Transient nephrotic syndrome after anaesthesia resulting from a familial cryofibrinogen precipitating at 35°C

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SUMMARY Transient nephrotic syndrome, haematuria, and cryofibrinogenuria in a child after anaesthesia were found in association with a plasma cryofibrinogen that precipitated at 35°C. Investigation of the family showed this to be a familial trait probably with dominant inheritance.

In 1955, Korst and Kratochvil1 coined the term cryofibrinogen to describe a plasma protein which precipitated on cooling and redissolved on rewarming to 37°C. Since then, cryofibrinogenemia has been found to occur in 3% of hospital patients.2 3 It has been described in association with a variety of conditions including malignancy,3-6 infection,5 7-9 autoimmune disorders,5 7 10 thromboembolic disease,3 5 7 11 glomerulonephritis,12 13 diabetes mellitus,3 pregnancy,3 14 and in women taking oral contraceptives.15 In rare instances when no underlying disease has been found, the cryofibrinogenemia has been termed primary or essential.3 5 16 Cold related symptoms usually suggest the diagnosis, but they may be absent.3 5 6 17

Heat loss is a common accompaniment of anaesthesia18 because of the use of cold and dry gases, exposure to a cool environment of often vasodilated patients, heat loss from the operation site, the infusion of cold fluids, and abolition of the shivering reflex by muscle relaxants. It is greatest in children because of their larger surface area to volume ratio, with most heat loss occurring in the first operative hour. We report an unusual presentation of the complications of a cryofibrinogen that precipitated at 35°C in a child after anaesthesia and a hitherto undescribed familial form of the condition.

Case report

The proband, a seven year old girl, was admitted to the National Hospital in June 1987 for a muscle biopsy because of a history of postoperative myalgia and 'myoglobinuria'. She was born after a normal pregnancy and delivery with spina bifida occulta and spinal dysraphism. She has two healthy sisters. The father had congenital dislocation of the hips and one of the paternal uncles is mentally subnormal. The father and the maternal grandmother were the only members of the family who were known to have had operations, both as adults, with uncomplicated recoveries. The proband had had seven operations between the ages of two weeks and six years, all under general anaesthesia, for the correction of foot deformities and a right eye squint. Four of the operations were followed by uneventful recoveries, but three were followed by nausea, vomiting, myalgia (with on one occasion a recorded creatine kinase activity (CK) of 24 000 U/l), and the passage of 'dark' urine, with spontaneous, full recovery three to five days postoperatively. Inheritance of a gene for malignant hyperpyrexia was excluded in both parents. The child's temperature had never been recorded as higher than 37.5°C, but had been 35°C (axilla) on at least one occasion. She had also had measles, chickenpox, and 'gastroenteritis' that had followed a 'normal' course. However, one month before the present admission she had a 'cold' and because she was febrile the mother had uncovered her for about an hour and had opened the windows. Several hours later the child developed the same symptoms and signs as above.

When admitted the child was well, cheerful, and active. She walked with orthopaedic supports and wore nappies because of frequent incontinence. There was severe wasting of the muscles below the
knees consistent with her spinal cord disorder and she had a right third nerve palsy. The muscle biopsy was performed on the left vastus lateralis under general anaesthesia using etomidate for induction, alfentanil, nitrous oxide in oxygen, and trichloroethylene from a ‘halothane free’ machine for maintenance, under standard hospital theatre conditions. During the 20 minute procedure the child’s extremities were left uncovered. Axilla temperatures varied between 35°C and 36-5°C. The operation and recovery from the anaesthetic were uneventful, but the child remained nauseated and irritable for the rest of the day. The next day she developed a temperature of 37-5°C, complained of pain in the thighs, was noted to have bilateral lumbar tenderness, and started passing ‘dark’ urine. She was treated with intravenous fluids only and by the fifth postoperative day she was well again and the urine was clear.

Detailed histories indicated that the maternal grandmother had had symptoms suggestive of Raynaud’s phenomenon in the fingers for most of her life, and that one maternal uncle developed joint and muscle pains and a rash in cold weather. However, in January 1988, nine members of the family, including the proband, went for the first time on a skiing holiday (in Austria), and encountered low temperatures (fig 1). Seven of them developed acrocyanosis over uncovered noses and cheeks when exposed to the cold, the symptoms being relieved only after several hours in the warmth. The proband was most affected. The mother had, however, stayed indoors most of the time and remained symptom free.

**Initial investigation and results on proband**

**Blood**

Routine preoperative investigations showed normal haematological and biochemical indices except for a slightly raised serum CK activity (83 U/l, reference range 10 to 70). However, on the first postoperative day the CK activity rose to 11 460 U/l (the serum CK activity was 400 U/l one day after performing a muscle biopsy under similar conditions in another young patient) and the white blood cell count was 17-5×10⁹/l (84% neutrophils). The plasma and serum samples received on that day were haemolysed. The blood urea remained normal throughout her hospital stay and postoperative serum creatinine level was normal. Further investigations showed normal clotting studies, fibrinogen degradation products of less than 10 mg/l, insignificant antibody titres to an extensive panel of viruses (including the Epstein Barr virus and mycoplasma pneumoniae), a negative autoantibody screen and IgM cold agglutinins, which, however, reacted at less than 20°C.

**Urine**

A routine mid stream urine (MSU) sample examined before surgery was clear and contained no protein, casts, or cells. A sample received during the first postoperative day contained brown and white granular material, comprising a third of the total volume after centrifugation, and with a clear supernatant. There was no excess of porphyrins. Dipstick (Labsticks, Ames, Slough, UK) analysis showed the presence of heavy proteinuria and haematuria.

Microscopy showed red and white blood cells, granular casts, and large amounts of amorphous deposit. The protein content of the supernatant (biuret method) was 10 g/l. Agarose electrophoresis (Corning Medical, Halstead, Essex) of the whole urine, the x100 concentrated supernatant, and of the sediment showed albumin and α₁, α₂, and β bands with, in addition, a prominent band in the βδ region (fig 2). Immunoelectrophoresis of the whole urine, supernatant, and sediment, using antisera against heavy (Guildhay, Surrey) and light immunoglobulin chains (both bound and free) (Daco, Denmark) and fibrinogen (Daco, Denmark), showed an excess of free light chains around the origin and fibrinogen in the βδ region. Myoglobinuria was excluded by spectroscopy, by electro-
phoresis using a myoglobin marker, and by ammonium sulphate precipitation. A further urine sample obtained on the fifth postoperative day was clear and after concentrating it ×300, only a trace of albumin was found on the electrophoretic pattern with no free light chains or fibrinogen being detected after immunoelectrophoresis (fig 2).

Muscle biopsy histology showed a predominance of type I fibres, with the few type II fibres present being very atrophic. The appearance was consistent with long standing denervation owing to spinal dysraphism.

The detection of free light chains and fibrinogen in the urine on the first postoperative day suggested the possibility of a cryofibrinogenuria and thus cryofibrinogenoemia, and led to a retrospective inspection of both heparin and EDTA plasmas and serum, obtained on the first postoperative day, for cryoproteins. Although the samples had been frozen, a precipitate which could be partially dissolved on warming at 37°C for 30 minutes was noted in both plasmas on thawing but not in serum.

Cryofibrinogen studies on the proband and her family

The proband and, where possible, each member of the family was investigated for the presence of cryofibrinogenoemia on at least three separate occasions in October and November 1987. The proband had been well since her previous admission.

Methods

The blood samples were collected with disposable plastic syringes and 20 gauge needles into 5 and 10 ml plastic and glass screw top bottles containing lithium heparin, EDTA, or no anticoagulant, and transported to the laboratory in a 37°C water bath. They were allowed to clot for three hours at 37°C and were centrifuged at room temperature at 3000 rpm for 10 minutes. Aliquots of each serum, EDTA, and heparin plasmas were stored at 4, 15, 28, 30, 33, 34, 35, 36, and 37°C and examined for the presence of a deposit every half hour. A portion of all the sera and the EDTA and heparin plasmas was also first incubated at 37°C and for half hourly intervals thereafter at temperatures decreasing by 1°C until a deposit was noted or the temperature of 25°C was reached. The time for the precipitate to redissolve completely at 37°C was noted. The precipitation and dissolution of the clots in the same samples were carried out several times. Control blood samples from two healthy volunteers from the laboratory were examined in parallel under identical conditions.

Aliquots of the EDTA plasmas and sera from the patient, her two sisters, and her mother were also electrophoresed at the above temperatures. Scanning densitometry of the plasmas was used to calculate the fibrinogen levels from total protein concentrations. Deposits from their cold EDTA plasmas were also isolated, washed three times in 0.9% saline, dissolved, precipitated again, washed,
and after dissolving in saline immunoelectrophoresed against antisera to IgG, IgA, IgM, and fibrinogen. In addition a washed precipitate from the patient’s EDTA plasma was dissolved in saline, some added to a control EDTA plasma, and two dimensional immunoelectrophoresis carried out on both.

Results

A cryoprotein, precipitating at between 32 and 35°C within one hour of incubation, was noted in the EDTA as well as heparin plasmas, but not sera, from the proband and nine members of her family on each of the three occasions when tested (fig 1). A cryoprotein was also detected in the EDTA and heparin samples from one other member of the family, precipitating within one hour of incubation, but at 28°C (fig 1, table). The precipitates comprised at least a quarter of the sample volume, redissolved totally on warming at 37°C, usually within 30 seconds although larger clots needed up to three minutes, and could be precipitated and redissolved totally several times. No cryoprecipitate was noted in control EDTA and heparin plasmas and sera.

The concentrations of the total fibrinogen in the EDTA plasmas from the proband, her mother, and her two sisters, electrophoresed at 37°C, are shown in the table together with the concentrations of the fibrinogen remaining in solution at decreasing temperatures. At 37°C the total fibrinogen level in all four subjects was significantly higher than the upper limit of the laboratory reference range. In three of them visible clotting was noted at 35°C and in one at 28°C. In all there was a significant fall in the fibrinogen remaining in solution at the relevant temperatures. After immunoelectrophoresis, the washed clots from the samples of the four subjects were confirmed as being fibrinogen, although a faint additional reaction was also noted with IgG antisera. After two dimensional immunoelectrophoresis no difference in electrophoretic mobility between the proband’s cryofibrinogen and the fibrinogen from a control EDTA sample was noted.

Discussion

Although secondary cryofibrinogenemia is relatively common in adults, the primary form is rare. In children both are rare. There have been occasional reports of transient or chronic secondary cryofibrinogenemia, but to our knowledge there have been only two reports of persistent primary cryofibrinogenemia.

Trace amounts of cryoprecipitate in heparin plasma left overnight at 4°C are frequently observed. Although many reasons for that have been suggested, heparin (as anticoagulant in the blood bottle) is thought to be the most important factor. The demonstration of a cryoprecipitate in plasma using other anticoagulants such as EDTA, the possibility of repeated precipitation and dissolution, as well as identification of the clot by immunochemistry, indicate the definite presence of a cryofibrinogen, which, if in a quantity of more than 1 g/l, is of pathological significance. The above could all be found in our study. In addition, parallel examination of control plasmas under identical conditions yielded no cryoprecipitate.

The clinical presentation of the child was unusual. Although we had not excluded other causes for myalgia and nephrotic syndrome, both were transient, occurred after a fall in body temperature, and were thus most likely to have been caused by the cryofibrinogen precipitating in the muscle and renal microvasculature. Cryofibrinogenemia is frequently associated with proteinuria and glomerulonephritis. Persistent cryofibrinogenemia may even cause nephropathy. However, transient heavy proteinuria has been described only once in association with cryoproteinaemia and was thought to be the result of ‘reversible embolism’ of the renal vasculature. Cryofibrinogenuria is also rare, occurring in only 5% of patients with cryofibrino-
genaemia, particularly if, as in our patient, they are also secreting an excess of free light chain immunoglobulins.27

The precipitation of the protein at 35°C was unusual. The highest recorded precipitating temperature to date for cryofibrinogen has been 27°C16 and for cryoglobulin 32°C.28 The latter was detected in the serum of an adult who died postoperatively in acute renal failure because of resulting globulin precipitation in the kidneys. Her lowest body temperature was 34.8°C.

While congenital fibrinogen abnormalities, including afibrinogenaemia, hypofibrinogenaemia, and dysfibrinogenaemia, although rare, are well documented,29-30 familial cryofibrinogenaemia has not been described before to our knowledge. Although this is the first such report, the condition may not be uncommon. Most of the affected members of the family gave no history of symptomatic cryofibrinogenaemia before the study and some did so only after detailed questioning, but all developed acrocyanosis when exposed for the first time to very low temperatures. Though asymptomatic cryofibrinogenaemia is frequently found,5 the paucity of symptoms in our family was surprising, since the fibrinogen precipitating temperatures were high. One of the reasons may have been the rapid dissolution of the clots which was total for larger clots within three minutes and for smaller clots within seconds of warming in vitro. Thus, any precipitate formed in the extremities in vivo may have dissolved rapidly on entering the central circulation. The patient developed serious symptomatic cryofibrinogenaemia, that is, myalgia and lumbar tenderness, only with cooling of large areas of the body when precipitation of fibrinogen may have been more extensive.

The cause of cryofibrinogenaemia is unknown. There may be abnormal synthesis or postsynthetic alterations in the protein.2 Interestingly, while the family studies strongly suggest a dominant pattern of inheritance of the abnormality, both parents of the proband are affected (the child may thus be homozygous for the gene concerned). Although they strongly deny consanguinity, they originate from the Welsh mining valleys where some congenital abnormalities are particularly frequent. Molecular genetic studies on both sides of the proband’s family are in progress, as is the analysis of the amino acid composition of the cryofibrinogen.

The electrophoretic mobility of cryofibrinogen is usually similar to that of normal fibrinogen5 6 as was the case in our study. The clotting studies may be normal,10 as in our proband, or abnormal.11 16 It is often associated with thromboembolic disease of disseminated intravascular coagulation.3 24 There is no correlation between the amount of cryofibrinogen and fibrinogen in the plasma of the same subject examined serially.6 25 However, the proband, her mother, and her two sisters all had raised total fibrinogen levels. They may thus have abnormal both fibrinogen synthesis and clearance from the circulation.

After the diagnosis in the proband, necessary orthopaedic operations which had been postponed will now be carried out since appropriate precautions and therapy can be applied,2 16 17 31 and the awareness of the condition in the proband and family may minimise future possibly life threatening complications.

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