Acute fulminant myoglobinuric polymyositis with picornavirus-like crystals

YUKIO FUKUYAMA, TSUNESABURO ANDO, AND
JUNKO YOKOTA

From the Department of Pediatrics, Tokyo Women's Medical College, Tokyo, Japan

SUMMARY Myoglobinuria was found in an 11 month old girl suffering from fever, dyspnoea, and muscle hypotonia. Muscle biopsy showed focal degenerative necrosis of the muscle fibres. Electronmicroscopically, picornavirus-like crystals were demonstrated in the muscle fibres. These and other findings strongly suggest that she suffered from acute myositis with myoglobinuria probably caused by Cocksackie B6 virus infection. The causal relationship of viral infection (Cocksackie, influenza, or myxo-viruses) and acute or chronic polymyositis with or without myoglobinuria is discussed.

The incidence of myoglobinuria seems to be rare in childhood. In Japan, a few childhood cases of symptomatic myoglobinuria have been reported: they are associated with acute polymyositis (Sakurai *et al.*, 1968), progressive muscular dystrophy (Kitahara and Fukuyama, 1972), or measles (Ando *et al.*, 1974), while an incidence of cryptogenic myoglobinuric myopathy in a sibship has also been described (Shomori *et al.*, 1969).

Recently we have seen a case of acute myoglobinuria which occurred in an 11 month old girl, who was admitted complaining of fever, dyspnoea, and muscle hypotonia. Electronmicroscopic examination of a biopsied muscle specimen revealed picornavirus-like crystals interspersed between myofibrils. The relationship between viral infection and the onset of these symptoms is also discussed.

Case report

An 11 month old girl was suffering from fever, dyspnoea, and muscular hypotonia. The family history was non-contributory. She was born after a 40 week pregnancy and her birthweight was 3200 g. There was no asphyxia at birth. She suffered from kernicterus as a consequence of severe neonatal jaundice in spite of exchange transfusions 10 days after birth. Spastic diplegia with

athetosis developed as a sequel so that she had regularly attended our clinic for medical advice and rehabilitation training.

On 22 April 1974 (the first day of illness), she had fever ranging from 38 to 40°C, but was doing relatively well. On the second day of illness she developed a high temperature (41.8°C), dyspnoea with cyanosis, and decreased muscle power, and she was brought to our emergency clinic and admitted.

On admission she was a moderately well nourished baby, somnolent but reacting to stimulation. The throat was slightly reddened. Although she had cyanosis and dyspnoea, no abnormality of the chest was found by physical examination. The abdomen was flat. The liver was one finger-breadth palpable. The spleen was not palpable. Patellar reflex was positive bilaterally and no pathological reflexes were elicited. Although she had usually assumed a spastic posture before the illness, the extremities were now flaccid without any spontaneous active movement. On the third day, she still had fever around 38°C, but the dyspnoea was somewhat relieved. On 25 April, she excreted dark reddish-brown urine, and hard swelling of both gastrocnemius muscles was noted for the first time.

LABORATORY DATA

Slight leucocytosis with neutrophilia was noticed. Her urine was brownish; the protein content was 3 g/l; occult blood test was markedly positive, but there were no abnormal findings in the sediment. The total serum protein was decreased,

Address for correspondence and reprint requests: Dr Yukio Fukuyama, Department of Pediatrics, Tokyo Women's Medical College, 10 Kawada-cho, Shinjuku-ku, Tokyo 162, Japan.

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blood urea nitrogen elevated, and serum enzyme activities markedly raised: GOT 2258 units, GPT 1128 units, LDH 2715 units, CPK 68 500 units per litre. Haptoglobin value was within normal limits (74.9 mg/dl). Creatine levels in the serum and urine were both elevated. Cerebrospinal fluid studies yielded normal findings except for elevation of CPK activity to 61 units. Virus isolation from the faeces, spinal fluid or throat swab was attempted, using monkey cells, but without success. Serum complement fixation tests for viruses were all negative except for Coxsackie B6 which showed elevation of the titre to 1/16 on the 27th day followed by a return to zero on day 180. Electromyographic exploration on the ninth day showed no diagnostic pattern.

The presence of myoglobin was clearly demonstrated immunologically in the urine but not in the serum on 26 April by the Ouchterlony method (Fig. 1), when the urinary colour was already slightly brownish. Myoglobin could not be detected in serum or urine electrophoretic and visual light absorption tests probably because the concentration of myoglobin in the material was too low.

On the ninth day of the illness, biopsy of the left rectus femoris muscle was carried out. The fundamental structure of muscle fascicles was

relatively well preserved in general, but necrotic fibres with or without vacuole and fragmentation were scattered irregularly. There were numerous small opacities in many of the fibres in the cross section, which could indicate the site of abnormal myofibrils though this is unconfirmed (Fig. 2).

Fig. 2 Light microscopic changes of biopsied femoral muscles. Haematoxylin-eosin.

Occasional waxy degeneration of fibres and peculiarly conglomerated, coagulated myofibrils were also encountered in other areas. Phagocytosis and central shift of the nuclei of slight degree were also recognised. There was very little perivascular and interstitial infiltration of small round cells. Histochemical stains for myosin ATP-ase, SDH and phosphorylase showed normal activity of enzymes within most muscle fibres. The vacuolated muscle fibres were almost exclusively of type I (Fig. 3). Electron microscopic studies showed a characteristic pattern in which almost normal myofibrils lay alongside those with degenerated amorphous structure and almost completely destroyed Z bands (Fig. 4a). Figure

Fig. 1 Immunological demonstration of urinary myoglobin by Ouchterlony method. A precipitation line was clearly visible between the patient's urine and the anti-myoglobin rabbit serum, but not between the patient's serum and anti-myoglobin rabbit serum.

PU=patient's urine (26 April 1974); PS=patient's serum (26 April 1974); Hb=haemoglobin; Mb=myoglobin; aMb=anti-human myoglobin rabbit serum.

Fig. 3 Myosin ATP-ase staining of biopsied femoral muscle.

Fig. 4 Ultrastructural findings of biopsied femoral muscles with picornavirus-like crystals.

4 (b and c) depicts the electronmicrographs of the portion of muscle fibres which appeared to be normal in light microscopy. The structure of myofibrils was relatively well preserved. The large vacuoles may have resulted from the distension of sarcoplasmic vesicles, and in the interspaces between the myofibrils around them there were crystalline structures with high electron density. As Fig. 4d illustrates, they were conglomerates of small particles (20 μm in diameter), and the distance between each particle was 25 μm . This regular crystalline structure and its morphology suggest that they are picornavirus-like crystals.

CLINICAL COURSE

The clinical course of the illness is summarised in Fig. 5. The more or less brownish urine was recognised by naked eye between the fourth and sixth days, but distinctly dark reddish brownish urine was excreted only once, on the fourth day. The occult blood in the urine was positive up to the ninth day. Muscle hypotonia and lack of movements were noted until the seventh day of illness, while the muscular tenderness and swelling persisted until the sixteenth day. Dyspnoea, prob-

ably due to respiratory muscle paralysis, was present on admission and subsided in a short period with symptomatic therapy. Serum enzyme activities remained at elevated levels for a considerable period; and the CPK level was 445 IU/l on the nineteenth day. It is of diagnostic significance that these enzymes had increased markedly before the excretion of myoglobin.

Discussion

The characteristic findings in this patient were: generalised muscle hypotonia with predominance in the lower extremities, presence of myoglobinuria and extremely elevated serum enzyme activities in the early stages of the illness, severe focal degenerative necrosis of the muscle fibres, and electronmicroscopic evidence of picornavirus-like crystals between myofibrils in the biopsied specimen of the rectus femoris muscle.

When urine is brownish in colour and occult blood is present with normal findings in the sediment, differentiation of myoglobinuria from haemoglobinuria should be considered. There are a number of biochemical diagnostic methods in-

Fig. 5 Clinical course of illness.

cluding electrophoresis and immunological tests.

Diseases which cause myoglobinuria in childhood seem to be relatively rare. Paroxysmal myoglobinuria was first described by Meyer-Betz in 1910. In 1959, Korein *et al.*, classified two types of myoglobinuria, one triggered by exertional loading and the second occurring secondary to infection. Type 2 is more frequent in children and, up to now, 27 cases have been reported in the world literature (Table). Seven patients who had recurrent episodes were included in the Table though some are of questionable validity. The average age of patients of type 2 was 4 years and 8 months. The ratio by sex was four males to three females. Fever was noted in all except in case 23 and those in which pertinent description was lacking. Cases following symptoms of upper respiratory tract infection were overwhelmingly frequent. There have been 10 fatal cases, so that this disease cannot be regarded as benign.

Myositis apparently due to viral infection is now designated as acute myositis or viral myositis (Middleton *et al.*, 1970; Sato, 1971a; Mejszenkier *et al.*, 1973). Coxsackie virus has been noted as a provocative agent of viral myositis, but more recently influenzal myositis has been described re-

peatedly (Middleton *et al.*, 1970; Simon *et al.*, 1970; Mejszenkier *et al.*, 1973; Minow *et al.*, 1974). In the recent literature, myoglobinuria secondary to infection (type 2 in the previous classification) is designated more and more frequently as acute myoglobinuria (Simon *et al.*, 1970; Berlin *et al.*, 1974; Minow *et al.*, 1974). We consider that acute myoglobinuria and viral myositis, although different in symptomatic severity, are a pathological entity.

Viruses reportedly responsible for acute myoglobinuria or viral myositis are limited to Coxsackie and influenza viruses. In 1967 Favara *et al.* isolated Coxsackie A9 virus from a boy aged 2.5 yr with paroxysmal myoglobinuria, and Berlin *et al.* (1974) found an elevated complement fixation titre for Coxsackie B5 virus in an adult patient with acute myoglobinuria. Simon *et al.* (1970) described acute myoglobinuria in adults associated with influenza. Middleton *et al.* (1970) also reported 26 cases of acute myositis of children convalescing from influenza. In 1973, Mejszenkier *et al.* reported influenzal myositis occurring in a five year old girl. They described the clinical course of this girl as acute, progressive, with hypotonia predominantly of the lower extremities

Table Review of childhood cases of paroxysmal paralytic myoglobinuria

Author	Age (yr)	Sex	Age at onset (yr)	Effect of exertion	Episodes	Fever	Associated illnesses	Fatality	Muscle degeneration histologically confirmed
1. Debré <i>et al.</i> (1934)	6	F	2.5	—	multiple	+	febrile in disposition	—	—
2. Huber <i>et al.</i> (1938)	4	M	4	—	1	+	r.i.*	—	—
3. Buchanan and Steiner (1951)	4	M	2	—	2	+	r.i.	+	+
4. Stokes (1953)	15	F	15	—	1	?	r.i.	+	?
5. Schaar (1955)	0	M	9	—	1	+	pneumonia	—	+
6. Berenbaum <i>et al.</i> (1955)	10	F	4	—	2	+	surgery	—	+
7. Bowden <i>et al.</i> (1956)	4	M	1.2	—	multiple	+	diarrhoea	+	+
8. " " " "	8	F	3.6	—	multiple	+	diarrhoea	—	—
9. " " " "	6.6	M	6.6	—	1	+	surgery	—	—
10. " " " "	4	F	4	—	1	?	r.i.	+	+
11. Watson and Ainbender (1959)	6	M	5	—	2	+	r.i.	—	+
12. Wheby and Ainbender (1960)	16	F	4	+	multiple	+	r.i.	—	+
13. " " " "	15	F	12	+	multiple	+	r.i.	—	—
14. Hasse and Engel (1960)	7	M	2.6	—	multiple	+	pneumonia	—	+
15. Bailie (1964)	3	M	1	—	2	+	surgery	—	not done
16. Bacon (1967)	14	M	14	—	3	+	r.i.	—	not done
17. Miller and Gross (1967)	11	M	11	—	1	+	r.i.	—	—
18. Favara <i>et al.</i> (1967)	2.6	M	2.6	—	1	+	diarrhoea	+	not done
19. " " " "	9	M	3.6	—	1	+	r.i.	—	+
20. " " " "	0.9	M	0.9	—	2	+	r.i.	+	+
21. Savage <i>et al.</i> (1971)	3	F	3	—	1	+	r.i.	+	not done
22. " " " "	1.6	F	1.6	—	1	+	r.i.	+	+
23. " " " "	7	M	7	—	1	—	r.i.	—	+
24. Ghatak <i>et al.</i> (1973)	3.6	M	3.6	—	1	?	r.i.	+	+
25. " " " "	0.9	F	0.9	—	1	+	r.i.	+	+
26. Kitahara and Fukuyama (1972)	3.3	M	2.4	+	multiple	+	r.i.	+	+
27. Ando <i>et al.</i> (1974)	3.8	F	3.8	—	1	+	measles	—	+
28. Current report	0.11	F	0.11	—	1	+	r.i.	—	+

*r.i. = respiratory infection.

which subsided spontaneously within several days. From the viewpoint of therapy and prognosis, they emphasised the importance of differentiation from polymyositis in childhood. In 1974 Minow *et al.* also reported acute myoglobinuria in adults associated with influenza. These authors were able to demonstrate influenza A or B virus as a causative agent by complement fixation tests or by virus isolation. In 1974 we described picornavirus-like crystals in a biopsy specimen in a girl aged 3 years 8 months with paroxysmal myoglobinuria. Furthermore, in polymyositis or dermatomyositis, picornavirus-like crystals were demonstrated in biopsied muscle specimens by Chou and Gutman (1970), Sato (1971b) and Ben-Bassat and Machtey (1972). Sato (1971a) suggested that the acute form of polymyositis may be related to Cocksackie virus and the chronic form to myxovirus. In a more recent report, Sato and Nakamura (1975) also found picornavirus-like crystals in the chronic form, thus suggesting that the pathogenetic relationship is more complicated. We assume that there exists a wide spectrum of inflammatory muscle pathology, extending from the chronic form of polymyositis to acute fulminant myositis with rhabdomyolysis and myoglobinuria. An acute form of polymyositis and acute myositis not accompanied by myoglobinuria would be situated between them. The differences of clinical pathology in these conditions may be determined by the relative importance of primary infectious (viral) and defensive immunological processes in the pathogenesis. It may be considered that a viral infection will play an important role in causing or triggering inflammatory changes in skeletal muscles either directly or indirectly.

Various structures such as nemaline body, honeycomb-like structure originating from the T-tube, or intramitochondrial fibrillar inclusion may appear as a crystalline structure in muscle fibres, but the small round particles with regular crystalline arrangement seen in the present case are quite different morphologically from any of the above, and resemble picornavirus particles. The presence of these crystals between almost normal muscle fibres in the present case may raise some concern. It should be noted that the same picture was observed by Sato and Nakamura (1975), although its meaning remains obscure.

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