Familial Presence of Primary Cryofibrinogenaemia, A Report of Three Cases

SIR—Cryofibrinogenaemia (CryoF) is defined by the presence of cold-precipitable fibrinogen in plasma. Primary CryoF usually manifests itself by a Raynaud’s phenomenon, acrocyanosis or skin necrosis [1–4]. It also occurs in association with a variety of disorders and is then described as secondary. The histology of affected skin shows a leucocytoclastic vasculitis and an intravascular proteinaceous clot consisting of fibrinogen, sometimes with IgG [3, 4]. We report here three cases of primary CryoF in children. The known causes of secondary CryoF were excluded. In all children there was a familial occurrence of Raynaud’s phenomenon and/or acrocyanosis (Table 1).

Patient 1, an 11-yr-old boy, was admitted to our clinic with a 5 yr history of relapsing fever, generalized muscle weakness and arthralgia in hands and feet. Prior to admission, there had been a prolonged exposure to cold. His mother and two brothers are healthy. His father suffered from a myocardial infarction several years earlier. The mother’s sister is affected by a Raynaud’s phenomenon and a ruptured aneurysm of the internal carotid artery. Her clotting tests were normal. The grandfather also suffered from a Raynaud’s phenomenon in association with a vascular disease; no clotting tests were available. Physical examination of the boy showed hypertension, leucocytoclastic, painful cyanotic swelling of the fingers and feet, and numerous purpura on the legs and arms. Biopsy of a skin lesion showed a leucocytoclastic vasculitis, subcutaneous thrombosis and endothelial immune complex depositions. In some vessels a proteinaceous clot was seen (Fig. 1). He was treated with prednisone 30 mg daily for 4 weeks. He showed a marked remission and the prednisone treatment was slowly withdrawn. One year later he was well, but the CryoF was still present. The second patient, a 10-yr-old girl, was referred for evaluation of a Raynaud’s phenomenon that had existed since infancy. One year ago, she developed purpura in reaction to minor trauma. Two older sisters had the same symptoms, but here the symptoms resolved spontaneously around age 5 yr. Her mother was healthy, but the father died suddenly at age 32 yr. Autopsy showed a fatty degeneration of the liver and cardiomyopathy. Physical examination of the girl showed purpura on the legs. A Raynaud’s phenomenon could be induced. No biopsies were taken. The purpura disappeared spontaneously, but the CryoF was still present 2 yr later.

Patient 3 is a 5-yr-old boy with a severe acrocyanosis of the hands and feet. Symptoms occur mainly in the morning after exposure to cold. There is also delayed wound healing. His mother and grandmother are affected with acrocyanosis and Raynaud’s phenomenon. The father is healthy. Physical examination of the boy showed a Raynaud’s phenomenon and superficial skin lesions on the feet.

The ESR was elevated in patient 1, but normal in patients 2 and 3. Whole blood cell counts, serum immunoglobulins and haemolytic complement were normal. In addition, ANA, RF, C1q binding and cryoglobulin tests were all negative. The plasma fibrinogen was elevated in patient 1 (7.8 g/l), but normal in patients 2 and 3, and all screened family members. Clotting tests were normal in all patients and their relatives. For the determination of CryoF, 5 ml blood were kept at 37°C in either heparin- or citrate-containing tubes. The plasma was stored at +4, 17 and 37°C for 5 days. The presence of a cryoprecipitate was then assessed by visual inspection.

If present, the cryoprecipitate was separated from the
plasma, extensively washed with cold phosphate-buffered saline and redissolved at 37°C. The suspension was analysed for the presence of fibrinogen and serum proteins albumin, IgM, IgG and IgA using immunoelectrophoresis with specific antisera (manufactured by the Central Laboratory for Blood Transfusions, Amsterdam, The Netherlands). Cryoglobulin (CG) was determined using the same method described above, using tubes with no anti-coagulant added. Cryofibrinogen (CryoF) was strongly positive in all patients. Immunoelectrophoretic analysis of the redissolved clots revealed the presence of fibrinogen. The unrelated parents of patient 1 were also positive for CryoF, as was the mother of the third patient. The fibrinogen clots obtained from both mothers also contained IgG and albumin.

The incidence of CryoF in adults is 3%, but the incidence in childhood is unknown [1, 2]. Secondary CryoF was described in four children with a respiratory infection [5]. As soon as the infection was adequately treated, the acrocyanosis and CryoF disappeared within days. Persisting CryoF has so far been described in one child with systemic cold urticaria [6]. To our knowledge, the only case of a familial occurrence of CryoF described so far was a 5-yr-old boy with a transient nephrotic syndrome after anaesthesia [7].

In our patients there was a familial occurrence of acrocyanosis and Raynaud's phenomenon, and in two of these there was a familial presence of CryoF. The fact that CryoF was also found in a healthy relative suggests that the mere presence of CryoF does not cause disease. Also, we found that in patients with primary CryoF the cryoprecipitins persisted for some years, while the skin manifestations disappeared much earlier. It is unknown why CryoF precipitates in the cold. It has been shown that congenital dysfibrinogenaemia is caused by genetic mutations. By analogy, a mutated fibrinogen with conformational changes or altered thrombin-binding capacities could cause clot formation on exposure to cold or other aspecific stimuli. The vasculitis seen in affected skin would reflect tissue damage from local thrombosis and vascular occlusion [4]. However, it cannot be ruled out that the vasculitis is the cause and not the consequence of the tissue damage and thrombosis. The observed familial clustering of CryoF does at present not permit any conclusions with regard to inheritance patterns.

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