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Case report

Vascular and myofibrillar lesions in acute myoglobinuria associated with carnitine-palmityl-transferase deficiency

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Summary. A case of severe exercise-induced myoglobinuria in a 14-year-old boy suffering from a carnitine-palmityl-transferase (CPT) defect is reported. Biopsies of the forearm muscle were examined using light and electron microscopy in the acute and recovery phases of the illness. The first biopsy showed the presence of scattered foci of necrosis where necrotic fibres with occasional disruptions of the basal lamina were seen around injured capillaries. Various degrees of damage and different stages of evolution were found in these foci, which also contained regenerating muscle fibres. In the second biopsy, performed 2 weeks later, most of the fibres displayed a normal structure. Necrosis was no longer present. However, in some areas perivascular fibrosis was prominent, the fibres were small and irregularly shaped, and their nuclei often centrally located. These data strongly suggest that circulatory disorders and ischaemia, brought about by premature acute metabolic imbalance, could be involved in the development of exercise-induced myolysis observed in CPT deficiency. The risk of fibrous cardiomyopathy in these patients is pointed out.

Key words: Carnitine-palmityl-transferase deficiency – Acute vascular lesions – Acute myofibrillar lesions – Ischaemia – Electron microscopy

Introduction

Myoglobinuria is observed during acute rhabdomyolysis and may lead to renal failure. Rhabdomyolysis has been reported to occur following acute poisoning, sepsis and acute metabolic disorders (such as severe hypokalaemia). Acute rhabdomyolysis is also observed in some congenital metabolic abnormalities, such as carbohydrate and lipid metabolism-related diseases. Recurrent myoglobinuria which has long been considered to be idiopathic (Meyer-Betz 1910), has been shown to be linked to carnitine palmityl transferase (CPT) deficiency (Di Mauro and Di Mauro 1973; Bank et al. 1975; Angelini et al. 1981). This enzyme, contributing to the transport of long-chain fatty acids, plays a key role in the mitochondrial energy-producing process. The part played by prolonged exercise, diet, viruses, as well as hypothermia in triggering the rhabdomyolysis has been pointed out in numerous reports (Bank et al. 1975; Patten et al. 1978; Reza et al. 1978; Brownell et al. 1979; Bertorini et al. 1980; Di Donato et al. 1981; Palmucci et al. 1981; Meunier et al. 1982). However, the mechanisms by which acute muscle necrosis occurs in patients with CPT deficiency are still unclear (Di Mauro and Papadimetriou 1986). Morphological analyses in myoglobinuria with CPT deficiency have shown the presence of zones of acute myolysis. The fat content in the muscle fibres has been emphasized, but the early morphological changes during acute muscle necrosis have not so far been examined.

We therefore report the case of a 14-year-old boy with CPT deficiency in whom morphological changes in forearm muscles were analysed by light and electron microscopy during both acute and recovery phases of a severe exercise-induced myoglobinuria.

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Case report

A 14-year-old healthy boy complained of acute pain in the muscle of the thighs after a 2-h heated handball game. Neither he nor his family had any previous history of similar episodes. His temperature rose to 38° C in the evening. Four days later, the boy was admitted to the intensive care unit with persistent diffuse pain in the four limbs. This was severe enough to prevent any movement and physical examination revealed muscle oedema and diffuse tenderness to palpation. Ideomotor and tendon reflexes were suppressed in the four limbs, except for the patellar reflex. Intense pain was present upon voluntary contraction of the abdomen. The trunk muscles and diaphragm were affected (vital capacity was 1.2 l).

Heart rate was 150 beats/min and blood pressure 120/80 mmHg. The heart size was found to be enlarged on chest roentgenograms. The electrocardiogram showed modifications of the

ST segment and the T-wave characteristic of hyperkalaemia. The urine was dark brown and contained myoglobin. Renal failure was present: there was oliguria, the blood urea nitrogen was 15.3 mmol/l, potassium was 7.6 mEq/l, serum creatinine was 115 mmol/l. Myoglobinaemia was high at 50000 ng/ml. The levels of muscle enzymes in the serum were also high: creatinine phosphokinase (CPK) was 722000 IU/l with an increased MB fraction (20% of total); aldolase 22.8 IU/l; lactic dehydrogenase 7000 IU/l. Intravascular disseminated coagulopathy of moderate intensity was present. Viral studies in serum were and remained negative. No antibodies against striated muscle fibre or antinuclear antibodies could be detected in the serum. Electromyographic examination showed an intensely disorganized pattern of muscle activity and a low-amplitude spontaneous denervation activity.

Two successive biopsies (11 and 25 days after the causal exercise) were performed in the back of the left forearm (extensor digitorum) under local anaesthesia, with the informed consent of the child's parents. Biochemical analysis of muscle homogenate (H. Carrier) obtained from the second biopsy showed normal levels of glycolytic enzymes, but abnormally low levels of enzymes involved in lipid metabolism: CPT activity was very low in C1 and C2 fractions, and non-measurable in the S2 fraction. Carnitine membranous fraction was only slightly lowered.

After restoration of normovolaemia by vascular filling (plasma 500 ml) and administration of furosemide (40 mg), diuresis reappeared without use of extrarenal epuration. Clinical improvement was associated with progressive disappearance of muscle pain and oedema, with recovery of muscle strength, of ideomotor, bone and tendon reflexes, and was marked by a rise of vital capacity to 2.5 l within a few days. Clarification of urine and normalization of renal function were also rapid. Two weeks after admission, the patient was able to walk. The boy was discharged 1 month after admission.

A year later, a mild attack of muscle pain in the legs and myoglobinuria occurred, 48 h after parotitis, without any previous physical exercise. The clinical outcome was favourable and the boy was discharged 3 days after admission.

With the informed consent of the child's parents, muscle biopsies were obtained from the back part of the left forearm (extensor digitorum), 11 and 25 days respectively after the causal exercise. For conventional histopathological studies, muscle samples were fixed in formalin and embedded in paraffin. Other samples were immersed in 5% glutaraldehyde in a 0.1 M phosphate buffer (pH 7.4), postfixed for 1 h with osmium tetroxide in the same buffer, dehydrated in graded alcohols, and embedded in an Araldite-Epon mixture. For light microscopy, semithin sections (1 μm) were stained either with toluidine blue in 5% sodium borate, or with periodic acid Schiff (PAS), or ferric haematoxylin, after removal of the embedding medium by sodium methoxide. For electron microscopy, thin sections were contrasted with uranyl acetate and lead citrate, and examined under a Jeol 100 CX electron microscope.

Results

In the first biopsy myolytic foci are distributed throughout the muscle samples (Fig. 1). Myolysis has several degrees of severity and on the longitudinal views the lesions are seen to be segmental (Fig. 2). Apart from completely necrotic fibers from which myofibrils have disappeared, others exhibit fragments of cytoplasm with homogenized fibrils. These fibres contain numerous cells of various types such as erythrocytes, macrophages and basophilic cells with a pale large nucleus. Strongly basophilic spindle-shaped cells (probably satellite cells) can be found closely applied to the surface of the injured fibres. Myotubes are noted. In the fibres where myofibrils are still present, contracture knots are found and transverse disassembly due to Z-line disappearance is observed (Fig. 4). Myolysis foci regularly concern fascicles of myofibrils in which most of the fibres (up to 80%) are damaged. Only a few fibres, located at the periphery of the fascicle, are apparently preserved. Vascular alterations are regularly present in these foci. The vessels are often filled with packed erythrocytes and their walls are disrupted in some places. Interstitial oedema and erythrocytes are observed between the fibres. Erythrocytes are often found within the fibres, either grouped together in the centre of the fibre or located under the surface of the fibre (Fig. 3). No inflammatory reaction can be noted, but pericyte proliferation is sometimes observed. Outside the myolytic areas, muscle fibres are intact and relaxed. Fine lipid droplets are regularly distributed between the myofibrils.

The second biopsy (taken 2 weeks later) showed most of the fibres to be intact, strongly PAS positive and containing fine lipid droplets. In some areas, however, the fibres are slender and irregularly shaped. Their nuclei are packed together or central. The structure of the vessels is normal in these areas, but fibrosis is prominent. It surrounds the vessels and erodes the fibres.

On electron microscopy in the first biopsy, the most typical features observed are those of focal necrosis. In such foci, the structure of the fibres is completely disorganized. The plasma membrane has disappeared and the basal lamina is disrupted (Fig. 5). These foci are regularly centred on necrotic vessels. Erythrocytes and fibrin are found within the surrounding fibres.

As already observed on light microscopy, myolysis is segmental and more or less complete. When necrosis is complete, the fibres are filled with a homogeneous material, moderately electron-dense. They can only be identified by the persistence of their basal lamina. Only sparse macrophages and more or less lysed erythrocytes can be found within the fibres. In the fibres where contractile material is still recognizable but fragmented and mixed with remnants of cell organelles, various cell types are observed (Fig. 6): macrophages, erythrocytes, exceptional leucocytes and mononucleated cells with a large nucleus and prominent nucleolus. These mononucleated cells contain glycogen fields together with aggregated contractile material which is generally membrane-bound. This picture suggests phagocytic activity in these mononucleated cells. Electron microscopy indicates that cytoplasmic areas surrounding myonuclei have been isolated from the necrotic material by a newly formed tortuous, even incomplete, membrane. Interestingly, neither typical nor degenerating myonuclei can be found in these damaged fibres. Spindle-shaped cells are located along the basal lamina of the degenerating fibres (Fig. 6). The cytoplasm of these satellite cells is homogeneous and rich in ribosomes. Typical myotubes with regularly spaced central nuclei can be seen. Myofibrils can be detected in the largest. In less damaged fibres, transverse dissociation of the myofibrils due to Z-line disappearance is observed (Fig. 10). The sarcomeres are disoriented and fragmented (Fig. 7). Dense granules are present within swollen mitochondria (Fig. 11). The plasma membrane is absent or fragmented and outlined by fibrin

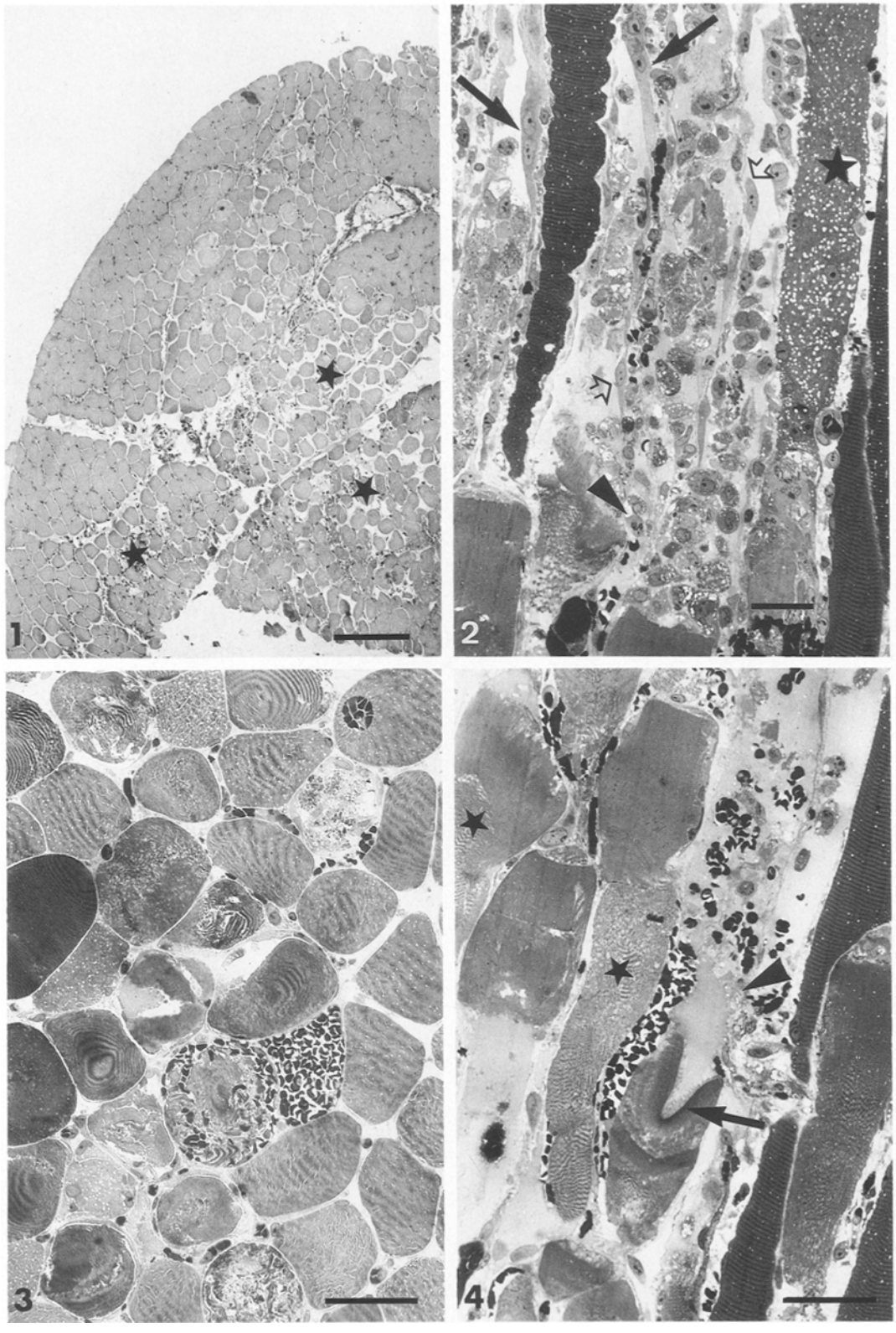
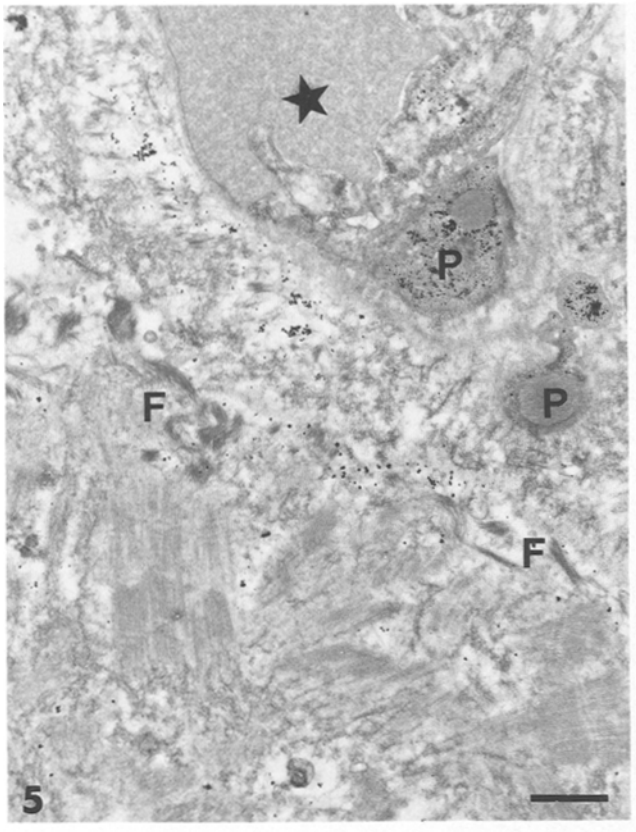


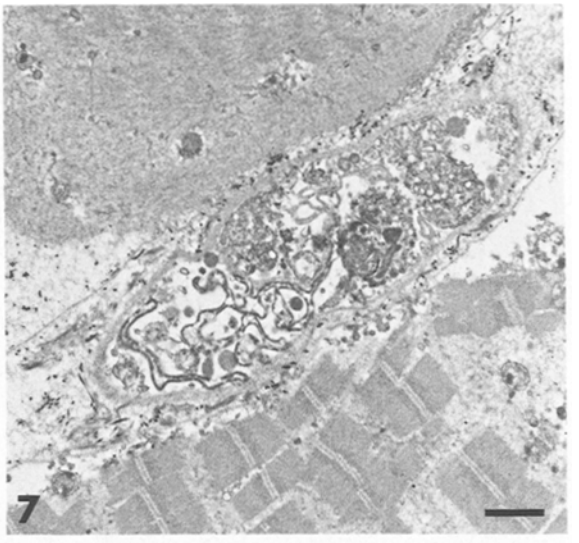
Fig. 1. Transverse paraffin section of muscle sample showing scattered myolysis areas (*asterisks*) where interstitial oedema is prominent. The surrounding fascicles are normal. H & E, ×58. *Bar* 200 μm

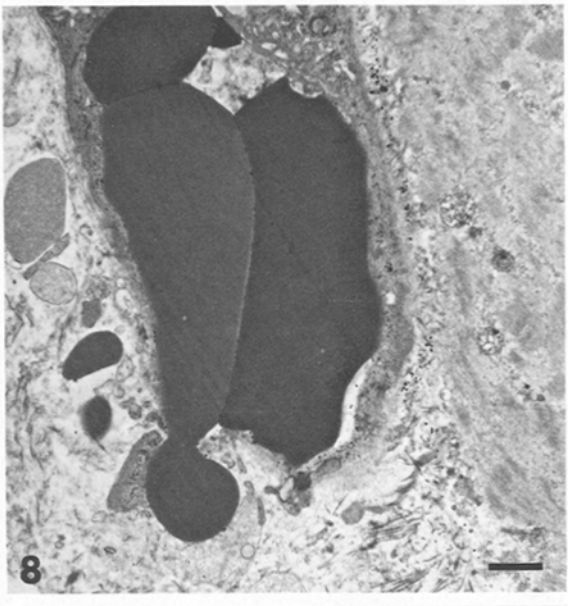
Fig. 2. Longitudinal section through a myolytic focus exhibiting fibres at various stages of necrosis and regeneration. Necrotic fibres contain myofibrillar debris and numerous cells, most of them macrophages. Note a dividing cell (*arrowhead*). In places, necrotic fibres are lined with elongated satellite cells (*light arrows*) and extending myotubes (*dark arrows*). A fibre contains abundant lipid droplets (*asterisk*). Semi-thin section, toluidine blue ×180. *Bar* 50 μm

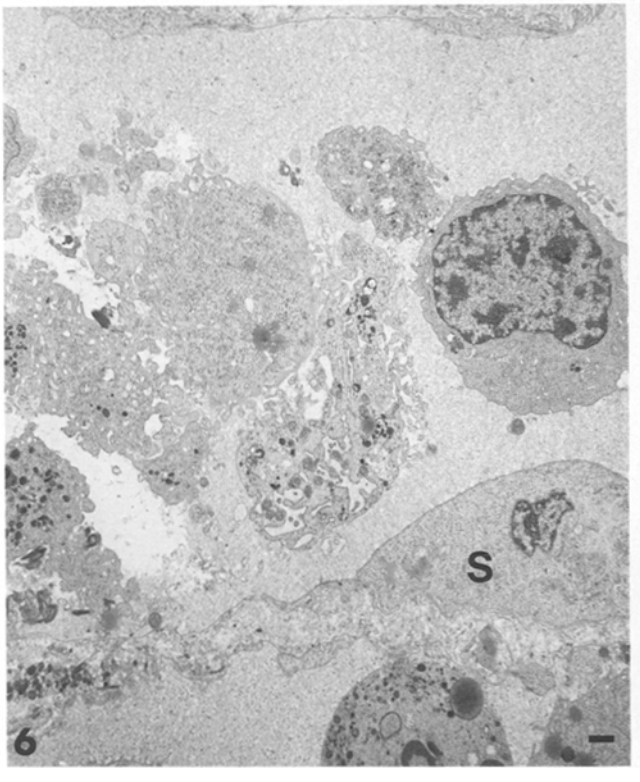
Fig. 3. Transverse section through a myolytic focus showing necrotic fibres, some of them filled with erythrocytes. Semi-thin section, toluidine blue, ×280. *Bar*, 50 μm

Fig. 4. Same myolytic focus as shown in Fig. 2. In a fibre a contracture knot (*arrow*) is seen near a totally necrosed segment (*arrowhead*). Other fibres (*asterisks*) exhibit myofibrillar disassembly. Erythrocytes are aggregated in the capillaries or extravasated in the interstitium and inside the fibres. Semi-thin section, toluidine blue, ×280. *Bar*, 50 μm









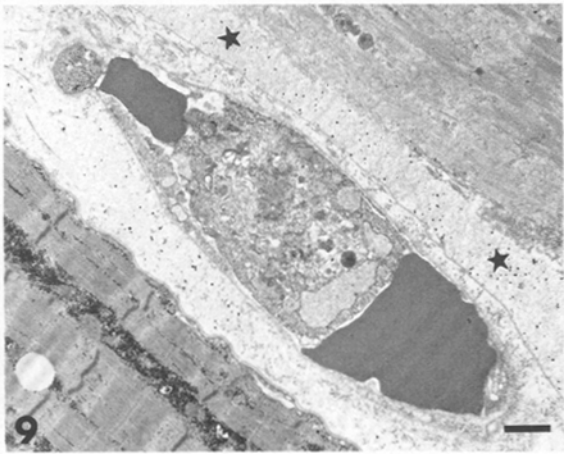


Fig. 5. High magnification of a necrotic focus: near a capillary with degenerated endothelial cells (*asterisk*), partially lysed myofibrillar debris are outlined by fibrin (*F*). The plasma membrane and the basal lamina of the muscle fibre have disappeared. Note the presence of pericyte extensions (*P*) beside the capillary. ×9700. *Bar*, 1 μm

Fig. 6. Within a necrotic fibre, a satellite cell (*S*) extends along the basal lamina and several macrophages are noted at various stages of evolution. ×2900. *Bar*, 1 μm

Fig. 7. Necrosed capillary still outlined by a conspicuous basement membrane between two damaged fibres. In the lower, sarcomeres are set free by Z-line disappearance. In the upper, myofibrillar organization has disappeared. ×7400. *Bar*, 1 μm

Fig. 8. Vascular disruption and passage of an erythrocyte into the interstitial space next to a damaged fibre. ×6500. *Bar*, 1 μm

Fig. 9. In a capillary, partial obstruction of the lumen by necrotic material and local disappearance of the endothelial coating. In the damaged fibre at the top, the plasma membrane has disappeared and the myofibrillar debris is separated from the basal lamina by a poorly electron-dense substance (*asterisk*). ×5450. *Bar*, 1 μm

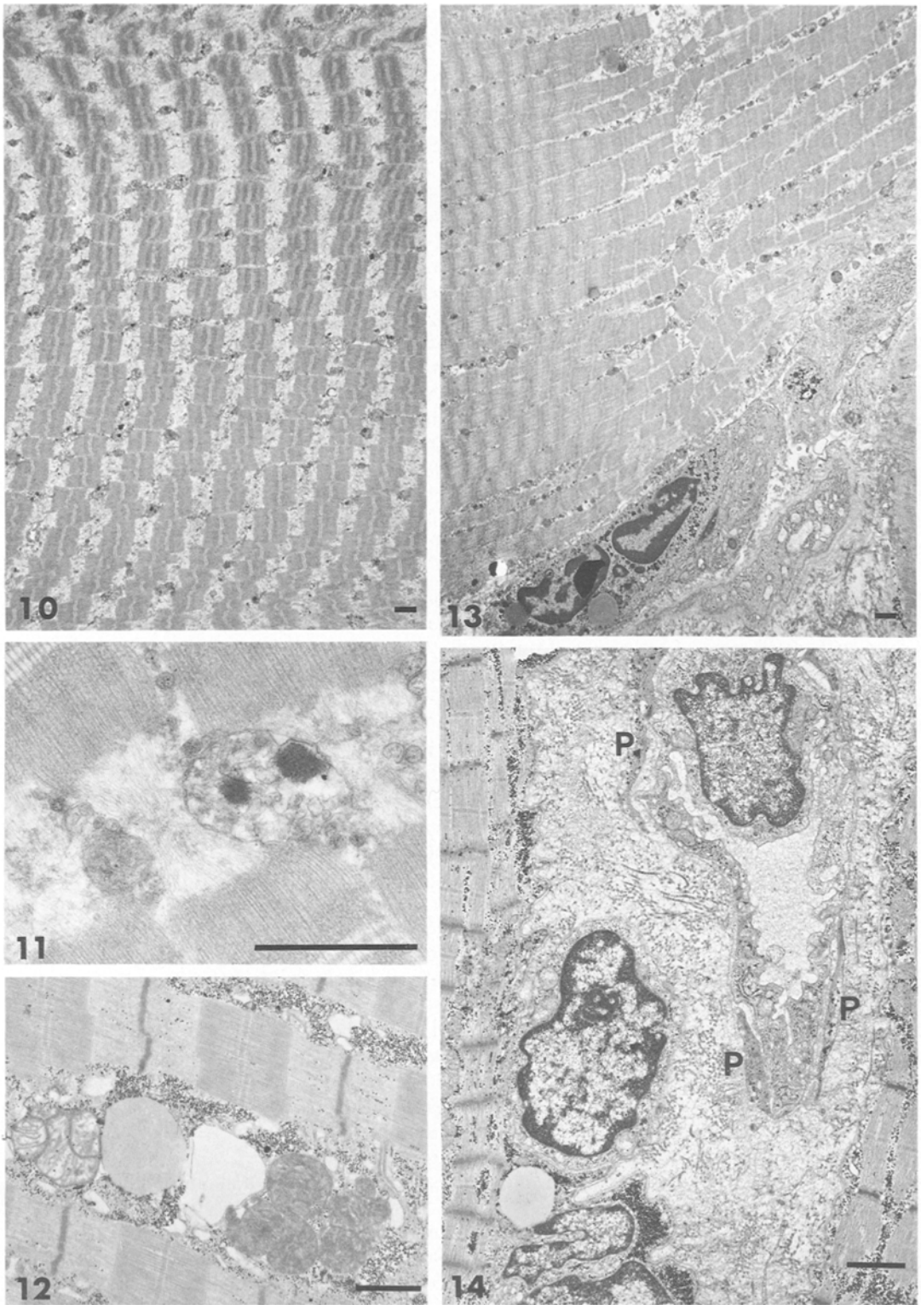


Fig. 10. Longitudinal view of the transversal disassembly of the myofibrils in a fibre after the destruction of the Z-lines. ×3400. *Bar*, 1 μm

Fig. 11. High magnification of the Z-line disappearance. Swollen mitochondria contain dense inclusions. ×25500. *Bar*, 1 μm

Fig. 12. Mitochondrial modifications (densification, fragmentation) in an otherwise unaltered fibre. ×10200. *Bar*, 1 μm

Fig. 13. Localized transverse dissociation of the myofibrils with fragmentation of Z-lines in a hypercontracted fibre. ×2900. *Bar*, 1 μm

Fig. 14. Second biopsy: perivascular fibrosis in an interstitial space, and presence of several pericyte extensions (*P*) surrounding a capillary. ×8700. *Bar*, 1 μm

deposits. When present, it is separated from the basal lamina by poorly electron-dense substance. In minimally damaged fibres, Z-line fragmentation and swollen mitochondria are found close to a local disruption of the plasma membrane (Fig. 13). At some distance from the disruption, myofibrils are normal but hypercontracted. Glycogen is not detectable in the whole fibre.

In the unaltered zones, outside the foci of necrosis, muscle fibres are fully relaxed. In most of them, abundant lipid droplets and glycogen fields are observed between the myofibrils. Abnormal densities are found in the mitochondria (Fig. 12).

Vascular lesions are systematically found in the myolytic areas. In capillaries, the endothelial cells are often turgescent and the number of pinocytic vesicles is reduced. Signs of endothelial degeneration, such as swelling of smooth endoplasmic reticulum and mitochondria, or cell necrosis can be observed in the endothelium (Figs. 7–9). Gaps between the endothelial cells are also observed. The basement membrane is disrupted in several places and erythrocytes are found crossing the vascular walls (Fig. 8). In places, aggregates of necrotic cells with fibrin occlude the vascular lumen. Fibrin clots are observed but platelets are absent. Capillaries are not easily identifiable when deprived of their endothelium (Fig. 7). In some vessels, however, thickening of the endothelium and abundance of ribosomes suggest that regeneration occurs. When not disrupted, the congested capillaries are filled with erythrocytes. Venular congestion is sometimes observed, but arteries and veins seem not to be altered. Vascular pericytes are often seen in the necrotic areas. Fibroblasts showing signs of high secretory activity are also present between the fibre. Oedema is obvious in interstitial spaces especially close to the damaged vessels. Fibrinous exudate, numerous erythrocytes but few leucocytes can also be found in the extravascular space.

In the second biopsy myolysis is absent from the samples. In contrast, interstitial fibrotic areas are often found. Pericytes frequently surround the walls of the vessels (Fig. 14) and perivascular fibrosis extends to the neighbouring interstitial spaces. Most of the fibres are intact and relaxed. Glycogen is abundant. In some fibres, myofibrils are thin, disoriented and sometimes lacking Z-lines. Centralized nuclei are observed within the fibres. Generally, the structure of the vessels is normal: they are wide open and contain blood cells. Platelets are present. Pinocytotic vesicles are abundant.

Discussion

Ultrastructural and light microscopic observations of muscle biopsies, taken in the acute and recovery phases of the illness from a patient suffering from severe excercise-induced myoglobinuria with a CPT defect, provide new information about the myolysis process in this disease. Our study shows that vasculomuscular lesions displaying the characteristics of microinfarcts are present during the acute phase of this disease, and that circulatory disorders have thus to be considered.

The acute myolysis process associated with CPT deficiency has been considered to be an intrinsic metabolic failure which leads to damage of the plasma membrane and further to destruction of the myofibre and to myoglobinuria (Di Mauro and Papadimetriou 1986). But the morphological features of the lesions are not consistent with this mechanism. An "intrinsic" metabolic origin, only, of the muscle fibre lesions is difficult to reconcile with the disposition of injured areas throughout unaltered tissue as observed in our study. The vascular alterations noted in the foci of necrosis and fibrinous exudate found within the fibres could be explained by another process. Several points suggest that circulatory disorders and ischaemia may be involved in the pathogenesis of the muscular damage we describe. Surprisingly, it does not seem that special attention had been paid to the changes in vessels of the damaged areas. Some vascular alterations that were observed close to the necrotic fibres have been reported as "associated capillary injury" (Knochel 1982). These were sometimes regarded as the consequences of the outflow of toxic metabolites from the fibres, but massive myoglobinuria of other origins can occur without any morphologically detectable vascular lesion.

The lesions observed in the foci of necrosis closely resemble those following localized ischaemia. We have found some damaged areas in paraffin sections displaying the typical pattern of a wedge-shaped infarct. Within the foci of necrosis, alterations such as endothelial change, fibrinous thrombi, vascular disruptions, extensive serofibrinous exudate and interstitial oedema were found. Vascular necrosis and muscle fibre necrosis with local destruction of the basal lamina itself were also noted. Moreover, the ultrastructural lesions are strikingly similar to those reported by Karpati et al. (1974), Mastaglia et al. (1975) and Makitie and Teravainen (1977) in experimental ischaemia. After aortic ligation in the rat, the earliest muscle lesions in solei and gastrocnemii, seen in electron microscopy 2 h after ligation, consist of interruption of the plasma membrane and dissolution of the Z-discs, together with mitochondrial modifications in muscle fibres. Four to 7 days after induction of ischaemia, necrotic fibres are undergoing phagocytosis and regenerating fibres are found. On longitudinal view, the necrosis appears to be segmental and to involve a variable length of the fibre (Karpati et al. 1974). These data are in agreement with our observations. The dense granules observed within swollen mitochondria in the early stages of necrosis in our preparations were also noted in experimental myocardial ischaemia (Grosgogeat et al. 1966). Z-line loss observed in myofibril disassembly is considered to be a prominent feature of ischaemic muscle (Cullen and Mastaglia 1982). In fact, a disruption in the plasma membrane is known to induce a rise in calcium levels up to external concentrations within the myocyte. The Ca^{2+} neutral proteinase (CAP) is able to extract Z-lines in vitro (Busch et al. 1972). Hence it has been speculated that CAP is involved in such a breakage of the myofibrils at the Z-line (Dayton et al. 1975). We have noted in slightly injured fibres that Z-line loss first occurred close to plasma membrane fragmentation.

It is interesting to bear in mind that exercise-induced myoglobinuria occurs when normal muscles have been submitted to "maximal fuel exhaustive exercise". Exercise-induced myoglobinuria has also been reported when abnormalities of muscle metabolism are present (Penn 1986). When metabolic disorders are brought about by the end of fatty acid utilization and the use of the last glycogen reserves in the fibre by anaerobic glycolysis (Stahl and Fruchart 1988), several factors modulating the blood flow can be altered (Jerusalem 1982). Rhabdomyolysis in long-distance runners is documented (Schiff et al. 1978; Penn 1980; Thomas and Motley 1984; Boudou et al. 1987; Lonka and Smith-Pedersen 1987; Fellmann et al. 1988) but morphological studies of exercise-induced muscular alterations in normal individuals are rare (Fridén et al. 1981; Hikida et al. 1983; Sjöström and Fridén 1984). Vascular disruption, interstitial oedema, endothelial lesions, plasma membrane fragmentation and loss of Z-line described in marathon runners (Hikida et al. 1983) are consistent with our observations. It has been claimed that depletion of muscle energy supply by exhaustive exercise can apparently cause "dissolution of the cell" (Knochel 1982) in normal individuals as well as in cases of hereditary enzyme defects.

Several causes have been proposed to explain exercise-induced muscle lesions: ionic imbalance within the muscle fibre (Trump et al. 1974; Knochel 1982) and mechanical trauma (Fellmann et al. 1988). Ischaemia has also been proposed (Vikho et al. 1979; Sjöström and Friden 1984); our observations favour this pathogenesis. Haemodynamic disorders have been reported in marathon runners, such as digestive bleeding caused by gastric acute vascular lesions (Gaudin et al. 1990). The problem is imprecise knowledge of the influence upon muscle blood flow of the different humoral factors creating acute imbalance in "maximal fuel exhaustive exercise". The fact remains that CPT defect lowers the critical energy threshold and causes premature damage in affected patients after sustained exercise.

The fibrous scars left by acute vasculomuscular necrosis in the skeletal muscles examined, the clinical and biological symptoms in our patient (enlargement of the heart, rise of the CPK MB), previous morphological studies in our laboratory (Sacrez et al. 1982) of skeletal and cardiac muscle samples from patients with primitive cardiomyopathy and CPT deficiency, the report of several cases of cardiomyopathy in CPT deficiency (Norman et al. 1979; Long 1980) all lead us to draw attention to the risk of progressive and insidious fibrous myocardiopathy for patients with CPT deficiency. The possibilities of recuperation following repeated fibre necroses are restricted in the case of myocardium, since satellite cells are absent.

In conclusion, our findings show that circulatory ischaemic disorders may be involved in the pathogenesis of muscle lesions in cases of myoglobinuria with CPT deficiency.

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References

Angelini C, Freddo L, Battistella P, Bresolin N, Pierobon-Bormioli S, Armani M, Vergani L (1981) Carnitine palmityl transferase deficiency: clinical variability, carrier detection, and autosomal recessive inheritance. Neurology 31:883–886

Bank WJ, Di Mauro S, Bonilla E, Capuzzi DM, Rowland LP (1975) A disorder of muscle lipid metabolism and myoglobinuria. Absence of carnitine palmityltransferase. N Engl J Med 292:443–449

Bertorini T, Yeh YY, Trevisan C, Stadlan E, Sabesin S, Di Mauro S (1980) Carnitine palmityl transferase deficiency: myoglobinuria and respiratory failure. Neurology 30:263–271

Boudou P, Fiet J, Laureaux C, Patricot MC, Guezennec CY, Foglietti MJ, Villette JM, Friemel F, Haag JC (1987) Variations de quelques constituants plasmatiques et urinaires chez les marathoniens. Ann Biol Clin (Paris) 45:37–45

Brownell AKW, Severson DL, Thompson CD, Fletcher T (1979) Cold induced rhabdomyolysis in carnitine palmityl transferase deficiency. Can J Neurol Sci 6:367–370

Busch WA, Stromer MH, Goll DE, Suzuki A (1972) Ca^{2+} specific removal of Z lines from rabbit skeletal muscle. J Cell Biol 52:367–381

Cullen MJ, Mastaglia FL (1982) Pathological reactions of skeletal muscle: regeneration. In: Mastaglia FL, Walton J (eds) Skeletal muscle pathology. Churchill Livingstone, Edinburgh, pp 99–102

Dayton WR, Goll DE, Stromer MH, Reville WJ, Zeece MG, Robson RM (1975) Some properties of a Ca^{++} activated protease that may be involved in myofibrillar protein turnover. In: Reich E, Rifkin DB, Shaw E (eds) Proteases and biological control, vol 2. Cold Spring Harbor Laboratory, New York, pp 551–557

Di Donato S, Castiglione A, Rimoldi M, Cornelio F, Vendemia F, Cardace G, Bertagnolio B (1981) Heterogeneity of carnitine palmityl transferase deficiency. J Neurol Sci 50:207–215

Di Mauro S, Melis-Di Mauro P (1973) Muscle carnitine palmityl transferase deficiency and myoglobinuria. Science 182:929–931

Di Mauro S, Papadimetriou A (1986) Carnitine palmityl transferase deficiency. In: Engel AG, Banker BQ (eds) Myology basic and clinical. Mc Graw-Hill, New York, pp 1697–1708

Fellmann N, Sagnol M, Bedu M, Falgairette G, Van Praagh E, Gaillard G, Jouanel P, Coudert J (1988) Enzymatic and hormonal responses following a 24 h endurance run and a 10 h triathlon race. Eur J Appl Physiol 57:545–553

Fridén J, Sjöström M, Ekblom B (1981) A morphological study of delayed muscle soreness. Experientia 37:506–507

Gaudin C, Zerath E, Guezennec C (1990) Gastric lesions secondary to long-distance running. Dig Dis Sci 35:1239–1243

Grosgogeat Y, Scebat L, Renais J, Lenègre J (1966) Etude au microscope électronique de l'ischémie myocardique expérimentale. Arch Mal Coeur 2:203–214

Hikida RS, Staron RS, Hagerman FG, Sherman WM, Costill DL (1983) Muscle fiber necrosis associated with human marathon runners. J Neurol Sci 59:185–203

Jerusalem F (1982) Circulatory disorders and pathology of intramuscular blood vessels. In: Mastaglia FL, Walton JN (eds) Skeletal muscle pathology. Churchill Livingstone, Edinburgh, pp 537–560

Karpati G, Carpenter S, Melmed C, Eisen AA (1974) Experimental ischemic myopathy. J Neurol Sci 23:129–135

Knochel JP (1982) Rhabdomyolysis and myoglobinuria. Annu Rev Med 33:435–443

Long JL (1980) Myocardiopathies primitives non obstructives avec surcharge lipidique et déficit en carnitine palmityl transférase dans le muscle squelettique. Description de 5 observations chez l'enfant et 6 observations chez l'adulte. Thesis, Lyon University, Lyon

Lonka L, Smith-Pedersen R (1987) Fatal rhabdomyolysis in marathon runner. Lancet II:857–858

Makitie J, Teravainen H (1977) Histochemical studies of striated muscle after temporary ischemia in the rat. Acta Neuropathol (Berl) 37:101–110

Mastaglia FL, Dawkins RL, Papadimitriou JM (1975) Morphological changes in skeletal muscle after transplantation: a light and electron microscopic study of the initial phases of degeneration and regeneration. J Neurol Sci 25:227–247

Meunier J, Perrot D, Bret M, Pissere-Meunier J, Bouletreau P, Pasquier H, Berthillier G (1982) Myoglobinurie paroxystique récidivante avec insuffisance rénale aiguë secondaire à un déficit en carnitine palmityl transférase musculaire. Une observation. Nouv Presse Med 11:2767–2771

Meyer-Betz F (1910) Beobachtungen an einem eigenartigen mit Muskellähmungen verbundenen Fall von Haemoglobinuria. Dtsch Arch Klin Med 101:85–127

Norman J, Carrier H, Berthillier G, Bozio A, Jocteur-Monrozier D, André M, Joffre B (1979) Myocardiopathie primitive de l'enfant avec surcharge lipidique des fibres myocardiques et musculaires et mise en évidence d'un déficit en enzyme palmityl-carnitine-transférase. A propos de 4 observations. Arch Mal Coeur 5:529–535

Palmucci L, Bertolotto A, Doriguzzi C, Mongini T, Ardizzone G (1981) Myoglobinuria: presentation of personal cases and review of the literature. Ital J Neurol Sci 3:275–282

Patten BM, Wood JM, Harati Y, Hefferan P, Howel RR (1978) Familial recurrent rhabdomyolysis due to carnitine palmityl transferase deficiency. Am J Med 67:167–171

Penn AS (1980) Myoglobin and myoglobinuria. In: Vinken PJ, Bruyn GW (eds) Handbook of clinical neurology, vol 41. Elsevier, Amsterdam, pp 259–285

Penn AS (1986) Myoglobinuria. In: Engel AG, Banker BQ (eds) Myology basic and clinical. McGraw-Hill, New York, pp 1785–1805

Reza MJ, Kar NC, Pearson CM, Kark RA (1978) Recurrent myoglobinuria due to muscle carnitine palmityl transferase deficiency. Ann Intern Med 88:610–615

Sacrez A, Porte A, Hindelang C, Bieth R, Merian B (1982) Myocardiopathie avec surcharge lipidique et déficit en palmityl carnitine transférase (PCT) leucocytaire. Arch Mal Coeur 12:1371–1379

Schiff HB, Mac Scarraigh ET, Kallmeyer JC (1978) Myoglobinuria, rhabdomyolysis and marathon running. Q J Med 47:463–472

Sjöström M, Fridén J (1984) Muscle soreness and muscle structure. Med Sport Sci 17:169–186

Stahl A, Fruchart JC (1988) Exploration biochimique des muscles. In: Métais P (ed) Biochimie clinique, vol 3. SIMEP, Paris, pp 193–211

Thomas Jr BD, Motley C (1984) Myoglobinemia and endurance exercise: a study of twenty five participants in a triathlon competition. Am J Sports Med 12:113–119

Trump FB, Laiho KA, Mergner WJ, Arstila AU (1974) Studies on the subcellular pathophysiology of acute lethal cell injury. Beitr Pathol 152:243–271

Vihko V, Salminen A, Rantamäki J (1979) Exhaustive exercise, endurance training, and acid hydrolase activity in skeletal muscle. J Appl Physiol Respir Environ Exerc Physiol 47:43–50