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Neuromuscular disease in patients with steatorrhoea[1]

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EDITORIAL COMMENT This report stresses that chronic muscle wasting, paralysis, and sensory loss may accompany or precede steatorrhoea. Gluten hypersensitivity may or may not be a feature of this syndrome in which the steatorrhoea is characteristically severe and refractory to treatment.

Although the association of neuromuscular disorders with steatorrhoea was recognized long ago (Woltman and Heck, 1937), it is not widely appreciated that some patients with steatorrhoea have disabling neuromuscular symptoms which sometimes overshadow or may even precede their digestive complaints. We describe here four patients with steatorrhoea with marked muscle weakness and wasting in whom neurological signs and symptoms were particularly prominent, and suggest that in every patient with a neuromyopathy of undefined origin steatorrhoea ought to be considered.

CASE REPORTS

A.J. A.J. was a 60-year-old white male admitted to the Yale-New Haven Hospital for the eighth time in September 1965. He had first noted the onset of pain and numbness in his feet in 1958, and soon thereafter experienced difficulty in walking and marked weakness in both lower legs. Neurological examination at that time revealed decreased muscle strength distally in both legs, absent deep tendon reflexes, and absent vibration sense below the neck without any other sensory disturbances. The only laboratory abnormality was a cerebrospinal fluid protein level of 280 mg.% without pleocytosis. A diagnosis of atypical polyneuritis was made. No evidence of carcinoma, diabetes mellitus, or other systemic disease was found.

Over the next three years, the sensory impairment persisted and he continued to have severe motor weakness of the arms and legs, particularly distally. Prolonged corticosteroid administration was of no benefit and was discontinued in 1963. No gastrointestinal symptoms of any kind were noted other than those associated with acute cholecystitis in 1961.

In May 1964, he was readmitted for evaluation of diarrhoea of three months' duration. He had noted an increase in abdominal girth and pedal oedema associated with eight to 12 non-bloody bowel movements a day. His neurological status remained unchanged. He was then a wasted, chronically ill man. The skin was pigmented. Prominent ascites and 2+ pedal oedema was present. Marked symmetrical distal muscle wasting and paralysis was present with absent deep tendon reflexes. There was a marked diminution in position and vibratory sensation over the lower extremities. No pathological reflexes were elicited.

An initial attempt to perform a jejunal biopsy was unsuccessful and the patient would not permit a second attempt. Liver and lymph node biopsies were not diagnostic. Because laboratory studies (Table I) suggested a general malabsorption syndrome, it was decided to try the effect of a gluten-free diet. Diarrhoea stopped promptly after the gluten-free diet was started. A jejunal biopsy, obtained three weeks later, demonstrated blunting and shortening of the villi, with crypts increased in depth and a slight increase of mononuclear cells in the lamina propria. In order to test whether the patient truly had gluten-induced enteropathy, he was given gluten-containing foods once again with prompt recurrence of diarrhoea. Thereafter he was treated with a gluten-free diet.

He was not seen until his final admission one year later when he complained of anorexia and weight loss. He was markedly cachectic. Neurological findings were unchanged from the previous year. He died suddenly on the day following admission.

R.J. R.J. was a 50-year-old white male admitted to the Yale-New Haven Hospital in September 1964 for the sixth time. From 1953 to 1960 he had noted intermittent episodic, non-bloody diarrhoea. In 1961, the diagnosis of non-tropical sprue was finally made when he was admitted because of massive oedema. Severe malabsorption was present (Table I). Jejunal biopsy demonstrated villous atrophy (Fig. 1). The surface epithelium was infiltrated with polymorphonuclear leucocytes and several 'crypt abscesses' were present.

Marked improvement followed the introduction of a gluten-free diet; however, a few months later the onset of explosive watery diarrhoea necessitated two short admissions. Over the next three years despite adherence to the gluten-free diet and treatment with corticosteroids,

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TABLE I

SUMMARY OF LABORATORY EXAMINATIONS

	Date	Serum Carotene (μg. %)	Urine d-Xylose (g./5 hr.)	72-Hour Stool Fat (% absorbed)	Schilling Test (% excretion)	Serum Tocopherol [2] (μg. %)	Electromyogram	Neurological Status	Ceroid-like Material in Smooth Muscle	Evidence of Myopathy
R.J.	3-61	11	1·9	78		—	—		Not present	—
	10-64	61	1·6	38	1·0	104	Neuropathy	Peripheral muscle weakness absent D.T.R.s	Present	Yes
A.G.	9-61	44	1·7	75		—	—	—	Not present	—
	[1]	80	—	92		—				
	1-65	22	3·1	61		84		—	Present	—
	2-66	9	—	50	10·5	224	Neuropathy	Marked muscle weakness and wasting; paraesthesias; absent D.T.R.s	—	No
	[2]	14	—	—		954	—	No change	—	—
	[3]	12	—	—		603	—	No change	—	—
A.J.	6-64	42	0·7	—		—	Neuropathy	Muscle weakness, paresis, diminished D.T.R.s and sensory perception	Not present	Yes
		96	4·0	91	11·6					
P.M.	4-66	3	5·5	25	13·8		Neuropathy	Some muscle weakness; paraesthesias and hyperalgesia	Not present	No
Normal		>70	>5·0	>94	>8	500-1,000	—	—	—	—

[1]On tetracycline.
[2]After one month of tocopherol acetate 100 I.U. intramuscularly.
[3]One month after cessation of parenteral tocopherol.
[4]After one month on gluten-free diet

he had frequent episodes of explosive watery diarrhoea, and he gradually lost about 40 pounds in weight.

He was admitted for the final time in 1964 following an acute exacerbation of diarrhoea. Laboratory evidence of severe malabsorption was present. Despite a rigid gluten-free diet, he continued to have frequent, watery, foul-smelling stools in the hospital, and therefore, exploratory laparotomy was performed in October 1964. There was marked brown discoloration of the serosal surface of the small intestine, and *Pneumocystoides intestinalis* was noted, but no other abnormalities were encountered. Microscopically, ceroid pigment was found in the muscularis. He recovered uneventfully, but diarrhoea persisted. From this time, until his death in December 1964, his principal problem was a severe peripheral neuropathy with marked muscle weakness bilaterally. Neurological examination revealed intact cranial nerve function. Gross generalized weakness of the motor system was present with absent deep tendon reflexes. No pathological reflexes were elicited. Decreased vibration and position sense of the lower extremities was marked. Electrodiagnostic studies revealed normal motor nerve conduction velocities, but diminished amplitude of sensory nerve fibre response. An electromyogram showed non-specific alterations. The patient suddenly expired following a massive haemoptysis on December 15.

A.G. A.G. was a 28-year-old white male admitted to the Yale-New Haven Hospital for the seventeenth time in February 1966, because of severe debilitating peripheral neuropathy. The patient had had repeated intermittent episodes of abdominal cramps since the age of 10, along with intermittent diarrhoea. In 1958, an acute episode of abdominal pain with signs of peritonitis led to a laparotomy and biopsy of a thickened region of the mesentery revealed a congenital jejunal diverticulum. Post-operative *x*-ray films revealed multiple jejunal diverticula. From 1960 to the time of death diarrhoea was a chronic problem and evidence of malabsorption was demonstrated repeatedly (Table I). Jejunal mucosa was normal. A low fat diet had been more successful in decreasing steatorrhoea than any other measures, including the intermittent use of tetracycline and other antibiotics.

Because of an increasing partial intestinal obstruction and persistence of diarrhoea, in January 1965, resection of approximately a foot of proximal jejunum containing at least 15 diverticula was carried out in the hope that the removal of a large region of stasis might relieve diarrhoea. There was, however, no significant improvement in either the diarrhoea or the abdominal cramps.

In 1958, the patient first noted the occurrence of paraesthesias and muscle wasting. At that time the question of arsenic poisoning was raised by the finding of arsenic in the urine on one occasion. Over the years no further evidence of arsenic has ever been found in multiple urine samples and whether the first urinary arsenic determination was significant cannot be ascertained. The neuropathy improved, only to recur in 1964 and to become much more severe in the fall of 1965. Thereafter, severe paraesthesias and cramps were present.

Marked muscle weakness and inability to perform movements with the fingers were prominent. Neurological examination demonstrated marked generalized symmetrical muscle weakness, proximal greater than distal, with marked atrophy of muscle groups and absent deep tendon reflexes. No abnormal reflexes were elicited. Vibration and position sense of the extremities was absent. There was also an inability to move the eyes.

Findings on electrodiagnostic studies, including an electromyogram, were interpreted as being consistent with a peripheral neuropathy. The course was unaffected by parenteral administration of pyridoxine, vitamin B_{12}, folic acid, thiamine, and other B complex vitamins. One month of tocopherol acetate (100 I.U.) parenterally did not lead to any improvement although there was a decrease in the sensitivity of erythrocytes to haemolysis in the presence of hydrogen peroxide and an elevation of the serum tocopherol.

The patient died after a continuing chronic course marked by severe debilitating peripheral neuropathy manifested by marked muscle weakness, paraesthesias, and muscle cramps. No necropsy was obtained.

P.M. P.M. was a 39-year-old white male admitted for evaluation of diarrhoea and weight loss in April 1966. In 1958, the patient had a severe episode of abdominal pain diagnosed at another hospital as acute pancreatitis. He had not had any further episodes of abdominal pain, but over the ensuing eight years he had gradually lost 90 pounds. Diabetes mellitus was diagnosed in January 1962, following a period of polydipsia, polyuria, and weight loss. Diarrhoea first occurred in 1964.

In the year before admission he had continued to lose weight and to have about 20 watery, loose bowel movements daily. He had little control over his bowel movements when the stools were loose and he had frequent nocturnal accidents. He had increasing generalized weakness and had difficulty in rising from a squatting position. Paraesthesias were present in the legs for two years.

On examination he was a chronically ill white male. Significant physical findings included a palpable liver 4 cm. below the right costal margin. Retinopathy was not found. Neurological examination revealed hyperalgesia of both feet and decreased proprioception in the lower extremities. Electrodiagnostic studies confirmed the clinical impression of a peripheral sensory neuropathy. A muscle biopsy of one of the quadriceps muscles revealed no significant microscopic abnormalities.

Laboratory studies indicated a severe fat malabsorption (Table I). A secretin test demonstrated a normal volume and low bicarbonate concentration (less than 15 mEq./l.). Serum amylase and lipase determinations were normal.

Pancreatic supplementation (Cotazym) resulted in a dramatic decrease in faecal fat excretion and decrease in bowel movements to four semi-formed stools a day. The patient was discharged on a low-fat diet with vitamin supplementation and pancreatic extract.

PATHOLOGY

SMALL INTESTINAL BIOPSIES Patients A.G. and P.M. had normal jejunal mucosa obtained by peroral biopsy. The only peroral biopsy in A.J. was obtained three weeks after the institution of a gluten-free diet, yet even then the mucosa was not normal. The villi were shortened with increase in the height of the crypts and there was a mild infiltrate of mononuclear cells in the lamina propria. Several biopsies obtained from the small intestine of R.J. (Fig. 1) all demonstrated similar features. Normal villi were never seen. The surface epithelium was cuboidal and infiltrated with polymorphonuclear leucocytes. In several regions there was destruction of crypts with the formation of 'crypt abscesses'. These features are atypical for non-tropical sprue.

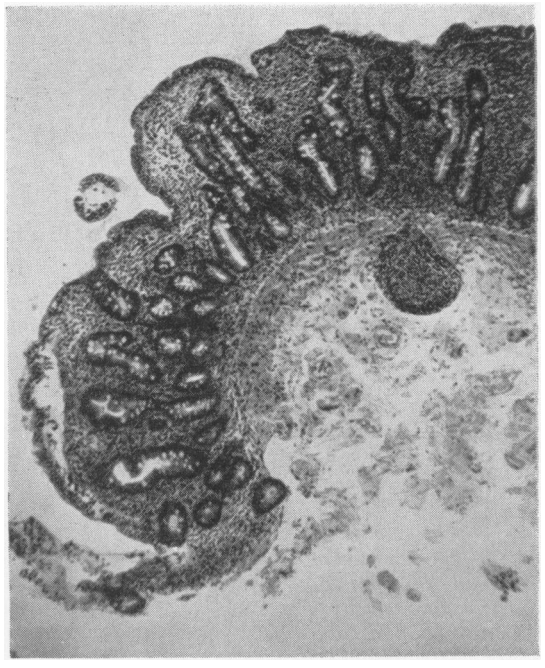

FIG. 1. *Peroral jejunal biopsy (R.J.) demonstrated severely blunted villi, abnormal surface epithelium, and heavy infiltrate in lamina propria. Haematoxylin and eosin: original magnification* × *35.*

SMOOTH MUSCLE P.A.S.-positive material was found in the smooth muscle of the small intestine of two of the four subjects. The P.A.S. positive granules were present in such great number as to lead to a brown discoloration of the serosal surface ('brown bowel') (Toffler, Hukill, and Spiro, 1963) in R.J. This material has been found in experimentally-induced tocopherol-deficient animals (Mason and Emmel, 1945).

SKELETAL MUSCLES, PERIPHERAL AND CENTRAL NERVOUS SYSTEMS While a muscle biopsy was un-

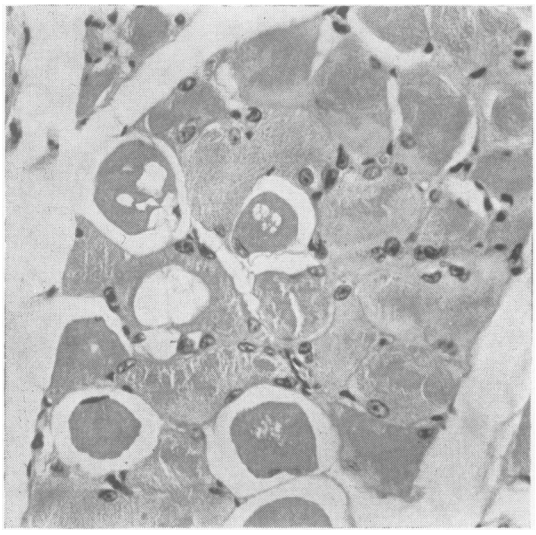

FIG. 2. *Cross section of diaphragm (A.J.) showing variation in size of muscle fibres, proliferation of sarcolemmal nuclei, and vacuolar changes in the sarcoplasm of some fibres. No leucocytic infiltrate or fibrosis is seen. Haemotoxylin and eosin: original magnification* × *250.*

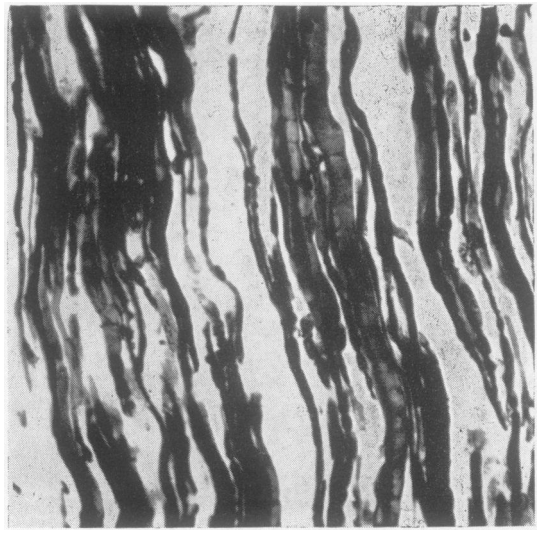

FIG. 3. *Longitudinal section of peripheral nerve (R.J.) with patchy, focal demyelination without reaction. Beading of the myelin is seen. Schroeder modification of Weigert stain for myelin, frozen section: original magnification* × *100.*

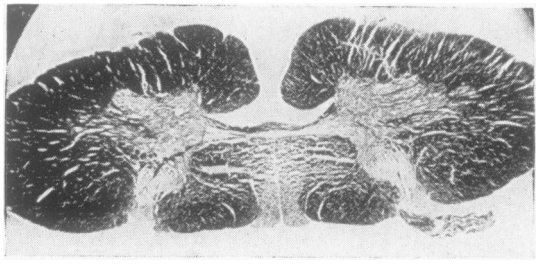

FIG. 4. *Cross section of cervical spinal cord (A.J.) showing demyelination in the dorsal columns limited to the fasciculi gracili. Schroeder modification of Weigert stain for myelin, frozen section: original magnification* × *5.*

revealing in one case (P.M.), in two subjects examination of skeletal muscle showed changes consistent with a myopathy and were characterized by marked variation in muscle fibre size in all bundles, proliferation of sarcolemmal nuclei, and occasional vacuolization of muscle fibres (Fig. 2). There were no leucocytic infiltrates and no fatty change, although fibrosis was noted in the more severely affected muscle bundles. In addition, a patchy focal demyelination of the peripheral nerves without cellular response or leucocytic infiltrate was seen in two cases (A.J. and R.J.) (Fig. 3), together with demyelination of the fasciculi gracili in one case (A.J.) (Fig. 4).

In light of the clinical neurological findings, it appears that the demyelination seen in the peripheral nerves was confined to sensory fibres. This supposition is not contradicted by the electrodiagnostic studies and is substantiated by the findings in the spinal cord (A.J.) of demyelination of the fasciculi gracili with intact anterior horn neurones and a pattern of muscle damage reflecting a primary myopathic process, rather than changes secondary to nervous system disease, *i.e.*, anterior horn (motor neurone), anterior root, or motor nerve. Together, then, we have the unusual combination of a sensory neuropathy and primary myopathy, both presumably related to nutritional deficiency. Similar changes in skeletal muscle have been described in tocopherol-deficient animals (Century and Horwitt, 1960).

DISCUSSION

In all four patients the steatorrhoea was persistent, massive, and refractory to all forms of therapy. Possibly as a consequence, the neurological disease did not improve. Our patients differed from the usual patients with steatorrhoea in their refractory and progressive course.

How often neurological signs and symptoms occur in patients with steatorrhoea of any cause is difficult to ascertain. To some extent the incidence of neuro-

muscular abnormality varies with the cause of the steatorrhoea. Neurological symptoms are rare in patients with coeliac disease and chronic pancreatitis (Parsons, 1932; Haas and Haas, 1957; Dreiling, Janowitz, and Perrier, 1964), but are relatively frequent in patients with steatorrhoea secondary to multiple jejunal diverticulosis or the 'blind loop' syndrome (Cooke, Cox, Fone, Meynell, and Gaddie, 1963; Badenoch, 1958). Here, of course, neuromuscular dysfunction may be related to an associated vitamin B_{12} deficiency. In a recent series, 13 of 30 subjects with jejunal diverticulosis had evidence of a neuropathy; only six, however, had steatorrhoea (Cooke *et al.*, 1963).

The failure to identify neurological manifestations in patients with massive intestinal resection is surprising. Reports of 12 patients with documented steatorrhoea followed for at least one year and up to seven years after resection failed to reveal any neuropathy; tetany, however, was not uncommon (Anderson, 1965; Opie, Hunt, and Finlay, 1964; Booth, MacIntyre, and Mollin, 1964; Clayton and Cotton, 1961; Todd, Dittebrandt, Montague, and West, 1940; Berman, Ulevitch, Haft, and Lemish, 1950; Bothe, Magee, and Driscoll, 1954; Trafford, 1956; Linder, Jackson, and Linder, 1953). Eight other patients with massive resections showed no neurological abnormalities (Althausen, Doig, Uyeyama, and Weiden, 1950; Berman, Habegger, and Billings, 1953; Fletcher, Henley, Sammons, and Squire, 1960; Holman, 1944; Martin, Robertson, and Dennis, 1948; Mayer and Criep, 1949; Pincus, 1951). In two patients with blind loops and documented steatorrhoea of long duration only paraesthesias were reported (Badenoch, Bedford, and Evans, 1955; Townsend and Cameron, 1957).

Several reports of large series of patients with non-tropical sprue either failed to mention neurological manifestations or regarded them as rare (Thaysen, 1932; Cooke, Peeney, and Hawkins, 1953; Adlersberg and Schein, 1947; Lindsay, Nordin, and Norman, 1956; Snell, 1939). Woltman recorded 20 persons with some evidence of organic involvement of the nervous system in a review of 200 patients (Woltman and Heck, 1937). Green and Wollaeger (1960), Bossak, Wang, and Adlersberg (1957), and Rodriguez-Molina (1954) observed paraesthesias in 25%, 18%, and 14% respectively of their series. In an abstract Smith (1955) reports 20 patients with steatorrhoea associated with a peripheral neuropathy, including subacute combined degeneration. Sencer (1957) found that 16 of his 94 patients with sprue had paraesthesias, absent deep tendon reflexes and/or sensory changes, 16 with tetany only and eight with both tetany and neurological signs. Of this large group, however, only two persons had severe debilitating neurological disease which did not improve on vitamin therapy.

Apparently the occurrence of peripheral neuropathy in an unselected steatorrhoea population is not common. Rarely, however, it may be a prominent complaint or may even occur in the absence of any gastrointestinal symptoms. What can be the cause of neurological disorders in patients with steatorrhoea? It is not always easy to determine whether a patient has peripheral neuropathy or subacute combined degeneration secondary to B_{12} deficit; when the steatorrhoea is the result of a disease associated with B_{12} deficiency, as in the blind loop syndrome, it may be impossible to be certain. Neurological disorders in patients with steatorrhoea may occur purely coincidentally. Peripheral neuropathy and/or myopathy are often associated with chronic alcoholism, malnutrition, diabetes mellitus, amyloidosis, or carcinoma. Obviously, in a patient with steatorrhoea neurological symptoms must raise the question of tetany secondary to hypocalcaemia or hypomagnesaemia. The possibility that the neurological disability is secondary to a compression fracture secondary to either osteomalacia or osteoporosis must also be considered. Neuromuscular abnormalities occur in patients with protein or mineral deficiency and if possible, this must be excluded (Cruickshank, 1961). Topopherol-deficient animals develop creatinuria and a dystrophic myopathy (Century and Horwitt, 1960), which may be important in our patients since both R.J. and A.J. showed microscopic evidence of a myopathy. Tocopherol-deficient patients with cystic fibrosis, however, did not show improved muscle strength following tocopherol administration (Levin, Gordon, Nitowsky, Goldman, di Sant'Agnese, and Gordon, 1961).

In A.J. the onset of a sensory neuropathy and muscle weakness antedated the appearance of intestinal symptoms. He had been given steroid therapy for about two years until about a year before intestinal symptoms first appeared so that consideration must be given to the possibility that steroid therapy prevented the development of intestinal symptoms. Nevertheless, the events in this case suggest that in any person with an undiagnosed or poorly defined neuromuscular disease, steatorrhoea ought to be excluded. Absence of marked intestinal symptoms should not be surprising: a patient with iron-deficiency anaemia and one with osteomalacia were both found to have non-tropical sprue without any evidence of steatorrhoea (McGuigan and Volwiler, 1964; Moss, Waterhouse, and Terry, 1965). In both patients the anaemia and the calcium deficiency improved on a gluten-free diet.

Although most patients with non-tropical sprue

will respond to a gluten-free diet, a small number will not. It is in this group of patients with refractory steatorrhoea where we might expect to find neurological and myopathic disorders. This was the situation in all four of our patients. In R.J. the intestinal mucosa showed villous atrophy with many features atypical of non-tropical sprue. He did not respond well to the gluten-free diet or to steroids. A.G. had jejunal diverticulosis and marked steatorrhoea refractory to the usual clinical manoeuvres. It is also pertinent to note that most of the patients with neurological symptoms and sprue were seen before the use of a gluten-free diet. In A.J. the refractoriness of the intestinal disease was related most to its not being apparent. The refractoriness of P.M. was related to the patient and not to his disease. Although the benefit of pancreatic supplementation was apparent 18 months before admission, the patient never regularly took the medication.

Therapy for neuromyopathy must be empirical and should be directed primarily at determining and treating the underlying cause of the steatorrhoea. Such replacement therapy as B-complex vitamins, vitamin B_{12}, folic acid, pyridoxine, and tocopherol also seem advisable. Whether medium-chain triglycerides, which are absorbed more efficiently in patients with small intestinal disorders than usual fats, may be helpful if uncertain (Iber, Hardoon, and Sangree, 1963; Zurier, Campbell, Hashim, and Van Itallie, 1966). It should be noted that in all three of our patients in whom medium-chain triglycerides were given, there was a significant fall in faecal fat excretion while they were taking medium-chain triglycerides (Table II). However, R.J. died before long-term administration of medium-chain triglycerides could be evaluated and A.J. was unable to tolerate the fat for any long period of time.

TABLE II

EFFECT OF MEDIUM CHAIN TRIGLYCERIDES ON FAECAL FAT EXCRETION

	72 Hour Stool Fat (g.)	
	L.C.T.[2]	M.C.T.[3]
A.G.	88·1	17·5
R.J.	218·5	54·5
P.M.[1]	121·5	31

[1]While on Cotazym.
[2]75 g. long-chain triglyceride diet per day.
[3]50 g. medium-chain triglyceride and 25 g. long-chain triglyceride diet per day.

These observations emphasize that neurological and myopathic complaints not only can be associated with steatorrhoea, but may completely overshadow the intestinal disease. Neuromuscular dysfunction seems to occur primarily in patients whose malabsorption is refractory to conventional therapy. The neurological disorder may occur, however, even in the absence of any intestinal symptoms for a long period of time. Steatorrhoea should be looked for in any patients with an unexplained peripheral neuropathy, particularly a sensory neuropathy, or with muscular weakness, which may be a reflection of the neuropathy or may represent a primary myopathic process.

SUMMARY

Four patients are presented in whom neuromuscular disorders were associated with steatorrhoea. In three of the four patients the neurological symptoms were extremely severe, progressive, and irreversible and represented the primary clinical problem. In one individual, neuromuscular dysfunction was present for at least three years before the occurrence of intestinal symptoms. This report emphasizes that neuromuscular disorders can occur in patients with steatorrhoea and that steatorrhoea should be looked for in any patient with an unexplained sensory deficit or muscular weakness.

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