Mediterranean macrothrombocytopenia and phytosterolaemia/sitosterolaemia

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We read with interest Nurden and Nurden's exhaustive review on inherited thrombocytopenias.[1] We can add that the nature of *Mediterranean macrothrombocytopenia* has recently been clarified.

As originally described in Australia, there were over 100 cases showing the unusual combination of stomatocytic haemolysis and macrothrombocytopenia. In some cases there was abdominal pain.[2,3] In no pedigree was the inference of *dominant inheritance* truly convincing. Almost all of the patients had emigrated from different regions around the Mediterranean. The reports ceased in 1975 and we have confirmed that the condition definitely disappeared.[4]

The Italian macrothrombocytopenic cases referred to by Nurden and Nurden, originally investigated by Savoia *et al*.[5] were simply hitherto-undiagnosed cases occurring in Italian (and therefore Mediterranean) patients, but did not show haemolysis.

We found that the combined red cell and platelet haematology originally described in Australia is associated with the metabolic disorder *phytosterolaemia* (also known as *sitosterolaemia*).[6] In this autosomal recessive condition, there is a defect in one of the genes ABCG5 or ABCG8, which code for subunits of an ABC carrier protein in the gut and liver.[7] This protein apparently ejects from the body unwanted sterols, including both cholesterol itself and the plant-derived sterol molecules such as sitosterol, iso-fucosterol and campesterol found in oily plants such as olives, soya, nuts and avocados. In the absence of a functioning transporter, these diet-derived sterols are allowed unrestricted access to the plasma. The plasma cholesterol can range from normal to very high, depending on the dietary intake. Phytosterolaemia has always been associated with abnormal haematology,[6] but we noted that it is very specifically associated with the highly characteristic combination of stomatocytic haemolysis and macrothrombocytopenia,[8] the original hallmark of Mediterranean macrothrombocytopenia. Some of our cases presented with abdominal pain, the third feature of the Australian reports. A further phytosterolaemia pedigree has been identified in China via the haematology.[9]

It seems unlikely to us that the Adelaide cases represented *genetic* phytosterolaemia: there were just too many cases of what remains a very very rare condition in a small population; and it simply went away over a five-year period. Nevertheless an acquired excess of phytosterols in the blood seems a likely explanation for the Australian cases. This haematology can occur as an acquired entity during intravenous feeding with soya-based lipid emulsions where presumably the intravenous infusion exceeds the excretory capacity of the biliary and intestinal epithelia.[10] We have postulated that in Australia there was some environmental factor, perhaps an inhibitor of the protein product of ABCG5/G8.[4] The disorder may have been most prominent in *Mediterranean migrants* simply because their diet is especially rich in phytosterol-rich plant oils, especially olive oil.

Whatever the explanation for the Australian experience, unexplained macrothrombocytopenia, especially if it is associated with either haemolysis or many stomatocytes or both, should prompt measurements of plasma phytosterols.

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