Intestinal lymphangiectasia

Long-term results with MCT diet

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Intestinal lymphangiectasia: long-term results with MCT diet. The clinical course of 6 children with primary intestinal lymphangiectasia who have been treated with low fat medium chain triglyceride-supplemented diets for between 3 and 8 years (4 for longer than 5 years) is described. Though laboratory findings indicate continuing chyle leak, evidence for long-term benefit from dietary treatment is provided by symptomatic relief while on the diet, clinical relapse upon relaxation of the regimen, and improvement in growth rates. In most patients the underlying lymphatic defect, and thus the need for dietary treatment, appears to be permanent.

The first demonstration of gastrointestinal protein loss was reported in 1957 by Citrin, Sterling, and Halstead, who recovered intravenously administered ^{131}I -labelled albumin from the gastric juice of a patient with giant hypertrophy of the gastric mucosa. 2 years later Gordon (1959), Holman, Nickel, and Slesinger (1959), and Schwartz and Jarnum (1959) published independent reports of exudative enteropathy in patients with idiopathic hypercatabolic hypoproteinaemia using radio-iodinated polyvinyl pyrrolidone (^{131}I PVP). The perfection of ^{131}I PVP and of ^{51}Cr albumin excretion tests and their widespread use soon led to the demonstration of protein-losing gastroenteropathy in association with a large number of disease states; over 35 such diseases have now been reported (Truelove and Reynell, 1972), many of which can occur in childhood. These include coeliac disease, Crohn's disease, ulcerative colitis, hypo- γ -globulinaemia, giant hypertrophy of the gastric mucosa, megacolon, nephrosis, acute gastrointestinal infections, hookworm infestation, kwashiorkor, and 'allergic gastroenteropathy' (Waldmann *et al.*, 1967). Patients not shown to have any other definable disease were originally classified as having idiopathic gastrointestinal protein loss, but this diagnosis has been virtually eliminated since the description of intestinal lymphangiectasia by Waldmann *et al.*, in 1961.

Intestinal lymphangiectasia is characterized by the presence in the submucosa of the small bowel of dilated lymph vessels which leak chyle into the intestinal lumen. This dilatation may represent a primary disorder of lymph vessels or may result from obstruction to lymph flow through mesenteric lymph channels. The obstruction to chyle flow seen in secondary intestinal lymphangiectasia may be either functional, as in constrictive pericarditis and severe right heart failure, or the direct result of organic obstruction, as in mesenteric panniculitis, α -ray arteritis, and primary diseases of the mesenteric or retroperitoneal lymph nodes (e.g. tuberculosis, lymphoma, and carcinoma) (Werbeloff Bank, and Marks, 1969). Primary intestinal lymphangiectasia probably represents a congenital disorder of mesenteric lymphatics and is often associated with lymphatic anomalies outside the gastrointestinal tract.

Treatment of secondary intestinal lymphangiectasia is that of the underlying disorder and may be successful in achieving cure of the intestinal protein loss. For primary intestinal lymphangiectasia, however, the abnormality is rarely sufficiently localized to permit cure by excision of the abnormal bowel (Ivey *et al.*, 1969; Waldmann, 1966). There has been one report of a surgical anastomosis between dilated lymphatics and the long saphenous vein which led to some improvement (Mistilis and Skyring, 1966). Medical treatment is palliative by restricting the dietary fat intake to the minimum possible, thereby reducing chyle flow

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and therefore the leak of protein. The introduction of medium chain triglycerides (MCT), whose fatty acids are largely transported by the portal vein and whose absorption does not appreciably increase lymph flow, has enabled strict low-fat diets to be made more palatable and has also provided an additional source of high energy food (Leyland *et al.*, 1969).

Primary intestinal lymphangiectasia is a chronic disorder, and treatment is likely to be lifelong. Though there are several encouraging reports of the short-term effects (less than 2 years) of dietary treatment (Leyland *et al.*, 1969; Amirhakimi *et al.*, 1969; Yssing, Jensen, and Jarnum, 1967; Jeffries, Chapman, and Sleisenger, 1964), information on longer term results is scarce. This paper describes the clinical course of 6 children with primary intestinal lymphangiectasia who have been treated with MCT diets for between 3 and 8 years (4 for more than 5 years) and illustrates the range of diagnostic and therapeutic problems that can arise. The early history of 4 of the children has already been briefly reported (Leyland *et al.*, 1969).

Patients

The main clinical features of the patients are summarized in Table I, and detailed case reports are given in the Appendix. In 3 children the diagnosis was made

before the age of 2½ years, and in 3 it was made between the ages of 6 and 8 years. In retrospect, however, 5 of the 6 patients had been noted to have oedema before the age of 2 years, and in 3 of these swelling had been present from birth. There was no family history of lymphangiectasia; one patient (Case 5) was the product of a first-cousin marriage. Results of the pertinent investigations at the time of diagnosis are given in Table II. Characteristic radiological findings were coarse mucosal folds throughout the small intestine without the dilatation seen in malabsorptive states. Dilution of barium in the ileum and puddling of barium were also seen (Shimkin, Waldmann, and Krugman, 1970; Werbeloff *et al.*, 1969; Waldmann, 1966). Typical small intestinal biopsy appearances included dilated but intact lymphatics in the submucosa. Goblet cells were often markedly enlarged with liquified granules being extruded into the lumen. Villous atrophy and cellular infiltration of the intestinal wall were absent (Ores *et al.* 1966).

Treatment. Before diagnosis was established various methods of supportive therapy had been tried, including systemic corticosteroids (Cases 1 and 2), injections of γ -globulin (Case 1), and diuretics (Cases 1, 2, 3, and 5). Neither corticosteroids nor γ -globulin were beneficial.

The dietary regimen used consisted of reduction of the amount of ordinary dietary fat containing triglycerides with fatty acids of chain length predominantly greater than 14 carbon atoms (long chain triglycerides), and

TABLE I
Clinical features and treatment

Case no.	Sex	Age at 1st symptoms (yr) (m)	Age at diagnosis (yr) (m)	Major clinical features	Treatment				Duration of follow up (yr) (m)	Other
					Drugs		Diet			
					Before diagnosis	After diagnosis	Fat (g/d)			
							LCT	MCT		
1	M	Birth	2 3	Symmetrical oedema, diarrhoea	γ-Globulin, prednisone, diuretics	Diuretics*, iron	11	50	7 11	Pericardiectomy at age 10 years
2	F	Birth	6 6	Asymmetrical oedema, pleural effusion, pericardial effusion	Prednisone, diuretics	Diuretics, iron, folate*	10	70	6 10	
3	M	Birth	5 11	Asymmetrical oedema, diarrhoea, severe infections	Prenisone, diuretics	Diuretics	7	40	6 7	
4	F	1 7	1 8	Symmetrical oedema, ascites, diarrhoea		Iron	10	40	3 4	Diet discontinued after 2 years
5	F	1 2	1 4	Symmetrical oedema, ascites, diarrhoea	Diuretics	Diuretics*	6	15	6 1	
6	F	6 0	8 1	Asymmetrical oedema, ascites			10	30	5 11	

*Now discontinued.

LCT, ordinary fat (largely long chain triglyceride); MCT, medium chain triglyceride: amount approximate and not strictly controlled.

TABLE II
Findings at diagnosis

Investigation	Case no.						Normal
	1	2	3	4	5	6	
Serum total protein (g/100 ml)	4.2	5.9	—	4.3	4.5	5.4	> 5.2
Serum albumin (g/100 ml)	2.1	2.7	2.0	2.5	2.6	3.3	> 3.6
Serum IgG (mg/100 ml)	300	1 080	510	—	160	640	> 700
Peripheral lymphocyte count (/mm ³)	490	600	700	1 480	1 089	1 625	> 1 500
Serum calcium (mg/100 ml)	8.1	8.7	7.2	8.6	8.5	8.3	> 8.5
Serum cholesterol (mg/100 ml)	120	189	116	—	116	142	> 120
Faecal fat (g/d) (mean 3-5 d)	4.5	2.2	5.7	—	3.5	4.1	—
⁵¹ Cr albumin excretion (%)	12.7	—	8.7	10.5	12.5	4.4	< 1.5
Small intestinal biopsy	Normal*	Typical	Typical	Normal	Typical	—	—
Radiology small bowel	Typical	Typical	Typical	—	Typical	Typical	—

*Typical biopsy obtained one month later at laparotomy.

addition of medium chain triglycerides with fatty acids of chain length 8 and 10 (MCT). The use of the MCT diet has been described by Leyland *et al.* (1969). In addition to the MCT diet, all patients were given ordinary vitamin supplements and 2 (Cases 2 and 3) still require chronic diuretic therapy.

Long-term progress. The marked improvement in general well-being which was reported for all patients within a few months of starting the MCT diet has

persisted. All children showed rapid and sustained improvement in dependent oedema, and of the 4 who initially required diuretic therapy (Cases 1, 2, 3, and 5), Cases 1 and 5 no longer need this. The asymmetrical oedema, which results from peripheral lymphatic anomalies, was unaffected by dietary and diuretic therapy. Diarrhoea ceased to be a problem in the 4 children who presented with that complaint (Cases 1, 3, 4, and 5). 4 of the 6 children had moved up in height centiles by the end of the first year on the diet (Fig. 1),

FIG. 1.—Cases 1-6. Growth in height.

and all have sustained this improvement. Of the 2 children who remained on the same centile, one (Case 2) showed a normal growth pattern on the 10th centile for height both before and after starting the MCT diet. The other child (Case 3), the most severely affected patient, grew along the 3rd centile both before and for 3 years after the introduction of the MCT diet. For the past 4 years, however, his height has fallen away from the 3rd centile (Fig. 1). At the age of 16 years he showed only early signs of pubertal development with a bone age of 11 years, and his fall-off in height centile may reflect simply a delay in the normal pubertal growth spurt.

The biochemical and haematological findings on the MCT diet are shown in Table III and Fig. 2. In general the low lymphocyte counts and reduced serum concentrations of albumin and IgG persisted. Faecal fat was predictably less on the MCT diet. One patient (Case 1) had a repeat barium meal and jejunal biopsy after 3 years on the MCT diet, both showing some improvement. In view of the evidence for continued gastrointestinal protein loss as judged by peripheral lymphocyte counts and serum albumin, formal studies by means of repeated ^{51}Cr albumin excretion tests were not performed in all patients. In those in whom the test was repeated the results confirmed the continuing protein loss and gave no indication that this had decreased in degree (Table III).

Deliberate attempts to relax the restriction of dietary long-chain fat have been made in 4 patients (Cases 3–6). In 3 (Cases 3–5) diarrhoea consistently recurred within 2–3 weeks of the introduction of even a modest amount of LCT; 2 children also developed dependent oedema

and one ascites. In all 3, symptoms and signs subsided with the return to the previous diet. In one child (Case 6) a normal diet was reintroduced after 2 years; dependent oedema did not recur, serum albumin remained normal, growth rate continued to accelerate, and reinvestigation failed to show continued gastrointestinal protein loss, though peripheral asymmetrical oedema persisted.

Discussion

Oedema with hypoalbuminaemia is the main clinical feature of patients with intestinal lymphangiectasia. Oedema was asymmetrical in 3 of our patients and in 8 of Waldmann's series of 40 patients (1966). Effusions are common, and 4 of our patients had ascites, pleural effusions, and/or pericardial effusions. These effusions may be secondary to hypoproteinaemia, or they may result from leakage in localized areas of lymphangiectasia and may then be chylous. 43% of Waldmann's (1966) patients had chylous effusions. Gastrointestinal symptoms are usually mild, consisting of intermittent diarrhoea with minimal steatorrhoea. Another feature reported by Waldmann was blindness secondary to macular oedema, present in 3 of his 40 patients.

Bulk loss of chyle results in loss of proteins of all sizes together with lymphocytes. The degree of reduction in serum protein levels varies depending upon the rates of synthesis of the different proteins.

TABLE III
Biochemical and haematological findings on MCT diets

	Before diet	Years on diet			
		1	2	4	5 +
Serum albumin (g/100 ml)					
Mean	2.5(6)	3(6)	3(6)	2.8(4)	3.3(4)
Range	2.0–3.3	1.9–3.9	2.3–3.7	1.4–3.9	2.3–4.0
Serum IgG (mg/100 ml)					
Mean	544(5)	494(5)	448(4)	320(1)	200(1)
Range	160–1 080	300–950	230–560	—	—
Peripheral lymphocyte count (/mm ³)					
Mean	997(6)	926(6)	1 330(5)	1 064(4)	1 016(4)
Range	490–1 625	460–1 500	450–2 380	756–1 750	700–1 764
Serum calcium (mg/100 ml)					
Mean	8.2(6)	8.9(6)	9.1(5)	8.4(3)	8.9(4)
Range	7.2–8.7	8.4–10.0	8.2–10.0	8.0–9.0	7.9–9.7
Serum cholesterol (mg/100 ml)					
Mean	137(5)	147(5)	164(4)	167(4)	173(3)
Range	116–189	118–167	148–180	136–233	130–207
Faecal fat (g/d) (mean 3–5 d)					
Mean	4(5)	1.2(5)	1.4(2)	1.2(1)	1.1(1)
Range	2.2–5.7	0.6–2.0	1.1–1.7	—	—
^{51}Cr albumin excretion (%)					
Mean	9.8(5)	14(3)	13.6(2)	—	—
Range	4.4–12.8	11.0–19.0	7.2–20.0	—	—

Numbers in parentheses represent no. of patients tested.

FIG. 2.—Serial peripheral lymphocyte counts, serum albumin, and plasma calcium in 4 children treated for more than 5 years on MCT diets.

Thus, albumin and γ -globulin are markedly reduced, transferrin and caeruloplasmin slightly reduced, and fibrinogen usually present in normal concentrations (Waldmann, 1966). Lymphopenia is a consistent feature, diminished serum levels of calcium and magnesium are frequently observed, and tetany has been seen as a rare complication (Waldmann, 1966; Mistilis and Skyring, 1966; Zimmet and Breidahl, 1968). Serum cholesterol is sometimes reduced and was at the lower end of the usually accepted normal range in 3 of our patients. Reduced serum levels of folic acid, vitamin B₁₂, and vitamin E are commonly found and are corrected by oral vitamin supplements. Mild anaemia may occur and usually responds to oral iron therapy.

Excessive gastrointestinal protein loss can be shown by measuring the 5-day excretion of intravenously administered ⁵¹Cr albumin or ¹³¹I PVP. Characteristic radiological findings after barium meal were present in all of our patients who had this examination performed, and were noted in 83% of Waldmann's (1966) patients. Upper small intestinal biopsy, if taken from an affected area, is diagnostic but normal biopsy appearances do not exclude the diagnosis. One of our patients (Case 1) had a normal peroral biopsy of the jejunum

one month before laparotomy which revealed extensive lymphangiectasia. The diagnosis of intestinal lymphangiectasia can be made with confidence in patients who present with oedema (especially if there is also asymmetrical lymphoedema) and who have hypoalbuminaemia, lymphopenia, and the characteristic abnormalities on barium meal. We consider that measurement of labelled protein excretion, which is a nonspecific investigation, and intestinal biopsy, which may miss the lesion, should only be performed in children who do not show all of the above features.

Intestinal lymphangiectasia may be regarded as an example of a secondary immune deficiency with hypo- γ -globulinaemia due to loss of protein and lymphopenia due to loss of lymphocytes. Serum levels of IgG, IgA, and IgM are usually reduced to less than half the normal levels, and shortened survival of radio-iodinated IgG, IgA, and IgM has been shown (Strober *et al.*, 1967). The fractional catabolic rate of the intravascular pool is increased to a similar degree for all 3 immunoglobulins (Strober *et al.*, 1967). This observation lends further support to the theory that the protein leak in intestinal lymphangiectasia represents a bulk loss of lymph fluid. Antibody production appears to be normal or near normal as evidenced by

antibody stimulation studies using Vi and tularaemia antigens (Strober *et al.*, 1967).

Impaired cellular immunity may be expected due to the severe and continuous lymphopenia. Skin allografts have been shown to survive in patients with intestinal lymphangiectasia for periods of 1 to 2 years (Strober *et al.*, 1967). In Strober's series of 18 patients delayed hypersensitivity was evaluated by means of skin tests using PPD, mumps, *Trichophyton*, and *Candida albicans*. Only 17% of patients had at least one positive skin test, as compared with 91% of control subjects. Weiden *et al.* (1972) have shown impaired *in vitro* transformation of circulating lymphocytes in response to stimulation by nonspecific mitogens, specific antigens, and allogenic cells. Lymphocytes taken from chylous effusions show much more normal transformation when exposed to the same stimuli. All of these observations can be explained by the relatively greater loss of long-lived T-cells as compared with short-lived B-cells. Since T-cells recirculate from the bloodstream to the tissues and then via the lymphatic system back to the bloodstream, they are more vulnerable to gastrointestinal chyle leakage than are short-lived B-cells which tend to stay in the peripheral circulation. This theoretical selective T-cell loss has recently been confirmed in a group of patients with intestinal lymphangiectasia (A. Hayward, personal communication, 1974).

Although patients with intestinal lymphangiectasia show impaired T-cell function (allograft rejection, delayed hypersensitivity, and mitogen stimulation) with normal B-cell function (antibody production), in fact, few patients develop serious infections. Of the 18 patients studied by Strober *et al.* (1967), 2 (both under 6 years of age) died after prolonged periods of debilitation associated with many bacterial infections, 2 had increased frequency of minor respiratory infections, and the remaining 14 patients showed no increased incidence of infections. Of our patients, only one (Case 3) developed serious infections (meningitis and recurrent pneumonia). This child, our most severely affected patient (as evidenced by the degree of hypoalbuminaemia, hypo- γ -globulinaemia, and lymphopenia), had impaired lymphocyte transformation in response to PHA stimulation and relative diminution in the number of circulating T-cells (A. Hayward, personal communication, 1974).

Conclusion

The short-term beneficial effects of a low-fat diet in intestinal lymphangiectasia have been well

documented (Jeffries *et al.*, 1964). Such a diet, with fat restricted to 5–10 g daily, however, is virtually impossible to maintain over prolonged periods under home conditions. The addition of MCT greatly improves palatability and acceptability (Leyland *et al.*, 1969). Evidence for long-term benefit from dietary treatment in our patients is provided by symptomatic relief while on the diet, clinical relapse in 3 of 4 patients in whom the regimen was relaxed, and improvement in growth rates. The fact that laboratory evidence of continuing chyle leak is present does not indicate that treatment has no effect; on the contrary, return of biochemical findings to normal should suggest re-evaluation of the patient in order to determine whether the chyle leak has ceased, as occurred in one child in our series (Case 6). For the majority of patients, however, it is likely that excessive gastrointestinal protein loss will continue. In order for such children to achieve their optimum growth rate, it appears necessary for a strict low-fat diet, supplemented with MCT, to be continued at least until after puberty.

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Appendix

Case 1. Male, younger child of unrelated parents; recurrent oedema of face, hands, and feet from the age of one month; vomiting and epistaxis during first year of life and intermittent diarrhoea from 8 months.

At one year he presented with marked oedema of the face and limbs and was found to have hypoalbuminaemia (2.1 g/100 ml). He was started on a gluten-free diet (with no improvement) and was given γ -globulin injections because of frequent upper respiratory infections and low IgG levels. At 27 months, he had a normal jejunal biopsy, x-ray evidence of rickets, and height and weight on the 3rd centile. Increased gastrointestinal protein loss was shown using ^{51}Cr albumin. Diagnosis of intestinal lymphangiectasia was suggested by barium meal and confirmed by laparotomy and intestinal biopsy. Peripheral oedema was controlled by diuretics; γ -globulin injections were stopped; and he was given a 9-month course of oral prednisone.

An MCT diet was started at age 3 with a subsequent reduction in faecal fat. During the next 2 years marked clinical improvement occurred, diarrhoea ceased, rickets healed, and oedema disappeared; diuretics were discontinued. Barium meal and jejunal biopsy after 3 years on the diet showed improvement in the mucosal pattern, but gastrointestinal protein loss remained raised. Height and weight increased to the 25th centile where they have remained to the patient's present age of 12 years. At age 10 he was found to have bilateral hearing loss, crossed laterality (left hand/right eye), delayed reading age, IQ of 80, and abnormal EEG.

Case 2. Female, second of 4 children of unrelated parents. Large right foot noted at birth, swelling of left hand and right side of face developed gradually over first 2 years of life. At age 4, she developed bilateral nonchylous pleural effusions and was treated with diuretics, steroids, antispasmodics, and antibiotics. Steroid therapy was stopped after one year but diuretics were continued, and repeated left pleural aspirations were necessary over the next 2½ years. Jejunal biopsy showed dilated lymphatics in the submucosa.

At the age of 6 years, increased gastrointestinal protein loss was shown and barium meal revealed coarse mucosal folds in the duodenum; there was no steatorrhoea. An MCT diet was started with marked improvement in the clinical condition, but diuretics had to be continued to control oedema. Her height continued along the 10th centile as it had before the diet. At age 10 she developed a pericardial effusion requiring surgical excision of the pericardium. Since that time she has continued to do well, and her height at age 13 is still on the 10th centile. Her only remaining problems are nocturnal enuresis and minimal dyspnoea on exertion.

Case 3. Male, second child of unrelated parents, oedema of right arm and right side of face from birth. At the age of one year he developed generalized oedema during pneumococcal meningitis and pneumonia. At age 2 years he developed diarrhoea and thereafter continued to have loose, offensive stools. At age 4 he was circumcised, and histology of the prepuce showed dilated lymphatics. After operation he developed ulcerative stomatitis, and one year later had a second attack of pneumonia.

At age 6 steatorrhoea and increased gastrointestinal protein loss were shown, barium meal showed coarse mucosal folds throughout the small bowel, and jejunal biopsy at laparotomy showed lymphangiectasia. On a low fat and low sucrose diet he remained well, but continued to develop dependent oedema during intercurrent respiratory infections. An MCT diet was started at age 10 with a subsequent decrease in faecal fat. At age 16 his diet was liberalized, and he has since required diuretics to control oedema. At his present age of 17 he continues to grow along the 3rd centile and exhibits stage I pubertal development. He has had learning problems with a delayed reading age, but is now successfully holding down a job as a bank messenger.

Case 4. Female, youngest of 5 children of unrelated parents, developed chylous ascites and oedema during an episode of diarrhoea at age 20 months. A small intestinal biopsy revealed normal histology, but gastrointestinal protein loss was shown by means of ^{51}Cr albumin. She was started on an MCT diet with prompt resolution of her ascites and oedema. During 3 years on this diet her height has increased from the 10th to the 50th centile. She has occasional episodes of mild ascites, which are usually related to increased LCT consumption.

Case 5. Female, third child of parents who are first cousins. Three episodes of diarrhoea in first year

of life; developed oedema and ascites during episodes of diarrhoea at 14 months of age. Mild steatorrhoea and excessive gastrointestinal protein loss were shown, and a barium meal was characteristic of intestinal lymphangiectasia. Jejunal biopsy revealed dilated lymphatics associated with short broad villi, cuboidal epithelial cells, and decreased number of goblet cells. She was started on an MCT diet and subsequently showed rapid improvement in well being, disappearance of ascites and oedema, and an increase in height from the 10th to the 25th centile. She continues to do well at age 7½, but even the slightest increase in dietary LCT produces diarrhoea.

Case 6. Female, third child of unrelated parents, oedema of left foot noted for the first time at age 6 years. Oedema subsided spontaneously, but one year later she developed dependent oedema and ascites

associated with documented hypoalbuminaemia (2.7 g/100 ml). Oedema and ascites again resolved without treatment, but she continued to have recurrent dependent oedema. At age 8, she was found to have increased gastrointestinal loss of protein without steatorrhoea. Barium meal was characteristic of intestinal lymphangiectasia. She was started on an MCT diet, and within 2 years her height had increased from the 3rd to the 10th centile. She was then placed on a normal unrestricted diet; there was no increase in oedema, and by the age of 14 she had reached the 50th centile for height. Her lymphocyte count remained slightly low, but her serum albumin returned to normal and an ¹³¹I PVP excretion showed no evidence of gastrointestinal protein loss. She has had one episode of cellulitis in the right leg and swelling of both legs remains a problem. A lymphangiogram revealed abnormal dermal lymphatics in the foot with no demonstrable deep lymph vessels.