Long-term management of abetalipoproteinaemia

Possible role for vitamin E

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SUMMARY Eight patients with abetalipoproteinaemia have been followed for 3·4 to 15·8 years. Management included dietary fat restriction and supplements of the fat-soluble vitamins A, E, and K. In the 3 oldest patients serial studies of retinal and neurological function suggest that treatment with large doses of oral vitamin E may have delayed the development or progression of the neurological and retinal lesions.

The clinical features of abetalipoproteinaemia were first described by Bassen and Kornzweig in 1950 and it is now 15 years since three independent groups showed the absence of betalipoprotein in this condition (Lamy *et al.*, 1960; Mabry *et al.*, 1960; Salt *et al.*, 1960). It has now been shown that the primary defect is failure of synthesis of apo B, which is the major apoprotein of betalipoprotein and is also essential for the formation of pre-beta-lipoprotein and chylomicra (Gotto *et al.*, 1971). The disorder usually presents in infancy with symptoms due to malabsorption of fat which can be satisfactorily treated by restriction of dietary fat (Lloyd and Muller, 1972). In occasional patients the diagnosis has been delayed until adult life when

neurological disability has generally been the presenting feature. The retinal and neurological abnormalities, which do not usually become apparent until the end of the first decade, are thought to progress to severe crippling and visual impairment and present a difficult management problem.

Although many case reports and several reviews have been published (Schwartz *et al.*, 1963; Sobrevilla *et al.*, 1964; Sturman, 1968; Kayden, 1972; Lloyd and Wolff, 1974), and individual aspects of the disorder have been studied in detail, there have been few reports of the natural history in individual patients or of the long-term prognosis. This paper presents a long-term follow-up (3·4–15·8 years) of 8 patients.

Patients

The age at diagnosis and at follow-up, and the treatment are shown in Table 1. Details of the

Table 1 *Treatment of abetalipoproteinaemia*

Case no.	Sex	Age (yr)		Treatment and current dosage				
		At diagnosis	At follow-up	Diet fat (g/d)*	Vitamin A (IU)	Vitamin E (mg/kg per day)	Vitamin K (mg/d)	
1 } sibs	F	0·1	5·2	10	50 000/w	83	10	
2 } sibs	M	0·2	8·2	10	50 000/w	100	10	MCT given initially
3	M	0·4	5·9	16	5 000/d	110	—	MCT given initially
4	F	0·9	4·3	8	50 000/alt day	62	2·5	
5	F	1·1	6·5	15–20	,,	100	10	
6	M	1·6	11·4	20	,,	100	10	
7	F	1·4	17·2	40	,,	60	5	Vitamin E since age 8 yr; some corn oil (approx 5 g/d)
8	M	7·2	19·3	20	,,	100	10	Low fat since age 7 yr; some MCT and corn oil (approx 7 g/d)

*Initially most children had lower intakes. MCT=medium-chain tryglycerides.

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management have been previously described (Lloyd and Muller, 1972). All were treated from the time of diagnosis by a diet restricted in long-chain fat and 3 (Cases 2, 3, 8) received medium-chain triglycerides (MCT) initially, but this has been discontinued as it appeared to exacerbate the malabsorption of long-chain fat. 2 children (Cases 7 and 8) have received additional polyunsaturated fat in the form of corn oil. Additional fat-soluble vitamins were given routinely as part of the management of children on low-fat diets (Francis, 1975). Supplementary vitamin A in amounts sufficient to maintain normal plasma levels, enough vitamin K to maintain prothrombin times, and oral vitamin E in a dosage adequate to correct abnormal *in vitro* red cell haemolysis, were also given.

Methods

Analytical. Serum vitamin A concentrations were estimated by the method of Bessey *et al.* (1946). Vitamin E status was assessed by measuring serum vitamin E concentrations and by two tests of red cell haemolysis: autohaemolysis and peroxide haemolysis (Muller, *et al.*, 1974). All other estimations were carried out by routine laboratory methods.

Clinical. Most of the patients were seen at 6- to 12-monthly intervals at The Hospital for Sick Chil-

dren, London, and examined by the same observer (J.K.L.). Where appropriate, psychological testing was carried out in the Department of Psychological Medicine. Motor nerve conduction velocities, and in older children sensory velocities, were estimated on nearly all occasions by Dr. E. D. R. Campbell in the Department of Physical Medicine; on isolated occasions this investigation was carried out at the National Hospital for Nervous Diseases. Retinal function was assessed by ophthalmoscopy, electro-retinography, electro-oculography, and tests of dark adaptation, and once the children were old enough to co-operate these were performed at Moorfields Eye Hospital under the supervision of Mr. A. C. Bird.

Results (Table 2)

Growth. With the exception of Case 8, all children showed 'catch-up growth' after starting a low-fat diet and growth rate has since been normal. Case 7 is the original patient described by Salt *et al.* (1960) and has now passed through a normal puberty. Case 2, in addition to abetalipoproteinaemia, had bilateral hydronephrosis and renal calculi due to congenital obstruction at the lower end of the ureters and several operations were required during the first 2 years of life. This apparently unrelated feature probably contributes to his short stature.

Table 2 *Long-term progress in abetalipoproteinaemia*

| Case no. | Growth | | | | Neurological status | | | |
| | Height centile | | Weight centile | | Clinical | | Nerve conduction | |
	D	FU	D	FU	D	FU	D	FU
1	3	15	3	25	Normal	Normal	—	Normal
2	<3	3	<3	10	,,	,,	Normal	—
3	<3	10	<3	<3	,,	,,	—	Normal
4	10	10	<3	3	,,	,,	Normal motor	?Slowing motor right lateral popliteal, otherwise normal
5	3	75	<3	50	Hypotonic; absent KJ,AJ	Normal; present KJ,AJ	—	—
6	10	50	<3	10	Absent KJ,AJ	Absent KJ,AJ	Normal motor	Normal motor; delayed sensory
7	10	90	10	75	Absent KJ,AJ	Absent KJ,AJ	—	Normal motor and sensory
8	<3	<3	<3	<3	Ataxic; absent reflexes pes cavus	Less ataxic; absent reflexes; pes cavus	Slow motor	Normal motor

D=at diagnosis; FU=at follow-up; KJ=knee jerks; AJ=ankle jerks; EOG=electro-oculogram; ERG=electroretinogram.

Case 8, whose early history has been fully reported (Forsyth *et al.*, 1965), was not diagnosed until the age of 7 years by which time there was already considerable stunting of growth.

Neurological and retinal function. In Cases 1, 2, 3, and 5 there has been no evidence of the development of abnormal neurological or retinal function. In Case 5 deep tendon reflexes in the legs could not be elicited at the time of diagnosis when she was also severely hypotonic and delayed in her motor development; motor power and tone are now normal and knee and ankle reflexes have returned. Case 4 had slight slowing of motor nerve conduction in the right lateral popliteal nerve (40 m/s) at the age of 4·3 years; all other tests were normal and the significance of this isolated observation is doubtful. Cases 6–8 are the oldest children in the group and all have some evidence of neuro-ophthalmological dysfunction.

Case 6. Deep tendon reflexes in the legs could not be elicited at the time of diagnosis and have not returned. At 11·4 years vibration sense in both arms and legs appeared to be reduced on clinical examination but all other forms of sensation were intact. Motor nerve conduction velocities have remained normal throughout the period of follow-up, but sensory action potentials in the right ulnar, median, and

sural nerves showed evidence of a sensory neuropathy with reduced amplitude (Dr. D. Smyth) at the age of 11·4 years. Retinal appearances and visual function tests have remained normal.

Case 7. Deep tendon reflexes in the legs could not be elicited at the time of diagnosis and have not returned; otherwise neurological examination has remained normal. At 5 years abnormal retinal pigmentation was noted at the periphery and macula in both eyes despite adequate vitamin A therapy (Wolff *et al.*, 1964), and the appearance has remained virtually unaltered. There is some field loss related to equatorial and pre-equatorial retinal disease, but other tests of retinal function have remained normal as have motor and sensory nerve conduction velocities in arms and legs.

Case 8. A marked pigmentary retinopathy and an ataxic neuropathy were already present at the time of diagnosis at 7 years (Forsyth *et al.*, 1965). During the next 3 years, despite adequate vitamin A therapy he became more ataxic and at 10 years neurological examination showed slight pupillary irregularity with poor reaction to light and accommodation. There was limited abduction of both eyes. Tone was reduced in the upper limbs and movements in both arms were clumsy and repetitive. Gait was broad based and ataxic. Romberg's sign was positive.

Ophthalmoscopy		*Visual function*		*Intellectual developmental*		*Other*
D	*FU*	*D*	*FU*	*D*	*FU*	
Normal	Normal	—	—	Normal	Normal school	—
,,	,,	—	—	Normal	Normal school	Congenital obstructive uropathy and renal calculi
,,	,,	—	—	—	'Normal'	—
,,	,,	—	Normal	—	IQ 80	—
,,	,,	—	—	Developmental delay	Normal	Dry skin
,,	,,	Normal	Normal	?Normal	1½ yr delay in reading; IQ 90–100	Behavioural problems; dry skin
,,	Slight pigmentary retinopathy	—	Normal	Normal	Normal	Paroxysmal tachycardia
Pigmentary retinopathy	Retinopathy unchanged	Abnormal EOG+ERG	Normal	IQ 65	Employed sheltered workshop	—

Tone and power were reduced in both legs and there was bilateral foot drop with pes cavus more marked on the right. Deep tendon reflexes were absent, plantar responses were extensor, sensation appeared normal. Motor nerve conduction velocities were slow (right lateral popliteal 40 m/s); electro-oculogram (EOG) showed a percentage light rise (peak/dark trough ratio $\times 100$) of 140% on the right and 130% on the left (normal >180%); electroretinogram (ERG) and dark adaptation were abnormal.

Rhodopsin bleaching studies showed a normal complement of rhodopsin in the rods. At this stage vitamin E was added to the therapeutic regimen. Over the next 2 years there was definite improvement in the degree of ataxia, and motor nerve conduction velocities also improved (right lateral popliteal 55 m/s, left lateral popliteal 50 m/s, right ulnar 60 m/s). Retinal pigmentation was unaltered but the EOG response had risen to 167% on both right and left sides. At the age of 14 motor nerve conduction velocities had not changed significantly and sensory action potentials (measured for the first time) showed slight impairment in the right ulnar nerve. By the age of 17 he was only slightly ataxic; power was slightly reduced in the lower limbs, the plantar responses remained extensor, and there was some diminution of vibration sense. Motor nerve conduction remained unchanged and no sensory potentials could be obtained; retinal appearances were unaltered but the EOG was now normal (248% in the right and 200% in the left), as were the ERG and tests of dark adaptation.

Intellectual development. Cases 1, 2, and 5 all attend ordinary schools and are progressing normally. Case 3 is a Chinese boy who speaks no English and is considered by his parents to be of normal intelligence; formal testing has not been done. Case 4 has not yet started school; psychological assessment at age 4·3 years gave an IQ (Stanford Binet) of about 80 which is comparable with a previous estimate made at 2·9 years. Case 6 has had problems at school with delay in reading. His IQ was recorded as 100 (verbal) and 92 (performance) at 9·6 years. Psychological assessment indicated considerable disturbance in mother-child relationship and psychiatric help was given. Recent assessment showed some improvement and he continues to attend a normal school. Case 7 who had an IQ of 111 at the age of 5 years completed normal primary schooling, entered grammar school at 11 years, and is about to enter a college of further education. Case 8 was known to be mentally retarded with an IQ of 65 at diagnosis and required special schooling; he is now employed in an upholstery workshop for the disabled.

Other features. Case 7 started to have attacks of paroxysmal tachycardia (mainly after severe exertion) at the age of 13. Her cardiovascular system was examined by Dr. Clifford Parsons and no other abnormality was detected. Attacks are now infrequent, but occasionally require control with digoxin. Cases 5 and 6 have both had unusually dry skin requiring local applications of emulsifying ointment.

Discussion

There is general agreement that symptoms referable to malabsorption improve with age in patients with abetalipoproteinaemia (Fredrickson *et al.*, 1972), and our study shows that, with the early institution of measures to control steatorrhoea, normal physical growth potential can be achieved. By contrast the neurological and retinal lesions, which usually develop towards the middle or end of the first decade, are thought to progress and lead to severe crippling in early adult life (Sobrevilla *et al.*, 1964; Schwartz *et al.*, 1963; Sturman, 1968). In our 5 youngest patients it is too early to say whether treatment has influenced this aspect as all are still under 10 years of age. In the 3 eldest, the original patient of Salt *et al.* (1960) has reached the age of 17 without evidence of progressive neurological disease and with only mild retinopathy which has remained unchanged since the age of 5 and does not interfere with vision. The patient of Forsyth *et al.* (1965) was known to have deteriorating neurological function between 7 and 10 years but since this time deterioration has halted and there has probably been improvement in both neurological and retinal function. The third patient developed minimal signs of sensory and motor nerve involvement in the legs at the age of 11½ but is otherwise well. It is not possible to be certain whether the condition of these 3 patients compared with those reported in the literature represents variation in the natural history of the disorder, or is the result of treatment.

The pathogenesis of the neurological and retinal lesions has not yet been established. The suggestion that prolonged exposure of retinal and/or nerve cells to serum deficient in betalipoprotein may result in impairment of cell function and ultimately in degeneration (Forsyth *et al.*, 1965) has not been substantiated or refuted. The low level of linoleic acid, shown in serum and the red cell membrane (Jones and Ways, 1967; Barnard *et al.*, 1970) may contribute to abnormal neurological function but is unlikely to be the sole cause. Recent evidence relating abnormal metabolism or incorporation of linoleic acid to multiple sclerosis (Thompson, 1972) suggests that this fatty acid may be important for normal myelination. It is of interest that our 2 eldest

patients have both had small supplements of poly-unsaturated oil for many years and the neurological state of one (Case 7) is excellent, and in the other (Case 8) deterioration has been halted with probable improvement.

Vitamin A deficiency was originally considered to be a contributory factor in the development of the retinopathy, but Case 7 developed retinal changes at the age of 5 years despite having normal serum levels from the age of 22 months (Wolff *et al.*, 1964). Additional vitamin A had also been given to Case 8 for several years before diagnosis but it did not prevent the development of severe retinitis and neurological impairment at the age of 7 years, nor continued deterioration in these features (Forsyth *et al.*, 1965). Furthermore the rhodopsin bleaching studies in this patient attested to normal vitamin A metabolism at least in respect of the receptor cells. Reports, however, that giving vitamin A may result in an improvement in dark adaptation and the ERG response (Carr, 1970; Sperling *et al.*, 1972) suggest that vitamin A may at least in some cases play a part in the retinal lesions and should certainly be given to all patients in doses sufficient to maintain normal serum levels.

The possibility that vitamin E deficiency might be important in the development of the neuro-ophthalmological features was considered because of pathological conditions caused by vitamin E deficiency in animals. Encephalomalacia with clinical signs of ataxia, spasms, or paralysis occurs in the chick (Pappenheimer and Goettsch, 1931) and impaired reproduction and muscular dystrophy have been reported in a number of species (Roels, 1967). In the human, reduced serum levels occur in many conditions in which fat malabsorption is a feature but the most severe degree of vitamin E deficiency is found in abetalipoproteinaemia in which serum levels are undetectable and tissue levels (as judged by *in vitro* tests of red cell haemolysis) very low (Kayden and Silber, 1965; Muller *et al.*, 1974). This deficiency, probably present from birth, results from impaired absorption due to lack of chylomicron formation, and defective transport due to lack of betalipoprotein, the principal carrier protein (McCormick *et al.*, 1960). The condition therefore provides an ideal model for studying the effects of vitamin E deficiency in man. In previous studies we showed that sufficient vitamin E is absorbed from large oral doses, presumably via the portal vein, to correct the abnormal red cell haemolysis and to produce detectable serum levels (Muller *et al.*, 1974).

It may be significant that none of our patients who were given vitamin E before the age of 1·5 years (Cases 1-6) has developed retinopathy,

whereas the 2 eldest children (Cases 7, 8) in whom vitamin E was not started until 8 and 10 years developed retinopathy at 5 and 7 years respectively. In the 3 eldest children (Cases 6-8), progressive neurological abnormality is absent in Case 7 now aged 17 years, is minimal in Case 6 aged 11 years, and deterioration has ceased in Case 8 aged 19 years with return of some functions to normal. It is tempting to speculate that vitamin E therapy has contributed to these results; no other major modification to the therapeutic regimen was made but possibly a synergistic effect between vitamin E and linoleic acid may be operating in the 2 oldest children. Vitamin E is thought to play an important role in maintaining the stability and integrity of biological membranes by interacting with polyunsaturated fatty acids (Diplock and Lucy, 1973) and interaction may also occur with vitamin A (Roels *et al.*, 1965).

Impairment of intellectual development is not a constant feature of abetalipoproteinaemia. Forsyth *et al.* (1965) suggested that it only occurred in children from families in which consanguinity was present and that the mental retardation might be a chance association. However, in our present series intellectual handicap is present in 3 children and in only one of the families is consanguinity present. The prognosis for intelligence should be guarded in the young child with abetalipoproteinaemia but deterioration in intellectual function need not be expected.

Cardiac abnormalities with dysrhythmia have been reported in 4 patients and were the cause of death in 3 (Fredrickson *et al.*, 1972). The pathogenesis is not known. In a 10-year-old boy who died suddenly 6 months after the onset of cardiac symptoms necropsy showed interstitial myocardial fibrosis and excessive lipochrome pigment in the cardiac muscle (Dische and Porro, 1970). In Friedreich's ataxia, which has many neurological features in common with abetalipoproteinaemia, similar cardiac abnormalities often occur. In Case 7 it seems likely that the paroxysmal tachycardia is part of her disorder and not simply a chance occurrence.

References

Barnard, G., Fosbrooke, A. S., and Lloyd, J. K. (1970). Neutral lipids of plasma and adipose tissue in abetalipoproteinaemia. *Clinica Chimica Acta*, **28**, 417–422.

Bassen, F. A., and Kornzweig, A. L. (1950). Malformation of the erythrocytes in a case of atypical retinitis pigmentosa. *Blood*, **5**, 381–387.

Bessey, O. A., Lowry, O. H., Brock, M. J., and Lopez, J. A. (1946). Determination of vitamin A and carotene in small quantities of blood serum. *Journal of Biological Chemistry*, **166**, 177–188.

Carr, R. E. (1970). Vitamin A therapy may reverse degenerative retinal syndrome. *Clinical Trends*, **8**, 8.

Diplock, A. T., and Lucy, J. A. (1973). The biochemical modes of action of vitamin E and selenium: a hypothesis. *Febs Letters*, **29**, 205–210.

Dische, M. R., and Porro, R. S. (1970). The cardiac lesions in Bassen-Kornzweig syndrome. Report of a case with autopsy findings. *American Journal of Medicine*, **49**, 568–571.

Forsyth, C. C., Lloyd, J. K., and Fosbrooke, A. S. (1965). Abetalipoproteinaemia; a case report. *Archives of Disease in Childhood*, **40**, 47–52.

Francis, D. E. M. (1975). *Diets for Sick Children*, 3rd ed. Blackwell, Oxford.

Fredrickson, D. S., Gotto, A. M., and Levy, R. I. (1972). Familial lipoprotein deficiency. *The Metabolic Basis of Inherited Disease*, 3rd ed., chap. 26. Ed. by J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson. McGraw Hill, New York.

Gotto, A. M., Levy, R. I., John, K., and Fredrickson, D. S. (1971). On the protein defect in abetalipoproteinemia. *New England Journal of Medicine*, **284**, 813–818.

Jones, J. W., and Ways, P. (1967). Abnormalities of high-density lipoproteins in abetalipoproteinaemia. *Journal of Clinical Investigation*, **46**, 1151–1161.

Kayden, H. J. (1972). Abetalipoproteinemia. *Annual Review of Medicine*, **23**, 285–296.

Kayden, H. J., and Silber, R. (1965). The role of vitamin E deficiency in the abnormal autohemolysis of acanthocytosis. *Transactions of the Association of American Physicians*, **78**, 334–342.

Lamy, M. J., Frézal, J., Polonovski, J., and Rey, J. (1960). L'absence congénitale de bêtalipoproteins. *Comptes Rendus des Séances de la Societié de Biologie (Paris)*, **154**, 1974–1978.

Lloyd, J. K., and Muller, D. P. R. (1972). Management of abetalipoproteinaemia in childhood. *Protides of the Biological Fluids*, p. 331. Ed. by H. Peeters. Pergamon Press, Oxford and New York.

Lloyd, J. K., and Wolff, O. H. (1974). Abetalipoproteinaemia and familial alphalipoprotein deficiency. *Handbuch der inneren Medizin*, 5th ed., Vol. 7, p. 605. Ed. by H. Schwiegk. Springer, Berlin.

McCormick, E. C., Cornwell, D. G., and Brown, J. B. (1960). Studies on the distribution of tocopherol in human serum lipoproteins. *Journal of Lipid Research*, **1**, 221–228.

Mabry, C. C., DiGeorge, A. M., and Auerbach, V. H. (1960). Studies concerning the defect in a patient with acanthocytosis. *Clinical Research*, **8**, 371.

Muller, D. P. R., Harries, J. T., and Lloyd, J. K. (1974). The relative importance of the factors involved in the absorption of vitamin E in children. *Gut*, **15**, 966–971.

Pappenheimer, A. M., and Goettsch, M. (1931). A cerebellar disorder in chicks, apparently of nutritional origin. *Journal of Experimental Medicine*, **53**, 11–26.

Roels, O. A. (1967). Present knowledge of vitamin E. *Nutrition Reviews*, **25**, 33–37.

Roels, O. A., Trout, M., and Guha, A. (1965). The effects of vitamin A deficiency and dietary alpha-tocopherol on the stability of rat-liver lysosomes. *Biochemical Journal*, **97**, 353–359.

Salt, H. B., Wolff, O. H., Lloyd, J. K., Fosbrooke, A. S., Cameron, A. H., and Hubble, D. V. (1960). On having no betalipoprotein; a syndrome comprising abetalipoproteinaemia, acanthocytosis and steatorrhoea. *Lancet*, **2**, 325–329.

Schwartz, J. F., Rowland, L. P., Eder, H. A., Marks, P. M., Osserman, E., Hirschberg, E., and Anderson, H. (1963). Bassen–Kornzweig syndrome; deficiency of serum beta-lipoprotein. *Archives of Neurology*, **8**, 438–454.

Sperling, M. A., Hiles, D. A., and Kennerdell, J. S. (1972). Electroretinographic responses following vitamin A therapy in abetalipoproteinaemia. *American Journal of Ophthalmology*, **73**, 342–349.

Sobrevilla, L. A., Goodman, M. L., and Kane, C. A. (1964). Demyelinating central nervous system disease, macular atrophy and acanthocytosis (Bassen-Kornzweig syndrome). *American Journal of Medicine*, **37**, 821–828.

Sturman, R. M. (1968). The Bassen-Kornzweig syndrome: 18 years in evolution. *Journal of Mount Sinai Hospital New York*, **35**, 489–517.

Thompson, R. H. S. (1972). Fatty acid metabolism in multiple sclerosis. *Biochemical Society Symposia*, **35**, 103–111.

Wolff, O. H., Lloyd, J. K., and Tonks, E. L. (1964). Abetalipoproteinaemia with special reference to the visual defect. *Experimental Eye Research*, **3**, 439–442.

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