Medical Memoranda

Reversible Encephalopathy and Acute Renal Failure after Cephaloridine

British Medical Journal, 1970, 4, 283-284

During intensive cephaloridine treatment in a patient with renal damage reversible encephalopathy and oliguric renal failure occurred.

CASE HISTORY

An Englishwoman aged 40 presented in June 1967 with 36 hours of haematuria. Her past history was noncontributory. Physical examination showed no abnormality. Urine was sterile and contained numerous erythrocytes and some protein. Haemoglobin was 12.2 g./100 ml. Blood urea was 54 mg./100 ml. I.V.P. showed a normal upper tract and a filling defect in the bladder. At cystoscopy two tumours above the left ureteric orifice were seen and fulgurated. Histology showed transitional cell papillary carcinoma. No recurrence has arisen.

After cystoscopy several urinary tract infections, usually with *Escherichia coli*, were treated with ampicillin or chloramphenicol. Continuous therapy became necessary. In January 1968 investigation revealed blood urea 120 mg./100 ml.; creatinine clearance 22 ml./min.; renal biopsy: compatible with chronic pyelonephritis; urine culture: *E. coli*.

Eight parenteral courses of antibiotics, including cephaloridine, were given over the next six months, but relapse invariably ensued with the same strains of *E. coli*, the drug sensitivity pattern being unchanged. High-dosage therapy was begun, using cephaloridine 8 g./day (160 mg./kg. body weight/day) intravenously for 12 days, then 4 g. daily intramuscularly for two days. On the 13th day she vomited and rapidly became semiconscious. Blood urea 170 mg./100 ml.; creatinine 6.4 mg./100 ml.; 24-hour urine volume 750 ml. On the 14th day the blood cephaloridine level was 35 µg./ml. and the C.S.F. cephaloridine level was 6.4 µg./ml. A cerebral abscess was thought possible. Carbenicillin and cloxacillin were added and cephaloridine was withdrawn (see Chart).

Patient's response to treatment.

In the C.N.S. there were no localizing signs; generalized myoclonus was present with brisk tendon reflexes. C.S.F., normal. Isotope encephalogram, negative. E.E.G.: diffuse cerebral disturbance suggestive of toxic or metabolic abnormality. Dialysis was required on the 15th and 21st days. After the first dialysis consciousness gradually improved, but after the second she became mildly hypomanic. Her mentality became normal by the 56th day. In May 1970 she was normally active. The blood urea was 95 mg./100 ml., and the creatinine clearance 24 ml./min.

COMMENT

Experience has shown that cephaloridine toxicity is very low (Proceedings of Conference on Cephaloridine, 1967). Some laboratory animals injected with cephaloridine show necrosis of the proximal renal tubular cells (Atkinson *et al.*, 1966); the dose producing this nephrotoxic effect is usually proportionately many times the human therapeutic dose. The cytotoxic effect is probably due to excessive accumulation of cephaloridine in the tubular epithelium. Currie *et al.* (1966) demonstrated localization of titrated cephaloridine between and inside proximal tubular cells of the dog. Nephrotoxic effects do not occur in man at any level of renal function in a dosage of 0.5-1 g./day (Gower, 1967). Foord (1970) reviewed the possible nephrotoxic effects of cephaloridine, especially in high dosage or in cases of impaired renal function. Lawson *et al.* (1970), having observed that the incidence of acute renal failure was increased in patients receiving cephaloridine and frusemide, suggest that such impairment might be due to increased renin production and consequent renal arteriolar vasoconstriction and decreased renal plasma flow and glomerular filtration.

Reports of cerebral toxicity of cephaloridine are sparse. In two patients hallucinations and nystagmus followed cephaloridine 100 mg. intrathecally, but not in other patients after 50 mg. (Murdoch *et al.*, 1964). Amaurosis in one 18-year-old girl occurred after treatment with cephaloridine, cloxacillin, and fusidic acid (Ballingall and Turpie, 1967). Neurological changes are unusual in tubular necrosis.

In our patient a marked depression of consciousness occurred while receiving only cephaloridine, implying that this directly or indirectly induced the neurological changes. Carbenicillin and cloxacillin were added later, which may have aggravated the encephalopathy in the presence of severe oliguria.

The C.S.F. cephaloridine level of 6.4 µg./ml. on the 14th day is commensurate with a serum concentration of 35 µg./ml. in a patient with a low glomerular filtration rate (Kabins and Cohen, 1966), but the serum concentration is much lower than anticipated. Considerably higher levels would probably have been found earlier in the therapy. It has been observed that the half-life of cephaloridine shortened progressively in patients on haemodialysis (Pryor *et al.*, 1967; Curtis and Marshall, 1970). Our patient had had a 10-day course of cephaloridine three months before the reported episode which possibly might have led to a reduction of the half-life of the drug on the occasion when encephalopathy developed.

Cephaloridine was given to the patient again five months after complete recovery in a dose of 20 mg./kg./day for 10 days with no alteration of mood or renal function.

It appears, therefore, that the induction of this encephalopathy required a prolonged high dosage of the antibiotic with significant penetration into the C.S.F. and possibly the presence of severe renal dysfunction.

We wish to thank Mr. H. K. Vernon of St. Peter's Hospital for permission to quote the results of investigations conducted on this patient while she was under his care. Dr. Ian McDonald of the National Hospital for Nervous Diseases gave much assistance at

the time of the encephalopathy, and has given permission to quote the results of the neurological investigations conducted.

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Gangrene of Digits after Chicken-pox

British Medical Journal, 1970, 4, 284

Chicken-pox is a highly contagious and therefore relatively common viral infection in children. In this age group peripheral gangrene is a particularly rare condition. A recent case is described here.

CASE REPORT

A 6-year-old white boy was admitted primarily for social reasons to the infectious disease unit of Hither Green Hospital eight days after developing the typical rash of chicken-pox. He had a rash compatible with eight-day chicken-pox involving the trunk and limbs. No other appreciable abnormalities were noted, except that he was mentally retarded. There were no signs of secondary infection.

Two days after admission a slight blue discoloration of the left hand was noticed (see Fig.), and in the next three hours the entire left hand and lower third of the ulnar side of the forearm became cyanosed. The area was tender and

Digital gangrene in a 6-year-old boy

swollen, though the skin was warm and did not blanch on pressure and the peripheral pulses were palpable. The right hand and foot showed similar changes but to a lesser degree. He remained unconcerned and afebrile. Over the next 18 hours the right hand and foot gradually resumed a normal appearance, but the left upper extremity remained grossly swollen, despite elevation. The changes persisted and the tips of all four fingers became

gangrenous three days later. Secondary infection with *Staphylococcus aureus* occurred as a result of persistent interference with the dressings by the patient but was controlled with penicillin.

At that time he had a white cell count of 15,000 mm.³ with an essentially normal differential. Serum protein electrophoresis showed an increase in the α_2 fraction and the immunoglobulin IgM level was 25 mg./100 ml. The A.S.O. titre was 320 Todd units and six weeks later was 160 Todd units/100 ml. All other routine investigations including coagulation studies and a search for agglutinins were negative. Subsequent plethysmographic measurements on the affected hand showed normal blood flow.

A month later he was transferred to the Evelina Hospital for surgical assessment. The finger-tips were dry, black, and necrotic. The gangrenous areas became well demarcated and six weeks after onset were trimmed. Despite mummification, histology demonstrated the digital arteries in a transverse section of the largest specimens. These were distended by what appeared to be organized thrombus, and the internal elastic lamina and media appeared well preserved and showed no evidence of arteritis. The fingertips healed satisfactorily and further progress was uneventful.

COMMENT

The mode of onset and distribution of the lesions corresponded to the description by Lewis and Pickering (1934) of "bilateral gangrene of the digits in the young and with infection." Their review of the literature on peripheral gangrene included many cases with associated generalized infections, but none with chicken-pox. Jepson (1956) tabulated disease processes described in conjunction with symmetrical digital gangrene and considered separately those without apparent cause. He thought the disease in this latter group to be self-limiting and to have a good prognosis. Wishik and Bullowa (1935) catalogued the complications seen in 2,534 cases of chicken-pox between 1929 and 1933. One of these was a 3-year-old boy with mild varicella who developed discoloration and eventually gangrene of the digits. They stated: "at no time did the patient seem very ill, toxæmic or prostrated."

The clinical findings in the present case were those of venous gangrene. The delay between the onset of the infectious disease and the appearance of the vascular disorder parallels that found in purpura fulminans. The laboratory tests, however, gave no indication of a generalized consumptive coagulopathy which might have been associated with intravascular coagulation. In retrospect measurements of the fibrin degradation products might have yielded more information at that time. Assuming endothelial damage to the peripheral vessels, which Cheatham et al. (1956) reported as a result of viral invasion, it is conceivable that platelets might have adhered locally but that irreversible aggregation took place only in the left hand.

No convincing evidence was found in this case for a causative lesion other than the preceding infection with chicken-pox and a suspicion of coexistent streptococcal infection, as shown by a small rise in the A.S.O. titre.

We wish to thank Dr. E. H. Brown, consultant physician, Hither Green Hospital, and Dr. R. C. Mac Keith, consultant paediatrician, Evelina Children's Hospital of Guy's Hospital, for advice and criticism.

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