Fatal varicella in a healthy young adult

S.W. Coppack, R. Doshi and A.R. Ghose

Departments of Neurology and Pathology, Brook General Hospital, London S.E.18, UK.

Summary: A healthy adult presented with severe neurological disturbance 4 d after developing chicken-pox. Although pneumonic and renal problems were also present the neurological state dominated the clinical picture. After the patient's sudden death an autopsy revealed that renal and cerebral problems were secondary to myocardial involvement. This was of an unusual type for varicella with features of dilated cardiomyopathy resembling that previously related to Coxsackie infections. We conclude that cardiac problems in this patient produced anoxic brain damage and subsequently death.

Introduction

Death was attributed to chicken-pox in 69 persons aged over 15 years between January 1978 and December 1982 in Britain. Of cases reported to the P.H.L.S. Communicable Disease Surveillance Centre the commonest reported causes of death were pneumonia, encephalitis and haemorrhagic varicella (disseminated intra-vascular coagulopathy; unpublished). Many deaths occur in immunosuppressed patients. We report a case of fatal varicella with myocarditis in an apparently previously healthy adult.

Our patient presented with severe neurological impairment. Several mechanisms of neurological damage in chicken-pox have been suggested, but anoxic brain damage comparable to this case has not been reported to our knowledge.

Case history

A previously healthy 22 year old plumber developed the typical exanthem of chicken-pox for the first time. He complained of malaise and pruritus, but no other symptoms until the fourth day of the rash. He then became drowsy and several hours later was found unconscious in a chair.

Later that day, on admission to hospital, his temperature was 40.9°C, blood pressure 110/70 mm Hg and pulse 140/min. He had closed eyes and no vocalization. Painful stimuli produced alternate flexion and extension. There was generalized rigidity, hypertonia and an indefinitely extensor right plantar. There was a florid varicella rash. A systolic flow murmur was present with fine inspiratory crepitations

at the lung bases, a respiratory rate of 48/min but no cyanosis or neck stiffness. The patient was treated with antipyretics and acyclovir (15 mg/kg/day).

Investigations revealed haemoglobin 15.3 g/dl, white cell count $13.3 \times 10^9/l$ (53% neutrophils, 24% lymphocytes, 10% monocytes and 13% atypical mononuclear). Serum electrolytes and immunoglobulin levels were normal, but urea was 7.4 mmol/l, creatinine 162 $\mu\text{mol/l}$, bicarbonate 18 mmol/l and aspartate transaminase 80 IU/l. A lumbar puncture showed clear cerebrospinal fluid (CSF); protein 2,150 mg/l, red blood cells (RBC) 165/mm³, lymphocytes 40/mm³, CSF glucose 3.9 mmol (serum glucose 7.2). No organisms were seen or cultured. Urinalysis showed 1000 RBC/mm³ and 1 g protein/l. The electrocardiogram showed sinus tachycardia with flattened T waves in leads I, aVI and V₆ (Figure 2). Chest X-ray showed a few small patches of consolidation towards the right apex. Transverse diameter of the heart appeared to be increased. The electroencephalogram showed diffuse slow activity up to 1500 mS. A brain computerized tomographic scan revealed patchy low density in the right parietal area and probably in the left parietal region also. No abnormal enhancement was seen. Herpes virus particles were demonstrated in cutaneous vesicle fluid by electron microscopy using negative staining with phospho-tungstic acid. Tissue culture of fluid was negative. Complement fixation test for varicella zoster gave a titre of 1 in 64.

Over the next 60 h the patient had no fits and he began to withdraw from painful stimuli. His varicella rash resolved markedly, the heart rate fell down to 120/min, and pyrexia to 38.0°C. Two short episodes of tachycardia around 170/min were observed. His respiratory rate remained around 50/min, blood pressure normal, urine output good with no further signs of heart failure. Serum biochemistry showed rises in

Correspondence: S.W. Coppack, B.Sc., M.R.C.P., Westminster Hospital, Horseferry Road, London S.W.1.
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Figure 1 Widely separated myocardial fibres contain hypertrophic nuclei. Mononuclear cell infiltration is seen in the interstitial tissue. H & E $\times 80$.

transaminases and creatine kinase (mainly skeletal muscle isoenzyme) and urea up to 20.9 mmol. The patient was found dead in bed 7 d after the start of the rash.

The heart (370 g) was large but otherwise macroscopically normal. The lungs showed mild bronchopneumonia. The brain was extremely congested with swollen hemispheres and mildly compressed mid brain and pons but no macroscopic infarction or haemorrhage. The cerebellum appeared normal. All arteries were in excellent condition.

Histological examination showed patchy lymphocytic infiltration of the leptomeninges, i.e. the

changes of viral meningitis. Some small intra-cerebral vessels were cuffed with lymphocytes but no features suggestive of a leuco-encephalitis were seen. Also present were patchy ischaemic changes in the deeper laminae of the cerebral cortex with shrunken nerve cells, densely eosinophilic cytoplasm and dark round nuclei. Other areas contained marked increases in pericellular spaces with loss or shrinkage of neurones. Ischaemic changes were also seen in the cerebellar cortex with a marked increase in glial cell nuclei and severely depleted Purkinje cells. Trigeminal ganglia and their roots showed mild degenerative changes and infiltration by inflammatory cells, mainly lymphocytes.

Myocarditis of varying severity was present in all sections of the myocardium. There was a patchy inflammatory cell infiltrate (predominantly lymphocytes and macrophages) and minimal myofibrillary necrosis. In addition histological features of a hypertrophied, dilated myocardium were also evident (Figure 1). Thus hypertrophied myocardial fibres were widely separated but in normal alignment with only occasional foci of irregular arrangement in some areas. The smooth muscle component of the endocardium was focally prominent, denoting that dilatation had been present for some time.

Histological examination confirmed bronchopneumonic changes in the lungs. There was renal tubular necrosis and the tubular lumen contained red cells. There was no evidence of immunosuppression.

Discussion

The autopsy suggested that cardiac involvement was the most important factor causing death in our patient. Myocarditis is a rare but recognized complication of adult varicella (Castleman & Kibbee, 1963), and may be occult in many cases (Hackel, 1953). In our case the importance of cardiac involvement was not appreciated before death. Serious arrhythmias may

Figure 2 Electrocardiograph on admission, showing T wave flattening in leads I and V₆.

accompany even 'mild' viral myocarditis (Heikkila & Karjalainen, 1982). Morales *et al.* (1971) attributed sudden death in varicella to arrhythmias.

In our case the cardiac involvement was atypical in that the inflammatory cell infiltrate was unusually sparse and the histological features conformed entirely with those of patients suffering from a dilated cardiomyopathy with myocarditis and high Coxsackie B antibody titres (Olsen, 1983). By analogy, the myocardial involvement may have been mediated by an immunological idiosyncrasy. Judging by the degree of hypertrophy seen the process had been going on for more than 7 d and cardiac involvement probably started in the incubation period.

Acyclovir treatment was followed by lysis of the fever and rapid resolution of cutaneous chicken-pox but the severe brain, kidney and myocardial damage found at autopsy almost certainly occurred before admission to hospital. The use of acyclovir seems to have prevented recovery of virus from post mortem material.

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