

Original articles

A connective tissue disorder similar to vinyl chloride disease in a patient exposed to perchlorethylene

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Summary

A patient is reported who had a connective tissue type of disease clinically similar to vinyl chloride disease. It is suggested that this may have been caused by abnormal sensitivity to perchlorethylene to which he was exposed in his occupation.

Case report*

A 19-year-old Caucasian male complained of constant coldness of the hands and feet for 3 months. On exposure to low temperature, his fingers and distal parts of his feet would develop white and blue discolouration, but would not become red on rewarming. Soon afterwards it involved all his fingers, the distal half of the palms, the feet, knees, elbows and even the tongue on very cold days. For the same period of time he had noticed weakness, stiffness and aching of the muscles of his arms, shoulders and legs, especially in the morning. Weights which he had previously lifted with ease seemed too heavy, and he could not stand from a squatting position. His fingers had become swollen and he could no longer grip tightly. He also developed impotence.

He had had alopecia areata intermittently since the age of 5 years, and at 14 developed alopecia totalis which persisted for 5 years before almost complete regrowth took place spontaneously. He had never been jaundiced. His paternal grandfather had symptoms suggestive of Raynaud's phenomenon, and his paternal uncle had had alopecia as a child.

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When he left school aged 15 years, he worked in a dry cleaning business. Most of the time was spent in pressing clothes, but once a week he assisted in cleaning the drums which he contained solvent (perchloroethylene). During this activity, which lasted a few minutes, he described heavy exposure to the fumes, which often left him lightheaded, dizzy and very sleepy after work. Others employed at work had experienced symptoms like this. The work premises were examined by the factory inspectors, who found on a random visit that the ambient levels of perchloroethylene were within safe limits. However measurements were not made during or shortly after drum cleaning. Other workers there were not examined.

On examination his hands and feet were markedly cold with variable mottled pallor and cyanosis. The lower legs and arms were involved to a lesser extent, and transient pallor of one side of his tongue was observed on exposure to cool external temperature (10°C). The skin of the hands was diffusely swollen and thickened, but changes suggestive of systemic sclerosis such as tapering of the fingers, telangiectasia and loss of finger pulps and skin appendages were absent. Multiple nail fold haemorrhages were prominent. His scalp hair was normal, but there was some patchy hair loss on the limbs. There was an area of depigmentation on the scrotum. Peripheral pulses were normal. No other abnormality was detected in the cardiovascular system, or in the respiratory, gastro-intestinal, genito-urinary or central nervous system. There was considerable muscular weakness, with some wasting and tenderness particularly of the proximal limb muscles. Inability to flex or extend the fingers fully was combined with some loss of power in the grip. Muscle tone and co-ordination were normal as were the tendon reflexes, and there was no fasciculation.

Investigations

The chief abnormalities were found in the patient's immune system, hepatic and musculoskeletal functions.

Antinuclear factor was strongly positive on several occasions, titre 1 in 10, 240, with a speckled pattern of fluorescence. Plasma protein electrophoresis was normal, but immunoglobulin levels showed a borderline high IgG at 1700 mg/ml (normal range 800–1700), absent IgA (140–400) and normal IgM at 120 mg/ml (50–200). No LE cells were found and no cold agglutinins, cryoglobulins, smooth muscle or antimitochondrial antibodies could be demonstrated. Circulating immune complexes were also not found. Levels of C₃, C₄ and DNA binding were normal.

Although serum bilirubin and alkaline phosphatase were normal, the serum gamma-glutamyl transpeptidase level was raised at 75 I.U./litre (normal level <54); bromsulphthalein retention was increased being 21% at 25 and 45 min; the prothrombin time was 16 secs (control 12) and the kaolin cephalin time 41 s (control 34). This was taken to be indicative of a mild hepatitis. Liver biopsy was performed at the same time but appeared normal histologically. Electromyography showed evidence of a myopathy. Serum creatine phosphokinase levels were increased, ranging from 117 to 162 units/litre (normal <90). Muscle biopsy showed a lymphocytic infiltrate between the muscle bundles. The urinary hydroxyproline excretion was raised at 55 mmol/mol creatinine (normal <39) suggesting a possible increase in collagen turnover. A right brachial arteriogram showed occlusion of the palmar digital

artery adjacent to the 2nd metacarpal. Histological examination of a skin biopsy taken from an affected finger showed some blood vessels to have mildly oedematous walls and to be surrounded by a sparse round cell infiltrate. There were no changes of scleroderma present.

Other normal findings included: Blood: haemoglobin, white cell differential, platelet count, ESR (5-10) urea, electrolytes, calcium, phosphate, sugar, uric acid, Coombs' test, latex test, TPHA, RPR, fibrin degradation products.

Urine: Urinalysis, creatinine clearance.

X-rays: Chest, abdomen, hands, feet, sacroiliac joints, barium swallow.

Treatment and progress

A trial of tolazoline and later phenoxybenzamine, did not lead to any clinical improvement, nor did a period of 6 weeks off work. Prednisolone 20 mg daily led to a rapid increase in well-being, disappearance of myalgia, improvement in muscle power and a decrease in swelling of the fingers. The serum creatine phosphokinase and liver function tests returned to normal. There was, however, no improvement in the Raynaud's phenomenon.

Discussion

This young man had an 18-month history of polymyopathy, severe acrocyanosis and a mild hepatic disorder. It would appear that his clinical features fall within the broad category of collagen disorders, but do not conform exactly with any of the classical patterns; in particular it was unlike systemic sclerosis in many respects. The features were similar to those of 'mixed connective tissue disease', (Sharp *et al.*, 1972) and the high titre of antinuclear antibody showing a speckled pattern was in favour of this. However, in this condition joint symptoms are prominent, and there are typical sclerodermatous skin changes. Raynaud's phenomenon is usually not as severe as in this case and lymphadenopathy and oesophageal involvement are common. Standard biochemical tests demonstrated an abnormality of liver function. Chronic active hepatitis was considered as a cause, but was thought to be unlikely in view of the normal liver biopsy. Perchloroethylene may have been responsible as it is known to be hepatotoxic (Von Oettingen, 1964; Meckler & Phelps, 1966).

A number of workers engaged in the polymerization of vinyl chloride to polyvinyl chloride (PVC) have been observed to develop a syndrome, the main features of which are Raynaud's phenomenon, skin changes and osteolytic lesions chiefly in the fingers. For some years it was called 'occupational acro-osteolysis', but recently this term has been abandoned in favour of 'vinyl chloride disease' as it has been shown to be a multisystem disorder in which the bones are not necessarily affected (Lange *et al.*, 1974). Involvement of the liver, lungs and muscles has been reported and there is also evidence of an immune disturbance. Angiosarcoma of the liver, which occurs in vinyl chloride workers, does not affect this particular group of patients. Hitherto this syndrome has not been found in workers in other industries.

In this condition changes in the skin of the hands may be striking, with diffuse thickening and an inability to flex or extend the fingers fully, combined with severe, but variable acrocyanosis. Dermal nodules have been described, but true sclerodermatous changes are absent.

Histological examination of the skin may show thickening of collagen bundles and disorganization of elastic fibres, or merely a perivascular lymphocytic infiltrate in early cases (Walker, 1976a). Lange's (1974) series of patients had thrombocytopaenia, splenomegaly, abnormal liver function with periportal fibrosis and pulmonary insufficiency. Osteolytic lesions of the terminal phalanges of the hands and sometimes of the feet and pelvic bones were previously thought to be an essential feature of the syndrome, but in Walker's series of 5 patients, only two had this change (Walker, 1976b). Her patients also had undue fatigue, limb pains, dyspnoea and impotence. Brachial arteriograms showed narrowing of digital vessels. Cryoproteins were common, and creatine phosphokinase was sometimes raised (Walker, 1975, 1976a). Further studies on the same group of patients have led to the suggestion that vinyl chloride may alter IgG molecules, allowing them to become antigenic with subsequent antibody production and complex formation (Milford Ward *et al.*, 1976).

Vinyl chloride disease is almost entirely restricted to those who clean the reactors in which polymerization takes place, but the incidence is low, for example, only 3% in the study of Wilson *et al.* (1967). This may be partly a dosage effect, but there is also some evidence of personal idiosyncrasy. Although over 200 different compounds including perchlorethylene (Moulin *et al.*, 1974) may be used or produced during the course of PVC formation, it is now thought that vinyl chloride itself is the aetiological agent. However, it is impossible to completely exonerate other chemicals and Dinman *et al.* (1971) suggested that the disease might be caused by several agents, each producing a component of the clinical picture.

The most striking similarity between our patient and those with vinyl chloride disease was the severe acrocyanosis and changes in the skin of the hands. Polymyopathy, mild hepatitis and impotence were also common features, as was the immunological disturbance. Anti-nuclear antibody has sometimes been reported as positive in vinyl chloride disease, although not in such a high titre. Arteriograms in both cases have shown narrowing of digital vessels. Among clinical differences were the lack of osteolytic lesions, the presence of multiple nail fold haemorrhages and the absence of circulating cryoproteins.

Our patient had never been exposed to vinyl chloride, but the chemical likeness between vinyl chloride ($\text{CH}_2 = \text{CHCl}$) and perchlorethylene ($\text{CCl}_2 = \text{CCl}_2$) suggests that the latter may have some of the actions of the former. Although vinyl chloride is a very reactive chemical and perchlorethylene a relatively inactive one, these and other small chlorinated hydrocarbons have certain toxic effects in common. They are anaesthetics and are hepatotoxic (Rowe *et al.*, 1952; Browning, 1965). Experimentally, they cause damage to peripheral nerves (Rumsby & Finean, 1966). Perchlorethylene is regarded as relatively free from these toxic actions, but chronic exposure has been shown to damage the liver and nervous system. Coler & Rossmiller (1953) found definite evidence of abnormal liver function in 4 of 7 workers in a degreasing plant using perchlorethylene. The Threshold Limit Value which indicates acceptable concentration has been reduced from 200 to 100 parts/ 10^6 in Great Britain, and in other countries is as low as 37 parts/ 10^6 (Czechoslovakia) and 7 parts/ 10^6 (USSR). (American Conference of Industrial Hygienists, 1974).

One of Lob's (1957) nine cases of chronic perchlorethylene poisoning had certain clinical features similar to our own. This patient had fatigue, myalgia, variable cyanosis of the finger tips (Raynaud's phenomenon) and biochemical evidence of hepatic dysfunction. Another

similar case was that of Reinl (1957). This was a young woman who had been exposed to trichlorethylene for 2 years, when she developed Raynaud's phenomenon and later sclerodermatous changes on the skin of the face and limbs with inability to extend the fingers. The paucity of reports of cases similar to our own does not exclude our patient being abnormally sensitive to perchlorethylene, for example through an idiosyncrasy in biochemical handling or through a pre-existing abnormality of his immune system. The latter is suggested by his long-standing alopecia areata and vitiligo and absent IgA, which may be associated with autoimmune disease (Hobbs, 1968). Although halogenated hydrocarbons have not been reported as causing a lupus erythematosus-like syndrome, this can give a picture very like that of our case, with myalgia, hepatitis, Raynaud's phenomenon and antinuclear antibodies (often in high titre). In procainamide-induced LE and in vinyl chloride disease it has been suggested that the chemicals in question combine with body proteins to render them antigenic (Blomgren, Condeemi & Vaughan, 1972; Milford Ward *et al.*, 1976). We suggest that perchlorethylene may have caused or exacerbated our patient's disease, possibly by an alteration of his immune system.

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