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Pathology of Chronic Vitamin E Deficiency in Fatal Familial Intrahepatic Cholestasis (Byler Disease)

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Summary. A case of fatal familial intrahepatic cholestasis (Byler disease) developed a neuromuscular syndrome similar to that in experimental vitamin E deficiency and abetalipoproteinemia, and died of hepatic and cardiac failure. Serum vitamin E level was extremely low. Autopsy revealed intrahepatic cholestatic cirrhosis without obliterative lesions in the bile duct system and marked splenomegaly with splenoma-like nodules. The other pathological lesions were considered to be due to chronic vitamin E deficiency caused by fat-malabsorption. They included almost all of the lesions previously described in the studies of experimental vitamin E deficiency as follows: 1. Mitochondrial changes especially of the hepatocyte and cardiac muscle. 2. Cardiomyopathy. 3. Myopathy. 4. Vasculopathy. 5. Systemic lipofuscinosis. 6. Lesions of the reproductive and endocrine organs. 7. Kyphoscoliosis and pes cavus. 8. Systemic neuroaxonal dystrophy with peripheral neuropathy.

Key words: Intrahepatic cholestasis – Vitamin E deficiency – Mitochondria – Cardiomyopathy – Lipofuscin

Fatal familial intrahepatic cholestasis is a rare but well recognized clinical entity, which was first described in an Amish kindred named Byler, and is called Byler disease after them (Clayton et al. 1965 and 1969). Thereafter, 12 other families of varied ethnic and racial backgrounds were reported (Schubert 1965, Juberg et al. 1966; Gray and Saunders 1966; Hirooka and Ohno 1968; Linarelli et al. 1972; Williams et al. 1972; Odawara and Shiraki 1972; Ballow et al. 1973; Odievre et al. 1973; Dahms 1979). Persistent cholestasis in Byler disease caused chronic deficiency of fat-soluable vitamins, induced ricket due to vitamin D deficiency, and haemorrhagic diathesis due to vitamin K deficiency in about a half of the reported cases. However, symptoms due to chronic vitamin E deficiency have been described in none of these cases. The authors experienced a case of Byler disease that developed a neuromuscular syndrome similar to that in experimental vitamin E deficiency (Einarson 1952), abetalipoproteinemia (Schwartz et al. 1963) and chronic liver disease in infancy (Rosenblum et al. 1981).

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The patient died of hepatic and cardiac failure. Systemic postmortem examination demonstrated full-blown chronic vitamin E deficiency including almost all of the lesions previously described in the studies of experimental vitamin E deficiency, in addition to typical hepatic lesions of Byler disease.

Case Report

The patient was the second child, born after 38 weeks of gestation weighing 2,130 g. Her brother died of hepatic failure at 34 months after a long history of jaundice. Her parents were first cousins. No hepatic disorder was noted in the other members of her pedigree, although, her mother complained of pruritus during the course of pregnancy.

Steatorrhoea was noticed soon after her birth, jaundice one week and pruritus 2 months later. Laparotomy at 6 months revealed normal extrahepatic bile ducts, and histological findings of the liver biopsy were interpreted as cholangiolitis. She complained of fever and increasing jaundice at 18 months, and was diagnozed as pyelonephritis. She became able to walk at 24 months. Intravenous pyelography at 3 years incidentally disclosed cholelithiasis. Cholecystectomy was performed 10 months later. Ascites developed postoperatively, and relieved by albumin transfusion and administration of diuretics. Thereafter, ascites and increasing jaundice were noted once or twice in a year during the episodes of diarrhea and fever. Developmental retardation and persistent pruritus were her continuing problems.

Staggering gait and weakness of the lower limbs were first noted at 9 years. Examination of serum vitamin E at 10 years disclosed an extremely low level (0.06 mg/dl, normal 0.8–1.5 mg/dl), and administration of fat-soluable vitamins including vitamin E (100 mg/day) was maintained thereafter. However, she became unable to stand without support at 11 years, and examination of the ocular fundi because of visual disturbance revealed retinitis pigmentosa.

At 12 years, she was admitted to Jichi Medical School Hospital. Her Fanconi index was 67%. Her intelligence quotient was 55. Vascular spiders were present in the face. The liver was palpable 1 cm below the right costal margin, and spleen 15 cm below the left costal margin. Both iliac joints were dislocated. Muscles of the legs were atrophic. Both foot joints were contracted with pes cavus formation. Laboratory examination revealed anaemia (Hb 7.3 g/dl), thrombocytopaenia ($58 \times 10^3/mm^3$), increased serum bilirubin (5.0 mg/dl, direct 3.9 mg/dl), normal serum cholesterol (148 mg/dl) and elevated alkali phosphatase activity (22.4 Bodansky Units). The serum ceruloplasmin, copper and alpha$_1$-antitrypsin levels were slightly elevated. Liver biopsy disclosed bridging fibrosis and cholestasis without obliterative changes in the cholangioles. She was diagnozed as fatal familial intrahepatic cholestasis (Byler disease). Neurological examination at 13 years revealed absent deep reflexes, decreased vibratory sensation, cerebellar symptoms and ophthalmoplegia. Her visual acuities of both eyes were 0.03. No color blindness was noted.

At the time of her last admission in July 1980, her height was 131 cm and weight 37 kg with generalized oedema. Laboratory examination revealed pancytopaenia (Hb 6.8 g/dl, WBC $2,600/mm^3$, Platelet $29 \times 10^3/mm^3$) hypoproteinaemia (4.0 g/dl), markedly increased serum bilirubin (23.9 mg/dl, direct 13.2 mg/dl) and extremely low choline esterase activity (0.01 delta pH). The heart was moderately enlarged with a systolic murmur (Grade 3/4). Symptomatic therapy temporarily relieved her complaints, and her weight fell to 34 kg. However, cardiac failure with Q waves in ECG developed 2 months later. She died after an attack of fever at 17 years and 8 months.

Materials and Methods

An autopsy was performed 2 h after her death. Examination of the retina and extremities was not permitted. Small tissues of the liver, heart and brain for electron microscopic study were fixed in 2% buffered glutaraldehyde, and post-fixed in 1% OsO_4. Sections from each organs were fixed in 10% formalin, embedded in paraffin and stained by H-E, Azan-Mallory, Masson trichrome, Elastica van Gieson, Orcein, Gomori's reticulin, PAS, PAM, Luxol fast blue, Sudan black, Prussian blue, Kossa method for calcium, rubeanic acid method for copper, and prolonged Ziehl-Neelsen Method. Unstained sections were examined by UV-light. Frozen sections of the heart and skeletal muscles were stained by Sudan III, Sudan black and Nile blue.

Results

The following lesions were demonstrated by pathological examination.

Intrahepatic Cholestatic Cirrhosis. The liver was moderately enlarged and weighed 1,120 g. The surface was finely granular. The large bile ducts were normal except for cholecystectomy. Histologically, extensive bridging fibrosis divided the liver parenchyma (Fig. 1a). Mild round cell infiltration was present both in the septa and the portal triads. The cholangioles were empty without obliterative change. Numerous bile casts were seen between the liver cell cords showing tubular formations. Degenerative hepatocytes were scattered in the centers of the pseudolobules. The cytoplasms of the other hepatocytes were swollen and contained bile, a small amount of lipofuscin and haemosiderin granules.

Electron microscopically peculiar, highly electron-dense, lamellar, curved structures were noted in the cytoplasm of the degenerative hepatocytes (Fig. 1b). In the swollen hepatocytes, a striking increase of enlarged mitochondria was observed. Endoplasmic reticulum was markedly reduced (Fig. 1c). Mitochondrial enlargement was also seen in the cholangiolar epithelium.

Splenomegaly with Splenoma-Like Nodules. The spleen was markedly enlarged and weighed 600 g. Several brown nodules up to walnut in size without a fibrous capsule were noted between the foci of old and recent haemorrhages (Fig. 2a). Histologically, nodules were composed of thin medullary cords and irregular shaped sinuses (Fig. 2b). Lymphocytes were sparse and no lymph follicle existed within these nodules.

Cardiomyopathy. The heart was moderately dilated, enlarged and weighed 250 g. Histologically, numerous foci of small scars and fresh myocardial necroses were distributed in the inner layer of the myocardium of both ventricles (Fig. 3a). Remaining myocardial fibers were clear and contained numerous minute fat droplets and a moderate amount of lipofuscin granules. The conducting system was intact. No luminal stenosis was noted in the coronary arteries. No mural thrombosis was revealed, although mild fibroelastosis was seen over the right atrial endocardium.

Electron microscopically, mitochondria in clear muscle fibers were enlarged, apparently increased in number and contained many electron-dense bodies. Electron-dense, tubular configurations probably derived from mitochondrial criatea were observed within the mitochondria of the degenerative myocardial fibers (Fig. 3b).

Myopathy. Psoas, pectoralis, intercostal and axillary muscles and diaphragm were histologically examined. In all of the examined muscles, irregularity in fiber sizes was prominent, and over a half of the muscle fibers were round with central nuclei in transvers sections. Numerous minute fat droplets and occasional lipofuscin granules were present within these muscle fibers (Fig. 4a). Foci of hyaline necroses were scattered in the psoas (Fig. 4b). No group atrophy was observed in the muscle fibers.

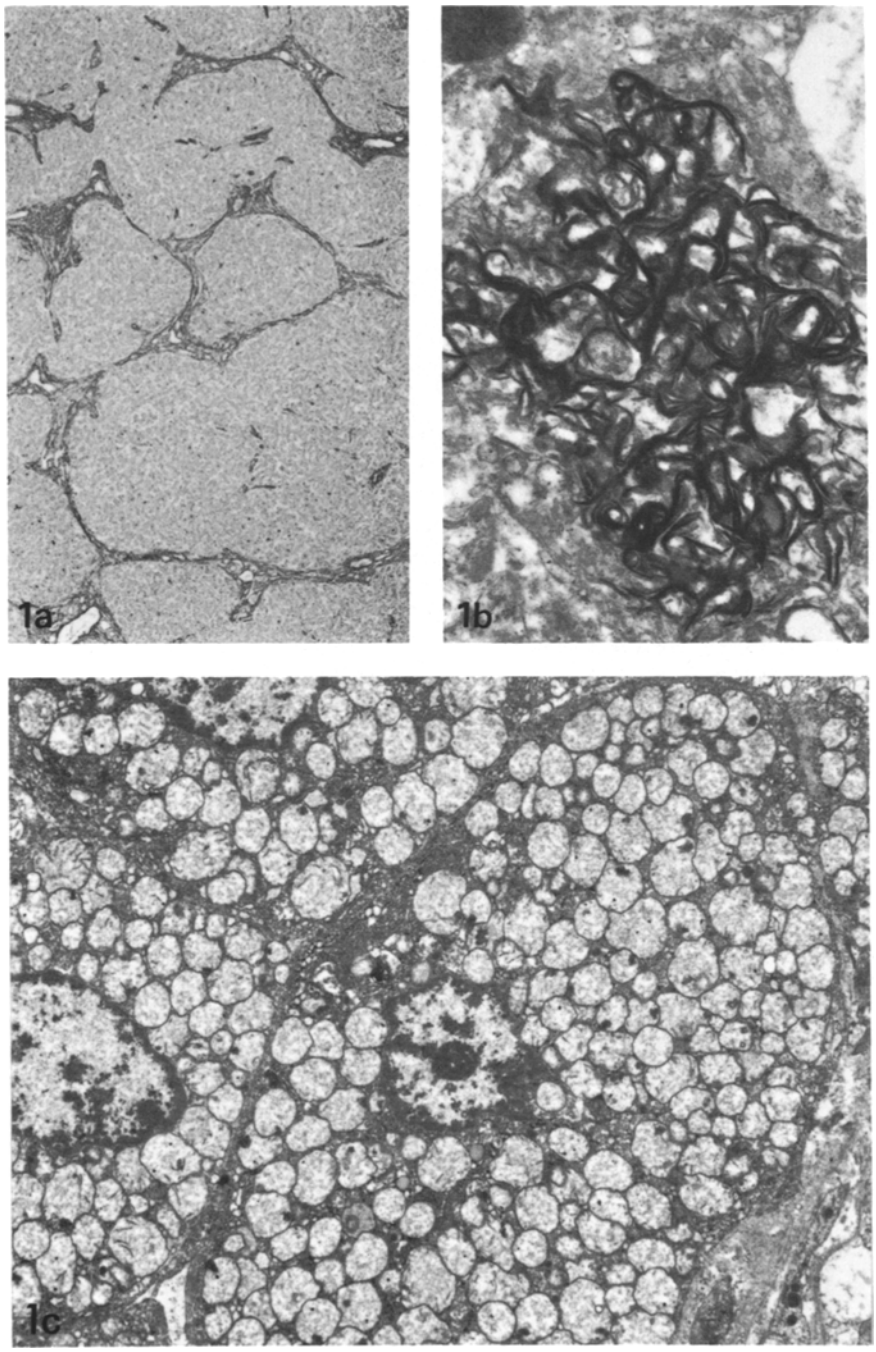

Fig. 1 a–c. Hepatic lesions. **a** Liver parenchyma is divided by thin septa rich in elastic fibers. Pseudolobules are small. Scattered minute dark dots are bile casts. EVG, ×25. **b** A peculiar, electron-dense, lamellar, curved structure in a degenerative hepatocyte. ×16,600. **c** Marked increase of enlarged mitochondria in swollen hepatocytes. Electron-dense bodies in mitochondria are increased in number. ×4,000

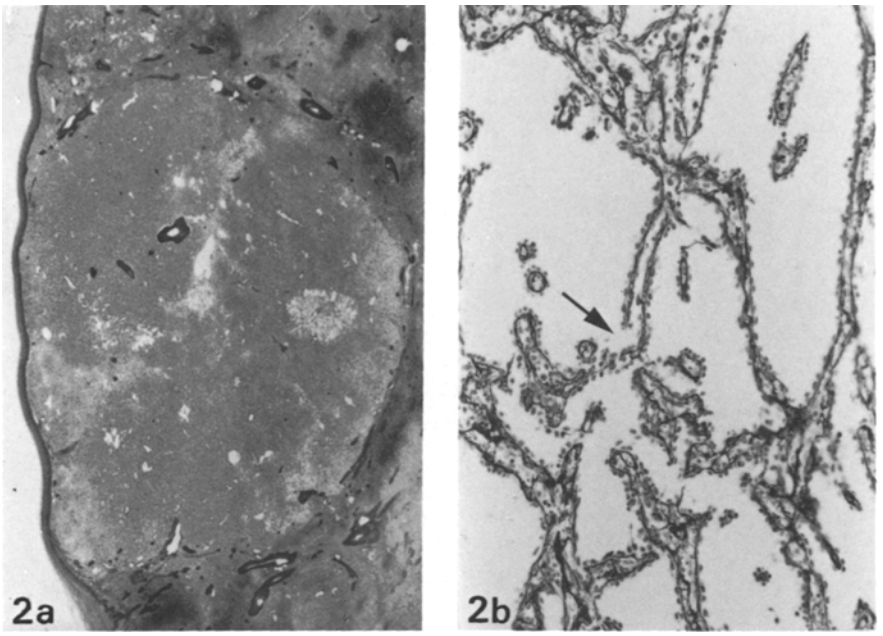

Fig. 2a, b. Splenic lesions. **a** The largest nodule in the subcapsular region of the spleen compressing the surrounding parenchyma. Reticulin, ×3. **b** Thin medullary cords and dilated sinuses in the nodule with sparse lymphocytes. An arteriole and dilated sinus are in direct communication (*arrow*). Reticulin, ×150

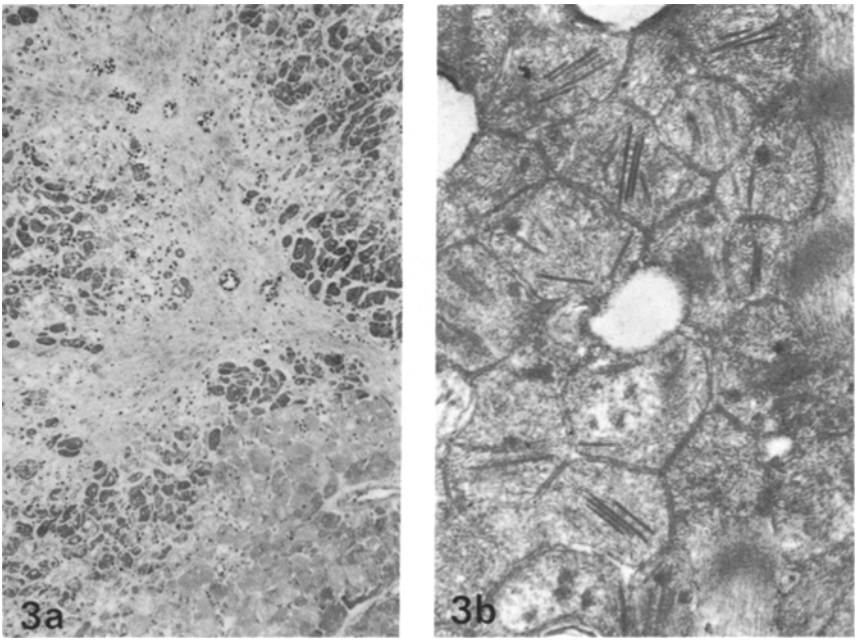

Fig. 3a, b. Cardiomyopathy. **a** A myocardial scar surrounded by degenerative cardiac muscle fibers. Azan-Mallory, ×75. **b** Electron-dense, tubular structures in mitochondria of a degenerative muscle fiber. ×20,000

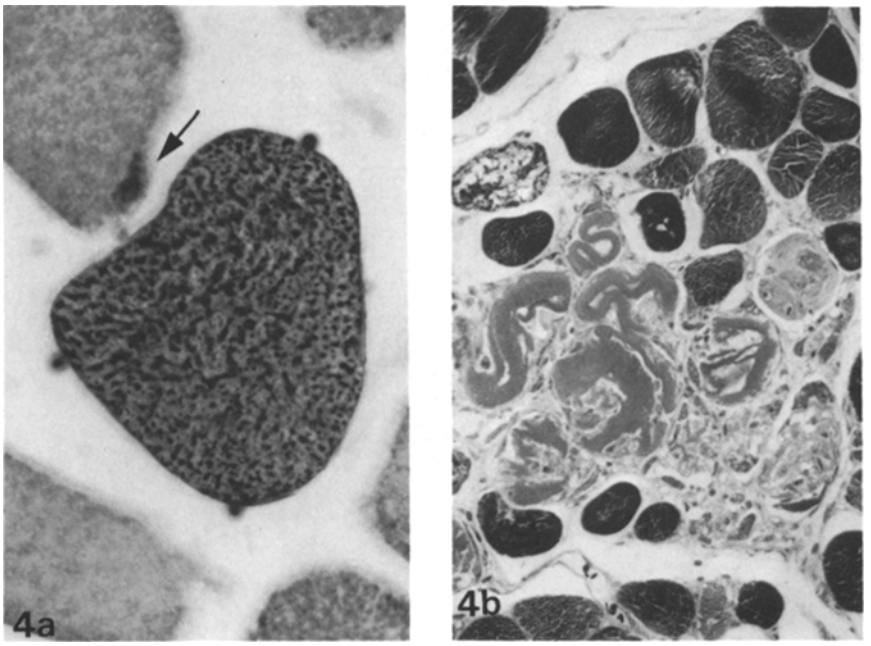

Fig. 4a, b. Myopathy. **a** Numerous minute fat droplets in a muscle fiber of the psoas. The larger granule (*arrow*) is a lipofuscin granule. Frozen section, Sudan black, ×700. **b** Irregularity in fiber sizes and a focus of hyaline necrosis of the muscle fibers in the psoas. Azan-Mallory, ×150

Vasculopathy. Disruption of the inner layer of the arterial walls (Fig. 5a), single cell necrosis of the medial smooth muscle cells and focal transmural fibrosis of the media were noted in the small branches of the coronary, pulmonary, renal, pancreatic, hepatic and femoral arteries. In addition, there were foci of angiomatoid proliferation of the sinusoidal vessels around the pulmonary arterioles. Elastic lamellae of the larger arteries were focally calcified and fragmented. Fibrinoid necrosis of the arteriole was not observed.

Electron microscopic examination of the capillaries of the brain stem and myocardium demonstrated deposition of lipofuscin granules in the endothelium along with mitochondrial enlargement (Fig. 5b).

Systemic Lipofuscinosis. In addition to lipofuscinosis of the hepatocyte, cardiac and skeletal muscles and vascular endothelium, systemic examination disclosed brown pigment deposition in all of the smooth muscle cells including vascular smooth muscle cells. The pigments were consistent with lipofuscin, since they were acid-fast by prolonged Ziehl-Neelsen method, argyrophile, PAS-, Luxol fast blue- and Sudan black-positive, and showed yellow autofluorescence by UV-light. Lipofuscinosis was most prominent in the oesophageal wall (Fig. 6a). Almost all of the epithelial cells except for those of the gastrointestinal and genitourinary mucosae and epidermis also contained small amount of lipofuscin granules. Among the endocrine organs, lipofuscinosis was severest in the adrenal cortex. Macrophages in the lymph nodes contained a large amount of lipofuscin,

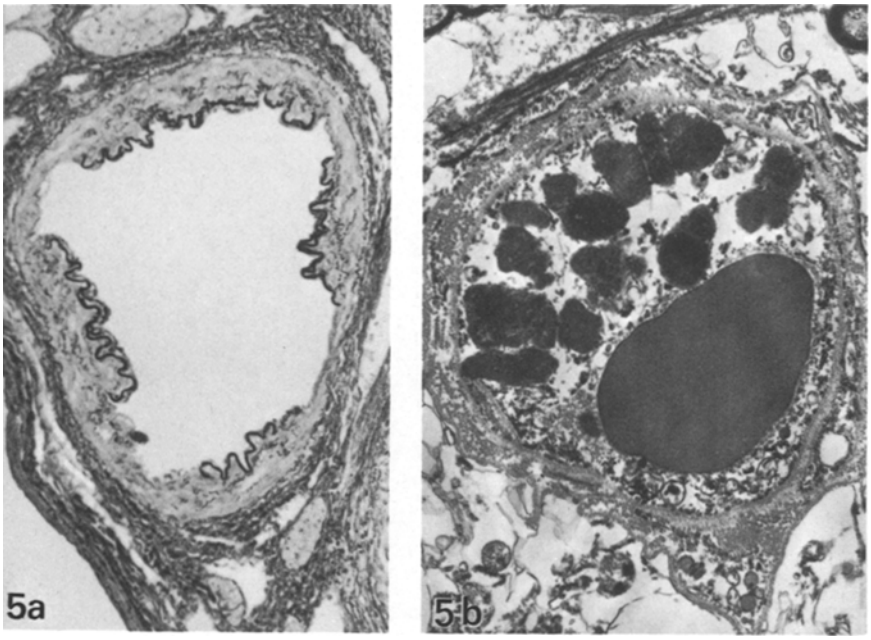

Fig. 5a, b. Vasculopathy. **a** Disruption of the inner layer of a hepatic arterial branch. EVG, ×60. **b** Lipofuscin granules along with mitochondrial enlargement in a capillary endothelium of the brain stem. ×7,500

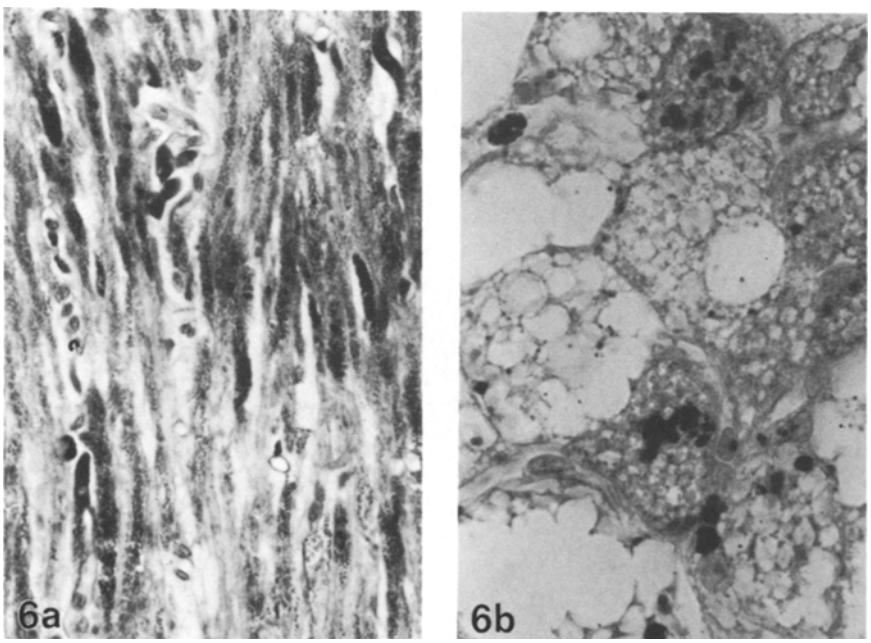

Fig. 6a, b. Lipofuscinosis. **a** Marked lipofuscinosis of the oesophageal wall. PAS, ×240. **b** Lipopigment granules in axillary fat cells showing reticular cytoplasm. Sudan black, ×600

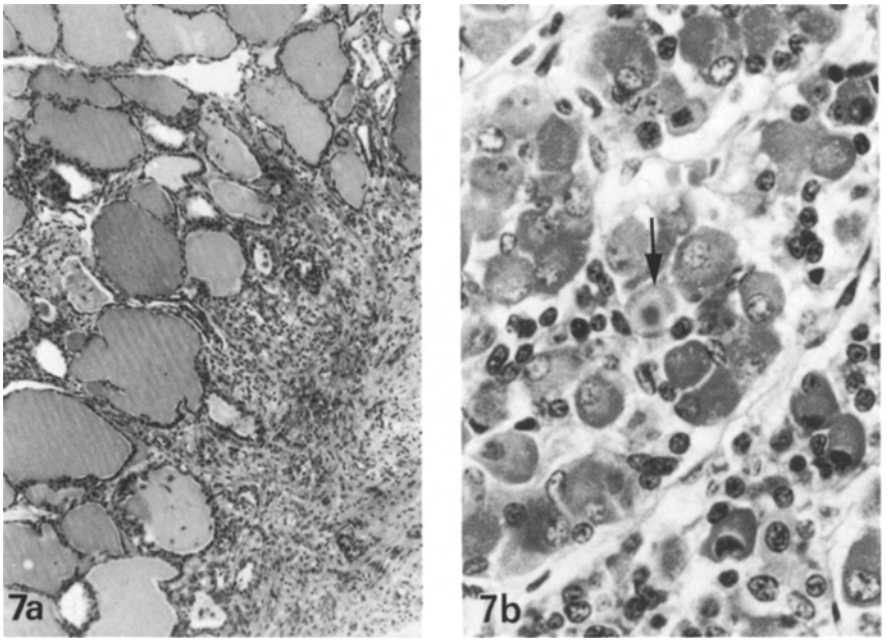

Fig. 7a, b. Endocrine lesions. **a** Fibrosis of the thyroid with round cell infiltration. HE, ×75. **b** Marked swelling of the beta cells in the adenohypophysis with a hyaline globule in a cytoplasm (*arrow*) HE, ×300

although lipofuscinosis of the spleen and bone marrow was slight. Fat cells had reticular cytoplasm and a few pigment granules similar to hibernating gland and human hibernoma (Fig. 6b).

Lesions of the Reproductive and Endocrine Organs. Atretic follicles were scattered, and no corpus albicans existed in the ovaries, although the patient had irregular menstruation. The endometrium was atrophic, and the myometrium was brown in color due to lipofuscinosis. The breasts were normal. The thyroid was small and revealed scattered foci of interstitial fibrosis with mild round cell infiltration (Fig. 7a) and focal C-cell hyperplasia. The parathyroids were hyperplastic. Hyperplasia of the islets were noted in the pancreas. Both adrenal cortices were atrophic. In the adenohypophysis, the alpha cells were apparently increased in number, and the cytoplasms of the beta cells were enlarged with occasional hyaline globules (Fig. 7b). Spheroids due to axonal dystrophy were scattered in the neurohypophysis.

Neuropathological Findings. Systemic axonal dystrophy involving the basal ganglia, grey matter of the spinal cord and dorsal root ganglia in addition to the nuclei of the brain stem, and degeneration of the posterior column, spinocerebellar tract and posterior roots of the spinal cord, peripheral neuropathy and marked neuronal lipofuscinosis were the main neuropathological lesions. Detailed neuropathology will be described in a separate report.

Other Findings. Mild kyphoscoliosis, osteoporosis and hyperplasia of haematopoiesis were noted in the vertebrae. No rachitic change was observed. Hyperkeratosis of the epidermis and sclerosis of the dermis were seen in the skin. There were scars of pyelonephritis in the kidneys.

Discussion

The cause of cholestasis in Byler disease has been considered to be due to disturbance in bile transport across the canalicular membrane, since no obliterative lesion of the bile duct system has been demonstrated in the reported cases. Abnormality of bile acid metabolism leading to accumulation of lithocolic acid in the bile and serum of the patients was reported as a possible cause of canalicular damage in subsequent studies (Linarelli et al. 1972; Williams et al. 1972). The peculiar, electron-dense, lamellar configurations discerned in the present study along with infantile cholelithiasis both in the present case and 3 other cases of Byler disease (Schubert 1965; Odievre et al. 1973) may be related to bile acid abnormality.

Chronic fat-malabsorption due to persistent cholestasis induced chronic deficiency of fat-soluable vitamins in Byler disease. However, clinical symptoms in Byler disease has been ascribed to chronic vitamin E deficiency in none of the reported cases.

Vitamin E deficiency is a cause of hepatocellular necrosis in swine (Porta et al. 1968), and may be an another factor contributing to the hepatic damage in the present case. Our observation of mitochondrial abnormalities such as enlargement and increase in number were consistent with the previous descriptions in the studies of experimental vitamin E deficiency in hepatocyte (Riede et al. 1972), dystrophic neuronal axon (Schochet 1971), endotheliun (Fischer and Nelson 1973), smooth muscle (Yarrington and Whitehair 1975), skeletal muscle (Dahlin et al. 1978) and cardiac muscle (Van Vleet et al. 1977).

Cardiomyopathy in vitamin E deficiency has been studied mainly in the field of veterinary medicine (Oksanen and Poukka 1972; Van Vleet et al. 1977). In human pathology, cardiomyopathy was the direct cause of death in 2 autopsy cases of abetalipoproteinaemia (Sobrevilla et al. 1964; Dische and Porro 1970), which was also characterized by chronic fat-malabsorption and low serum vitamin E level without hepatic disorder (Herbert et al. 1978). Cardiac enlargement was also described in Byler disease (Juberg et al. 1966) and mucoviscidosis (Sung 1964).

Myopathy in experimental vitamin E deficiency has been studied since 1931 (Goettsch and Pappenheimer). Myopathic lesions in human fat-malabsorption was first described in mucoviscidosis (Oppenheimer 1956). Gait disturbance in an older patient with Byler disease (Juberg et al. 1966) may be related to myopathy and neuropathy caused by vitamin E deficiency. A recent report described clinical improvement of myopathy in a patient with infantile intrahepatic cholestasis after administration of a large dose of vitamin E (Tomashi 1979).

Vasculopathy in vitamin E deficiency was extensively considered after discovery of vasculogenic cerebellar lesions in chicks (Wolf and Pappenheimer 1931).

Fibrinoid necrosis of the arterioles was shown in subsequent studies. Endothelial damage was described as the cause of the vascular lesions (Van Vleet et al. 1977). Degeneration of the smooth muscle cells (Yarrington and Whitehair 1975) may be another factor contributing to the vasculopathic lesion in vitamin E deficiency. The pulmonary arteriolar lesion in the present case resembled angiomatoid lesion in pulmonary hypertension. Pulmonary hypertension was noted in chronic obstructive liver disease (Rosenblum et al. 1981), although no vasculopathic lesion has been thus far identified in human chronic fat-malabsorption.

Lipofuscinosis in human fat-malabsorption has been reported in mucoviscidosis (Kerner and Goldbloom 1960), congenital biliary atresia (Sung and Stadlan 1966), abetalipoproteinaemia (Dische and Porro 1970) and Byler disease (Dahms 1979). However, systemic study including skeletal muscle, endocrine organs, fatty tissue and nervous system has been performed in none of the human material. The present study confirmed the same extensive lipofuscinosis as the results of old experiments (Menschik et al. 1949; Einarson 1952), although cytotoxicity of lipofuscin accumulation was not apparent.

Lesions of the reproductive and endocrine organs in experimental vitamin E deficiency (Lee 1960) resembled those in the present case. The beta cell lesion seen in the present study probably reflects increased activity of FSH and TSH cells noted in an animal experiment (Ichihara 1969) secondary to ovarian and thyroid damage. No lesion in endocrine organs has been thus far documented in human vitamin E deficiency.

The neurological syndromes and neuropathological lesions of the present case also closely resembled those in experimental and human vitamin E deficiency (for references, see Rosenblum et al. 1981).

Chronic deficiency of fat-soluable vitamins other than vitamin E seems to have caused morphological changes in the present case. Kyphoscoliosis and deformity of foot joint were observed in pure vitamin E deficiency (Einarson 1952). However, chronic vitamin D deficiency must taken into consideration as another cause of other bone and joint deformities such as retardation in bone growth and dislocation of the iliac joint. Hyperplasia of the parathyroid glands due to vitamin D deficiency may be the cause of osteoporosis, metastatic calcification and C-cell hyperplasia of the thyroid. Hyperkeratosis of the epidermis may be sequalae to vitamin A deficiency. The severe visual disturbance noted in the present case may partly be related to vitamin A deficiency, since combined vitamin E and A deficiency is known to cause marked neuronal loss in the retina of rats when compared with pure vitamin E deficiency (Robison et al. 1980).

The nodules in the spleen of the present case resembled hamartomatous splenomas (Ross and Schiller 1971), although the effects of longstanding portal hypertension and vasculopathy due to vitamin E deficiency must also taken into consideration as possible causes of these lesions. Splenoma complicated by portal hypertension was once reported (Bhagwat et al. 1975).

Our systemic examination demonstrated almost all of the lesions documented in the previous studies of experimental vitamin E deficiency. Administration

of vitamin E after the age of 10 years was unable to prevent the development of these variegated lesions in the present case. The authors consider that supplementation of fat-soluable vitamins, especially vitamin E, should be started in early infancy in children with persistent fat-malabsorption due to severe cholestasis, mucoviscidosis and abetalipoproteinaemia.

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