weeks plasma total thyroxine and thyroid stimulating hormone concentrations were normal. He had no diarrhoea or allergic symptoms and was more active and lively. Iodine supplements were stopped. After eight weeks his response to thyrotrophin releasing hormone was normal. He had gained 1·5 kg in weight and 2·0 cm in height.

Comment

The reversal of hypothyroidism in this child within eight weeks of a normal diet including cows' milk being reintroduced suggests that inadequate iodine intake was the cause of his hypothyroidism. Cows' milk and dairy products are an important source of dietary iodine.[2] Their exclusion from his diet coupled with the consumption of large amounts of soya milk, which has been reported to cause hypothyroidism by increasing faecal loss of thyroxine,[3] were probably the cause of the illness. The dramatic increase in growth rate after reintroduction of a normal diet suggests that his previous diet caused his growth failure either indirectly, due to hypothyroidism, or directly, due to undernutrition.

The criteria for diagnosing intolerance to cows' milk or multiple food allergy are strict.[4] Unorthodox procedures , usually used by doctors operating from private allergy clinics or centres of alternative medicine, have not been validated objectively, and their use has been criticised.[5] This case shows that the inappropriate use of restrictive diets may lead to iatrogenic illness.

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Necrosis of skin induced by coumarin in a patient deficient in protein S

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Necrosis of the skin induced by coumarin is a rare complication of oral anticoagulation that generally occurs in the initial phase of treatment. Why this process is localised to the skin remains unexplained. An association has been described between skin necrosis induced by coumarin and protein C deficiency.[1] Protein C depends on vitamin K and exerts its anticoagulant effect by proteolytic inactivation of the clotting cofactors Va and VIIIa.[2] Protein S, which also depends on vitamin K, acts as a cofactor for activated protein C.[2]

In the initial phase of oral anticoagulation the concentration of protein C falls more rapidly than that of the other vitamin K dependent factors (except factor VII), resulting in a transient hypercoagulable state. This is more pronounced in patients deficient in protein C and is probably responsible for the development of thrombi in the microvasculature of the skin. We report a case of skin necrosis induced by coumarin in a patient with functional deficiency of protein S and normal concentrations of protein C.

Case report

A 63 year old man, operated on for an aneurysm of the left superficial femoral artery, developed necrosis of the toes postoperatively. Prophylactic intravenous heparin was given and, after two days, replaced by nicoumalone at the following daily doses: 6, 4, 3, 3, 1, 1, and 2 mg. Three days later he developed a large ecchymosis over the left elbow (25×15 cm) and a smaller one on the extensor surface of the right foot that rapidly became necrotic. Nicoumalone was stopped and subcutaneous heparin introduced; the lesions healed slowly.

On two occasions thereafter, oral anticoagulation was started at low, gradually increasing doses in combination with therapeutic doses of heparin according to a scheme recommended for patients with protein C deficiency.[3] On the first occasion nicoumalone was introduced at 2 mg daily and no further necrosis occurred, whereas on the second occasion it was restarted at 3 mg daily and a small recurrence of necrosis was observed. On day 73 after the onset of skin necrosis his left leg was amputated above the knee. The table shows the results of laboratory investigations of plasma samples obtained on days 8, 15, 79, and 142.

Coagulation variables and C4b binding protein concentration in patient with skin necrosis induced by coumarin

Variable	Normal range (mean ±2SD)	Time after onset of necrosis (days)			
		8	15	79	142*
Thromboplastin time (%)	70-140	65		95	22
Activated partial thromboplastin time (s)	26-36	33		34	41
Antithrombin III activity (%)	80-120	120	120	115	105
Protein C activity (%)†	70-140		120	125	
Protein C antigen (%)‡	63-134	115	120	115	60
Total protein S antigen (%)‡§	56-150	62	70	75	23
Free protein S antigen (%)‡	52-157	<1	<1	<1	<1
C4b binding protein antigen (%)‖	68-140	200	195	220	100

*Patient being treated with oral anticoagulants.
†Measured by chromogenic assay after activation with *Agkistrodon contortrix* snake venom (Behring, FRG).
‡Measured by enzyme linked immunosorbent assay (ELISA) (Stago, France).
§To promote dissociation of protein S/C4b binding protein complex, samples were diluted 400-fold and incubated for 18 hours at room temperature before testing.[4]
‖Measured by rocket immunoelectrophoresis.

Comment

Skin necrosis induced by coumarin has been described in association with protein C deficiency.[1] In our patient, however, protein C antigen and activity values were normal. Concentrations of total protein S antigen were at the lower limit of the normal range when the patient was not being treated with coumarin and below normal during stable anticoagulation (day 142).[4] The free (active) portion of protein S was consistently below the limit of detection of the assay. The skin necrosis was therefore associated with a functional protein S deficiency.[5] In 10 members of the patient's family no abnormalities were found in protein S concentrations.

Concentrations of total protein S at the lower limit of the normal range could not explain the almost complete absence of free (active) protein S. In normal plasma there is an equilibrium between the free (active) form (about 40%) and its complexed (inactive) form

(about 60%) with C4b binding protein. The concentrations of this protein were twice the reference values but became normal after the leg was amputated and the clinical condition stabilised (day 142). This may have been due to the reactant behaviour of this protein in the acute phase.[2] The concentrations of free (active) protein S calculated from total protein S and C4b binding protein with a dissociation constant of $0{\cdot}7\times10^{-7}$ mol/l for the protein S/C4b binding protein complex[4] agreed with those measured. This confirmed protein S deficiency as we found moderately decreased concentrations of protein S and a shift from its free form to the complexed form with C4b binding protein.

As protein S is necessary for the anticoagulant activity of protein C, a decrease in the functional concentration of protein S may have the same consequences as a defect of protein C. Possibly in our patient the functional protein S deficiency was important in the pathogenesis of the skin necrosis induced by coumarin.

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Screening for hepatitis B and vaccination of homosexual men

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Adler *et al* concluded that screening for and vaccination against hepatitis B virus among male homosexuals were worth while and cost effective.[1] The diminished response to the vaccine of homosexuals positive for HIV has, however, complicated the issue.[2] We conducted a postal survey to find out about the use of hepatitis B vaccines and the management of hepatitis B virus infection in genitourinary medicine clinics in the United Kingdom.

Patients, methods, and results

In January 1988 we posted a questionnaire to the 129 consultants in charge of all the genitourinary medicine clinics in the United Kingdom as listed in the revised list of sexually transmitted diseases clinics issued by the Department of Health and Social Security in August 1985. The 19 questions were designed to determine whether all homosexual and bisexual men attending the clinics were routinely screened for hepatitis B surface antigen; whether, if they were positive for the antigen, they routinely underwent liver function tests; and whether those with abnormal liver function were referred to a doctor with a specialist interest in hepatitis B. Other questions were aimed to assess policy on vaccination of homosexual and bisexual men without markers of hepatitis B virus infection and views on the impact of HIV infection, safer sex, and the recombinant hepatitis B vaccine. The format of the questionnaire was such that we were not aware of exactly where the respondent worked.

The responses were coded according to yes, no, don't know, and no response; analysed with the statistical package for the social sciences X program; and subdivided according to whether they came from London or the rest of the United Kingdom. Altogether 121 (94%) clinics replied within eight weeks; 18 of the 19 London clinics and 103 of the 110 clinics in the rest of United Kingdom responded.

Ninety eight (81%) of the clinics screened for hepatitis B surface antigen, but, surprisingly, only 13 of the 18 London clinics did so. Sixteen of the London clinics (89%) compared with 70 of the clinics in the rest of United Kingdom (69%) requested liver function tests for subjects positive for hepatitis B surface antigen and referred patients with abnormal liver function, whether or not they were positive for HIV. Vaccination of subjects negative for hepatitis B surface antigen was advised in only 76 of 119 clinics. Eight of the 10 Scottish clinics but only 10 of 17 London clinics routinely advised vaccination.

Only 36 of all the clinics in the United Kingdom offered vaccination, including seven of the 10 Scottish clinics. A higher proportion (13/16) of London clinics performed tests for immunity, measuring antibodies to hepatitis B surface and core antigens before vaccination (51/88). Over half (63/120) of all clinics had no preference for the type of hepatitis B vaccine, but among those with a preference the recombinant vaccine was the most popular (41/57). Forty five clinics did not offer vaccination because it was not available locally. Sixty three of the 75 clinics that did not offer vaccination advised their patients to seek vaccination from their general practitioners.

Sixty three clinics thought that homosexuals positive for HIV should not be vaccinated against hepatitis B. One hundred and seven thought that vaccination of susceptible homosexuals was necessary despite the onset of the AIDS epidemic, and most (93) considered it necessary even if the patient was practising safer sex. In areas where hepatits B virus and HIV are less prevalent, however, contrary views were often held.

Comment

There is a striking discrepancy between current recommendations on vaccination against hepatitis B virus[3] and actual clinical practice, with noticeable differences between London and the rest of the United Kingdom. A more vigorous programme of screening and vaccination in the genitourinary medicine clinics would reduce acute and chronic hepatitis B virus infection in susceptible homosexual and bisexual men.[3]

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