditary and acquired forms of TMAs mention an inherited disorder of intracellular cobalamin (vitamin B12) metabolism, so-called cbl C disease, as a differential diagnosis.[2,3] Biallelic pathogenic variants of the *MMACHC* gene—causing methylmalonic aciduria and homocystinuria cbl C type—are a rare cause of a TMA, mainly manifesting in childhood. Elevated serum and urine levels of methylmalonic acid and homocysteine are seen and seem to be caused by defective synthesis of adenosylcobalamin and methylcobalamin associated with dysfunction of methylmalonyl-CoA mutase and methionine synthase, respectively.[7] The present case report shows that not only the inborn error of cobalamin metabolism, cbl C disease, but also acquired vitamin B12 deficiency in the context of pernicious anaemia, may cause a clinical picture of TMA. Additional cases of acquired vitamin B12 deficiency presenting with features of TMA have been reported[8–10] (and references given in [1]).

The International Working Group on thrombotic thrombocytopenic purpura and related thrombotic microangiopathies led by Professor Marie Scully from University College London, and including all clinicians and scientists from many countries interested in TMAs would be an ideal forum to review the differential diagnostic list of TMAs[3] and, after thorough evaluation of the literature, add acquired vitamin B12 deficiency, besides the hereditary cbl C and cbl G diseases,[1,7] as a cause of TMAs and try to further elucidate the underlying pathomechanisms.

ORCID

Bernhard Lämmle https://orcid.org/0000-0003-4538-5154

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