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NUTRITIONAL ANEMIAS

Megaloblastic Anaemia (MA)

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Megaloblastic Anaemia (MA) is caused by retarded purine and pyrimidine (notably thymidylate) synthesis. Therefore DNA does not replicate, but RNA and protein (including haemoglobin) synthesis continues leading to typical cell changes, especially in rapidly dividing tissues such as the bone marrow, testicles, gastrointestinal and bronchial epithelia. Excepting some rare metabolic errors, MA is due to lack of or inability to absorb or to deliver to tissues and subcellular structures folate (FA) or cobalamin (Cbl or vitamin B_{12}) or to produce enzymes which contain their coenzyme forms. Typical changes in the peripheral blood are pancytopenia, high MCV, MCH and red cell diameter (MCD) indexes and granulocytes with polylobulated nuclei. Low haemoglobin concentration is a late sign of deficiency. Specific treatment causes reticulocytosis and haematological remission, probably the most reliable diagnostic evidence for deficiency. In Cbl deficiency there is typical neurological damage; in children especially the brain is vulnerable.

The mechanism causing MA (which does not occur in non-primates) is a disturbance in the regeneration of active tetrahydrofolate (THFA) needed for transfer of one-carbon units. Methyl-Cbl is a cofactor in the transfer of methyl from 5-methyl-THFA to homocysteine (Hcy), which becomes methionine. The latter is then converted to S-adenosylmethionine and used for methylation reactions. Serum-Hcy increases both in folate and Cbl deficiency. Deoxyadenosyl-Cbl (Ado-Cbl) is a mitochondrial coenzyme needed for the conversion of methylmalonyl-CoA to succinyl-CoA, then processed in the Krebs cycle. In Cbl deficiency, serum-methylmalonate (MMA) increases. Accordingly, Hcy and MMA are used to diagnose FA and Cbl deficiency. The mechanism causing the neurological damage in Cbl deficiency is not quite clear, MMA may damage the myelin sheaths.

The traditional ways of diagnosing these deficiencies is to assay serum Cbl and FA and red cell FA (all mixtures of numerous compounds), then to investigate the cause of the deficiency by measuring radio-vitamin-B_{12} absorption (especially the Schilling test), assaying intrinsic factor (IF) antibodies, performing gastric function tests, etc. During recent years, transcobalamin (TC or TCII) bound Cbl has become popular as the rest of the serum vitamin is bound to haptocorrin (HC, R-protein or TCI) and does not reflect the rapidly mobilizable body stores.

At present there is no generally accepted gold standard test for diagnosing Cbl or FA deficiency, nor agreement on decision limits. The matter is complicated by the fact that based on the tests and therapeutic trials, large sectors of the population, especially the aged, have been considered to suffer from FA or Cbl deficiency, which may manifest itself as atherosclerosis, mental retardation, Parkinson's disease, osteoporosis and infertility, maybe even problems with vision. In addition to low intake and gastric and pancreatic maldigestion, possible components in the causation of these conditions are slowly functioning genetic variants of enzymes and transport proteins involved in the metabolism of the vitamins. As lack of FA during pregnancy is known to cause neural tube defects, fortification of foodstuffs has been instituted, –a debatable practice, as FA tends to worsen the neurological damage in Cbl deficiency. Considering the very large sectors of the general population suspected to be deficient, the cost of the tests and their fallacies, one might consider prophylactic treatment of selected groups with FA and Cbl,

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which are relatively cheap. Sufficient amounts of Cbl have then to be given to prevent neurological damage.

These problems are of less importance in children, but may become important if one begins to look for predisposition to adult diseases. FA deficiency is a rare cause of MA in Scandinavia. In children deficiency may become apparent following treatment of iron deficiency anaemia in coeliac disease. Relative FA deficiency has been observed in babies that are not breast-fed, who have undergone extensive surgery or are premature. For monitoring these cases, the MCV index is useful. MA is sometimes observed in analogous adults or who are alcoholic or take antiepileptic drugs. Intake of poor food, boiling of vegetables and intestinal damage due to tropical diarrhoeal diseases probably partly explain the higher frequency of FA deficiency elsewhere in the world.

Cbl deficiency is also rare in children. Overt MA is usually preceded by failure to thrive and gastrointestinal and respiratory infections. Fish tapeworm anaemia was once frequent in Finland and not uncommon in children. An extensive field study permitted correlating the serum Cbl level with the blood picture, and revealed that the red cell count, the MCV, MCH and MCD indexes responded earlier to low Cbl levels than haemoglobin. The mean red cell diameter was measured with a halometer, a simple and forgotten instrument that can be used under primitive conditions. Other causes include selective Cbl malabsorption, often combined with proteinuria and very early shown to be due to an error in the intestinal receptor for the Cbl-intrinsic factor (IF) complex. Today we know that the receptor has two components, cubilin which are lacking in the patients first described by myself and amnionless, which is lacking in Imerslund's Norwegian patients, who, incidentally, have anatomical anomalies. Lack of the receptor in the kidney tubules explains the proteinuria.

Genuine pernicious anaemia with atrophic gastritis and anti-IF antibodies occurs in children, but is rare (eradication of Helicobacter may reverse the atrophy). More common is congenital lack of IF. These cases have been mistaken for selective malabsorption, especially as Schilling tests and other relevant assays have become unavailable. The proper diagnosis can be provided by genetic tests. Nutritional lack of Cbl is not uncommon in breast-fed children of Vegan mothers. Neurological and especially brain damage is a real threat here.

That congenital lack of TC can produce MA was once predicted by the author, but no cases have been reported from his part of the world. The same applies to mutations in the enzyme systems producing and requiring the Cbl coenzymes. Some of these conditions have MA and respond to large doses of Cbl. Low, but largely innocuous serum-Cbl is observed in congenital HC deficiency. However, HC may have the important task of removing antagonistic Cbl-related compounds. Their role in producing Cbl deficiency is largely unknown but worth looking into. We have recently biosynthesised ^{32}P-Cbl which may provide a tool for such studies.

Under primitive conditions, MA may be best diagnosed counting the red cells, leukocytes and platelets in peripheral blood and determining the MCV, MCH or MCD indexes, inspecting the morphology of the cells in a blood smear and observing the effects of a therapeutic test, giving first small amounts of FA, then Cbl.