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 Kratochvil\(^1\) coined the term cryofibrinogen to describe a plasma protein which precipitated on cooling and redissolved on re-warming 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,\(^4\)\(^5\)\(^6\) infection,\(^7\)\(^8\)\(^9\) 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 anaesthesia\(^18\) 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 meases, 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 trichloro-
ethylene 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,
never 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 11460 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
17.5×10³/l (84% neutrophils). The plasma and
serum samples received on that day were haemo-
lysed. 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 agglu-
tinins, 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 super-
natant. 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
protein deposit. The protein content of the supernatant
(biuret method) was 10 g/l. Agarose electrophoresis
(Corning Medical, Halsted, Essex) of the whole
urine, the ×100 concentrated supernatant, and of
the sediment showed albumin and α₁, α₂, and β
bands with, in addition, a prominent band in the β\(\delta\)
region (fig 2). Immunoelectrophoresis of the whole
urine, supernatant, and sediment, using antisera
against heavy (Guildhay, Surrey) and light immuno-
globulin 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 β\(\delta\) region. Myoglobin
uria was excluded by spectroscopy, by electro-

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**FIG 1** Pedigree of family showing the subjects
with or without cryofibrinogenenaemia, with or without
cold related symptoms, or with other disease. The
cryofibrinogen precipitating temperatures are indicated.
The proband and, where possible, each member of the family was investigated for the presence of cryofibrinopenaemia 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,
TABLE The fibrinogen content in the same EDTA plasmas from the patient, her two sisters, and her mother, calculated from the peaks obtained after the samples were electrophoresed (with previous incubation at the corresponding temperature for half an hour) on agarose gel at decreasing temperatures. The differences in the fibrinogen amount were thought to reflect the amount of cryoprecipitation occurring during the incubation stage. The albumin levels are shown in parentheses to show the consistency of other protein separations as temperatures fall.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Fibrinogen content in EDTA plasmas (g/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proband</td>
</tr>
<tr>
<td>37</td>
<td>6.72 (42.8)</td>
</tr>
<tr>
<td>35</td>
<td>5.74 (41.0)</td>
</tr>
<tr>
<td>34</td>
<td>5.74 (43.1)</td>
</tr>
<tr>
<td>33</td>
<td>4.40 (44.0)</td>
</tr>
<tr>
<td>32</td>
<td>3.90 (43.1)</td>
</tr>
<tr>
<td>30</td>
<td>3.90 (44.0)</td>
</tr>
<tr>
<td>28</td>
<td>4.90 (43.2)</td>
</tr>
<tr>
<td>25</td>
<td>4.11 (42.0)</td>
</tr>
<tr>
<td>4</td>
<td>3.43 (42.4)</td>
</tr>
</tbody>
</table>

( ) = the concentration of albumin calculated from the albumin peak on the same electrophoretic pattern. The actual albumin concentration measured on Technicon AA II was 43 g/l. The reference range for plasma fibrinogen in the laboratory is 1.46 to 3.8 g/l.

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 antisem. 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 cryofibrinogenenaemia is relatively common in adults, the primary form is rare.5 16 In children both are rare. There have been occasional reports of transient or chronic secondary cryofibrinogenenaemia,8 9 20 21 but to our knowledge there have been only two reports of persistent primary cryofibrinogenenaemia.16 22

Trace amounts of cryoprecipitate in heparin plasma left overnight at 4°C are frequently observed. Although many reasons for that have been suggested,2 23 heparin (as anticoagulant in the blood bottle) is thought to be the most important factor.2 24 The demonstration of a cryoprecipitate in plasma using other anticoagulants such as EDTA,25 the possibility of repeated precipitation and dissolution,17 as well as identification of the clot by immunohemistry,17 indicate the definite presence of a cryofibrinogen, which, if in a quantity of more than 1 g/l,7 17 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. Cryofibrinogenenaemia is frequently associated with proteinuria and glomerulonephritis.12 13 Persistent cryofibrinogenenaemia may even cause nephropathy.12 However, transient heavy proteinuria has been described only once in association with cryoproteinemia and was thought to be the result of ‘reversible embolism’ of the renal microvasculature.26 Cryofibrinogenenaemia is also rare, occurring in only 5% of patients with cryofibrino-
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genemia, particularly if, as in our patient, they are also secreting an excess of free light chain immuno-
globulins.\textsuperscript{27}

The precipitation of the protein at 35°C was unusual. The highest recorded precipitating
temperature to date for cryofibrinogen has been 27°C\textsuperscript{16} and for cryoglobulin 32°C.\textsuperscript{28} The latter was
detected in the serum of an adult who died post-
operatively 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,\textsuperscript{29} \textsuperscript{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 symptom-
atic 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 asymptom-
atic cryofibrinogenaemia is frequently found,\textsuperscript{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
dissolve rapidly on entering the central
circulation. The patient developed serious symp-
tomatic 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 cryofibrinogenemia is unknown.
There may be abnormal synthesis or postsynthetic
alterations in the protein.\textsuperscript{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 homo-
ygous for the gene concerned). Although they
strongly deny consanguinity, they originate from the
Welsh mining valleys where some congenital
abnormalities are particularly frequent. Molecular
study on the 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 fibrinogen\textsuperscript{5} \textsuperscript{6} as was the
case in our study. The clotting studies may be
normal,\textsuperscript{10} as in our proband, or abnormal.\textsuperscript{11} \textsuperscript{16} It is
often associated with thromboembolic disease of
disseminated intravascular coagulation.\textsuperscript{3} \textsuperscript{24} There
is no correlation between the amount of cryofibrino-
gen and fibrinogen in the plasma of the same
subject examined serially.\textsuperscript{6} \textsuperscript{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,\textsuperscript{2} \textsuperscript{16} \textsuperscript{17} \textsuperscript{31} and the aware-
ness of the condition in the proband and family may
minimise future possibly life threatening complica-
tions.

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