MYOGLOBINURIA WITH ACUTE RENAL FAILURE POSSIBLY INDUCED BY SUXAMETHONIUM

A Case Report

BY

KNUD-AAGE BENNIKE AND STIG JARNUM

Department of Anaesthetics, Medical Department B, Surgical Department A, and Department of Clinical Biochemistry, Bispebjerg Hospital, Copenhagen, Denmark

SUMMARY

A case of myoglobinuria with acute renal failure in a 29-year-old male is presented. The attack followed a minor operation under general anaesthesia during which suxamethonium was administered as muscle relaxant. Immediately after the injection of suxamethonium vigorous generalized fasciculations occurred which very likely proved to be the precipitating factor for the episode of rhabdomyolysis. It is concluded that the use of depolarizing agents in patients with myoglobinuria is hazardous and should be avoided.

Since its first description by Meyer-Betz in 1910 idiopathic myoglobinuria or idiopathic recurrent rhabdomyolysis has been reported in about seventy cases. Although its characteristic presenting features—a syndrome of muscle pains and red, benzidine (or guaiacum) positive urine in the absence of intravascular haemolysis and with a normal urinary sediment—ought to make it an easily recognizable condition, it has sometimes been misinterpreted. This may lead to many unnecessary investigations and put patients to considerable discomfort, for instance because of repeated cystoscopies on account of presumed haemoglobinuria (Bradley, 1963). There may be a prolonged hospital stay for “glomerulonephritis” (Duma, Trigg and Hammack, 1962).

Up till 1960 about fifty cases of idiopathic myoglobinuria had been reported in the literature. Recent reviews have been published by Wheby and Miller (1960) and by Farmer, Hammack and Frommeyer (1961). The conclusions drawn in these reviews have not been modified by reports of about twenty further cases within the last three years, with the possible exception that more cases now seem to be recognized in older age groups.

The age at onset has been between 1 and 30 years in 70 per cent of the cases. The majority of patients were males. Often they gave a history of a year or more of recurrent attacks of “cramps” or extreme muscular weakness during which they may or may not have noticed dark red urine.

The most common precipitating factor was exercise, but in a few cases alcohol or barbiturates were held responsible. It is a striking feature that the episode of muscular pain and succeeding myoglobinuria developed a few hours after the provocation and never lasted longer than 24 hours.

The sequence—muscular pains, myoglobinuria, renal failure—has occurred in about one-third of the cases reported. Clinically the renal affection is indistinguishable from acute renal failure from other causes, such as burns, shock, and poisons.

The frequency of development of renal insufficiency makes the prognosis of idiopathic myoglobinuria dubious. It has been the cause of death in most cases with fatal outcome (about 20 per cent of the total number reported ended fatally). On the other hand, it is the rule that normal renal function is re-established, and it is to be expected that modern methods of treatment including haemodialysis will minimize the danger considerably.

The aetiology of the syndrome remains obscure. Familial occurrence is rare. In 1951 McArdle reported a case in which exercise did not produce the normal rise in the lactic acid concentration of serum. He inferred that breakdown of
glycogen was impaired. An absence of muscle phosphorylase necessary for a normal breakdown of glycogen to glucose-1-phosphate has been demonstrated in a few cases (Schmid and Mahler, 1959; Pearson, Rimer and Mommaerts, 1961). However, this enzymatic defect, McArdle's syndrome, is not a constant finding.

Attempts to identify an abnormal myoglobin have been unsuccessful. Idiopathic myoglobinuria is probably not, for instance, similar to sickle-cell anaemia in which the basic defect is the abnormal haemoglobin S.

The diagnosis of idiopathic myoglobinuria is easily verified by a few laboratory tests. Initially the combination of red, benzidine-positive, urine without red cells and clear, not red, serum is highly suggestive. It has been calculated that visible myoglobinuria occurs after destruction of approximately 200 g of muscle tissue (Berenbaum, Birch and Moreland, 1955). Myoglobin has a low renal threshold (15–20 mg/100 ml plasma, according to Javid et al., 1959), since its molecular weight is low, about 17,000, and it is easily verified by a few laboratory tests. Initially the combination of red, benzidine-positive, urine without red cells and clear, not red, serum is highly suggestive. It has been calculated that visible myoglobinuria occurs after destruction of approximately 200 g of muscle tissue (Berenbaum, Birch and Moreland, 1955). Myoglobin has a low renal threshold (15–20 mg/100 ml plasma, according to Javid et al., 1959), since its molecular weight is low, about 17,000, and it is bound to haptoglobin to a very limited extent. Consequently it is unable to discolour plasma. Haemoglobin, on the other hand, escapes renal excretion up to plasma concentrations of about 120 mg/100 ml, because it is bound to haptoglobin (Laurell and Nymann, 1957). This is far beyond the limit which produces visible haemolysis of plasma (about 40 mg/100 ml according to Yuile and Clark, 1941).

Spectroscopic analysis of urinary proteins has often been used as a diagnostic procedure. It is based on different absorption maxima for haemoglobin and myoglobin in their oxy- or carboxy-forms. However, it is not entirely reliable. This also applies to a very simple test in which an 80 per cent saturated urine solution of ammonium sulphate is prepared. The added salts should precipitate haemoglobin but not myoglobin.

A highly reliable test is electrophoresis of urinary proteins on filter paper or starch gel. Like haemoglobin, myoglobin is stainable with benzidine but its mobility is only half that of haemoglobin.

Ultrafiltration through a millipore filter, which permits the myoglobin molecules to pass through, but retains haemoglobin molecules (molecular weight of haemoglobin about 68,000), is equally successful.

Muscle biopsy is often useful but may be inconclusive (Duma, Trigg and Hammack, 1962).

The treatment of idiopathic myoglobinuria is purely palliative and preventive, in so far as the patients are advised to refrain from severe muscular effort, this being the main precipitating factor. During the acute attack it has been recommended to alkalinate the urine by administration of bicarbonate, the purpose being to prevent metmyoglobin formation which takes place in acid urine. Metmyoglobin, like methaemoglobin, is supposed to precipitate more easily than myoglobin (and haemoglobin), and consequently it should be more liable to produce renal tubular blockage leading to renal failure. The basis and the value of this treatment in both myoglobinuria and intravasal haemolysis is, however, still controversial.

The present report serves to illustrate that the disease may also represent a potential danger in modern anaesthesia when certain muscle relaxants are applied.

**CASE REPORT**

A 29-year-old male was admitted because of a swelling in the left groin of two months duration. His history was considered initially to be non-contributory. Later he revealed that he had suffered from periodic painful swelling of his thighs since the age of 14, no precipitating factors having been recognized. He spent 4 days in hospital when he was 16 because of this. The tentative diagnosis was femoral neuritis. No unusual colour of the urine was noticed.

At the present admission the physical examination revealed nothing abnormal except an assumed left inguinal hernia. Besides this he had no complaints. His general condition was excellent. Blood pressure, erythrocyte sedimentation rate and haemoglobin concentration were normal. The urine contained no protein or sugar. On November 20, 1963, at operation a small lipoma was found instead of a hernia, and this was removed without complications.

For general anaesthesia halothane 1 per cent with nitrous oxide 66 per cent and oxygen 33 per cent was used, administered by a Fluotec vaporizer mark II, in a semi-open system with a non-rebreathing valve (Ruben). No premedication was given. Before induction of the anaesthesia atropine 1 mg was injected intravenously. Prior to the intubation suxamethonium chloride 100 mg was given intravenously as a muscle relaxant. Just after this injection vigorous muscle fasciculations were observed. Tracheal intubation was easily performed, and the lungs were manually ventilated at a rate of 12 l./min by a well-trained nurse. The anaesthesia lasted 70 minutes and passed without complications, such as episodes of hypoxia,
hypotension or excitation. At the end of the anaesthesia the patient was fully awake.

Three to four hours after the operation he complained of pains in both thighs. On the following morning he had passed 800 ml of dark red urine which contained protein and urobilin and gave a strongly positive benzidine reaction. Microscopic examination of the sediment failed to reveal any erythrocytes. During the day he suffered from generalized muscular weakness and pains in his arms and legs. Another 24 hours later, two days after the operation, the pains had disappeared, and the colour of the urine was normal. At this time, however, acute renal failure had developed, the serum creatinine and serum urea values steadily increasing. The succeeding course is depicted in figure 1. It should be noticed that oliguria was absent. The minimum daily urinary output, 450 ml, occurred during the second postoperative day. The peak value of serum creatinine was 8.5 mg/100 ml and of serum urea 183 mg/100
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ml. Hyperkalaemia did not develop. One week after the operation a spontaneous improvement of renal function began, and six weeks after the admission he was discharged with an almost normal serum creatinine (1.4 mg/100 ml) and without any sign of muscular disease.

SPECIAL INVESTIGATIONS

Enzymes in serum.

Creatinine phosphokinase activity was determined by a modification of the method given by Tanzer and Gilvarg (1959). A marked increase of serum concentration was found in the period following myoglobinuria (fig. 1). This enzyme, normally occurring as an intracellular enzyme in muscular tissue, reflects extensive muscular damage when present in high concentration in serum.

Lactic acid dehydrogenase, glutamic acid-oxalacetic acid and glutamic acid-pyruvic acid transaminases were also present in elevated concentrations in serum. All of them occur in muscular cells but in several other types of tissue as well.

Tests for haemolysis.

No evidence of intravascular haemolysis could be found. A decrease of haemoglobin concentration did not follow the episode of myoglobinuria. The serum bilirubin concentration remained within normal limits, the reticulocyte count was normal, the plasma was clear and yellow, and contained no haemoglobin. Haptoglobin concentration was elevated contrary to the low value to be expected in case of haemolysis. Various serological tests to exclude paroxysmal haemoglobinuria (Ham's, Crosby's, and Donath-Landsteiner's tests) were all negative.

Porphyria was not present.

No evidence of collagen disease was found (negative LE-cell preparations, negative anti-nuclear factor test). A serological test for syphilis was negative.

Hepatic function was uninfluenced (normal prothrombin level, normal electrophoretic pattern of serum proteins, and normal serum cholinesterase).

Muscle biopsies were taken from the vastus medialis of the right thigh and from the left brachial biceps 7 days after the operation (fig. 2). The vastus medialis contained widespread areas of acute severe degeneration of muscle threads with partially lost striation, but without inflammatory reactions. The picture agreed well with the changes described in other cases of rhabdomyolysis. The brachial biceps was normal, a fact which fitted well into the clinical course. The initial and most severe muscle pains were present in the thighs, especially the right one, whereas the pains and weakness of the arms did not occur until later after which they subsided rapidly.

Kidney biopsy was planned, but not performed, because the patient refused permission.

Urinary proteins.

When red the urine gave a positive protein and benzidine reaction. Unfortunately no sample was saved for further analysis. Urine from a later period, about 48 hours after the operation, was subjected to paper electrophoresis after concentration by ultrafiltration of the dialyzed urine. It contained several protein fractions including haemoglobin and serum albumin, but even after staining of the strips with benzidine no trace of myoglobin could be detected. Gel filtration was applied (Sephadex 75) in an attempt to demonstrate the presence of the low molecular myoglobin. No detectable fraction of low molecular weight could be separated.

Also immunoelectrophoresis using anti-serum against human myoglobin failed to reveal this protein. The even more sensitive passive haemagglutination test, however, gave strong evidence of the presence of myoglobin. Erythrocytes pretreated with formaldehyde and tannic acid were coated with a dialyzed concentrate of the urine and then exposed to anti-human myoglobin serum.* A typical haemagglutination occurred. No agglutination followed in control experiments in which uncoated cells were tested against anti-human myoglobin serum or when normal serum was used for coating.

DISCUSSION

The case history presented here shows features typical of the syndrome of idiopathic myoglobinuria. The patient was a male, his disease presented itself before the age of 20, it succeeded a brief period of heavy muscular activity, and he had a severe attack of myoglobinuria followed by acute renal failure which gradually subsided and left him with normal renal function. The diagnosis was well established, partly due to the clinical findings, partly because intracellular enzymes, especially creatine phosphokinase, were present in elevated concentrations in serum, partly because typical lesions were found in a muscle biopsy, and finally by the detection of myoglobin in urine.

It should be noticed that oliguria was absent in spite of a renal function reduced to about 10 per cent of normal level (fig. 1). This apparent paradox has also been observed in other types of acute renal failure (Swann and Merrill, 1953).

In the present report paper filter electrophoresis and gel filtration in a Sephadex column (rather analogous to ultrafiltration), immunoelectrophoresis and the passive haemagglutination test were employed. The urine was not analyzed until about 24 hours after the episode of myoglobinuria, and only by the last method was it possible to detect myoglobin in the urine. This serves to demonstrate how short is the period of actual rhabdomyolysis.

The pathogenesis of the acute attack of myoglobinuria is regularly some type of exercise. The present case seems to be no exception to

*Anti-human myoglobin serum (from immunized rabbits) was kindly supplied by Ortho Pharmaceutical Corporation, Rariton, New Jersey, U.S.A.
Muscle biopsies from vastus medialis (above) and from brachial biceps (below) (×140).

Fig. 2
this rule, but the type of "exercise", vigorous fasciculations produced by the muscle relaxant suxamethonium, has not been reported before.

Among the cases of idiopathic myoglobinuria published there are four who underwent an operation without ensuing episodes of rhabdomyolysis.

Two cases have been reported, in which attacks of myoglobinuria occurred shortly after the operation.

One patient, a boy of 17 years, contracted his first attack of myoglobinuria twelve days after an appendicectomy, two days after the discharge from hospital. (Junod, Chafizadeh and Hurlimann, 1963).

The other one, a 7-year-old-boy, had his third attack four days after an operation for atrial septal defect. (Haase and Engel, 1960). The anaesthetic agents employed were pentobarbitone, cyclopropane and nitrous oxide.

However, since the interval between the precipitating event and the actual attack does not usually exceed a few hours, a causal relationship between the operations and the paroxysms is improbable in either of the two cases.

Another two cases have been reported in whom attacks of myoglobinuria developed in close relation to an operation.

One, a girl of 8 years, was appendicectomized because of abdominal pains (Berenbaum, Birch and Moreland, 1955). At the age of 4 she had passed dark urine. She developed myoglobinuria immediately following the operation. The appendix was found to be normal. According to the report, the patient suffered from pains of both abdomen and extremities during the preoperative period. The anaesthesia was not described.

The other patient, a girl of 6 years, had her third attack of myoglobinuria after a tonsillectomy under ethyl-chloride and ether anaesthesia (Bowden et al., 1956). The anaesthesia was not described in detail and the use of relaxants was not mentioned. She had her teeth extracted under local anaesthesia without complications at the age of 8.

In the former case the attack probably began before the operation and very likely, it was virtually the reason why the patient was subjected to appendicectomy. In the latter case, anaesthesia cannot be excluded from being wholly or partially responsible for the episode of myoglobinuria.

In the present case, the onset of pain and the appearance of red urine followed so soon after operation as to suggest that the precipitating factor must be searched for in the anaesthesia, during which vigorous muscular fasciculations were observed after suxamethonium. Fasciculations occur in most patients after injection of suxamethonium (Bennike and Nielsen, 1964). They are the result of the initial depolarizing action of suxamethonium on the neuromuscular endplate and may be so powerful that the extremities are moved. They differ from voluntary movements by the absence of co-ordination both between the individual muscle bundles of one muscle and between synergistic and antagonistic muscle groups. When only a very limited shortening of the muscles can take place despite a high energy release, the possibility of muscular injury is present (Paton, 1959). Histological changes in thoracic and abdominal muscles cannot be demonstrated in normal persons after suxamethonium (Mayrhofer, 1959). Most patients complain of muscular pains 12–24 hours after injection of suxamethonium. The pains are similar to those felt after unusual work. They are not necessarily associated with or preceded by fasciculations (Bennike and Nielsen, 1964). Their cause is obscure.

These considerations lead to the conclusion that suxamethonium is likely to precipitate an attack of myoglobinuria in a patient suffering from paroxysmal idiopathic myoglobinuria. Furthermore, in the present case no generalized injury was inflicted on muscular tissue, since undamaged tissue was found in the brachial biceps muscle, while severe pathological changes were present in a muscle biopsy from the thigh, to which the patients had referred his complaints, since he was 16 years old.

As mentioned previously, attacks of paroxysmal idiopathic myoglobinuria can be provoked by intoxications, for example, by alcohol and barbiturates (Fahlgren, Hed and Lundmark, 1957), and possibly by ethyl-chloride followed by ether as referred to earlier.

In the present case no barbiturates were used for the anaesthesia, and no episodes of hypoxia occurred. For anaesthesia halothane was used. Reports of a possible hepatoxic action of halothane have been published (Lindenbaum and Leifer 1963).

There is at present no evidence of a toxic effect of halothane on striated muscles. As a precipitating factor in the present case of myoglobinuria,
halothane seems to be an unlikely possibility, the more so since suxamethonium, which interferes strongly with physiological processes in muscular tissue, was administered during the same anaesthetic.

In conclusion, it would appear from this case report that the evidence that myoglobinuria can be precipitated by suxamethonium in a patient with idiopathic myoglobinuria is so overwhelming that the use of suxamethonium or other depolarizing agents must be considered dangerous and should be avoided when a syndrome of idiopathic myoglobinuria is present.

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REFERENCES


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