Leukoencephalopathy associated with extensive burns

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SUMMARY Unusual neuropathological changes were observed in two cases following extensive burns. These consisted of perivascular areas of demyelination distributed symmetrically in the brain and affecting the white matter predominantly. One case in addition had widespread petechial and ring haemorrhages characteristic of brain purpura. Both patients sustained second and third degree burns in greater than 50% of the body surface area, developed metabolic acidosis, sepsis, disturbance in consciousness and multiple episodes of cardiorespiratory arrest prior to death. A toxic metabolic state related to a burn toxin released from the damaged tissue or from bacterial action to the tissue in addition to low platelet level is proposed as the major pathogenetic factor in the development of the neurological symptoms and the patients' demise.

There is now increasing evidence for the presence of burn toxin in animals. Human full-thickness skin scalded in vitro has produced crude degradation products which were toxic and lethal to mice when injected intravenously or intracerebrally.¹ Animals injected with human burn toxins developed neurological manifestations in addition to inhibition of clotting time, in direct relation to the concentration of the skin extract. Sepulchre *et al*² noted abnormal flattening of EEG tracings 30 to 60 minutes after injection of purified Cohn fraction from the sera of patients with extensive burns to rabbits and rats. Allgower³ found that homogenates from thermally injured skin in mice had a lethal effect and caused neurological deficits when injected to recipient animals while native skin treated in the same manner was completely inactive. A neurotoxic substance with a high molecular weight ($2-3 \times 10^6$ daltons) had been isolated by gel filtration and ultracentrifugation.²⁻⁴ It was non-dialysable, non-ultrafiltrable and could be salted out with 30% ammonium sulphate or centrifuged down at 100,000 g. It was destroyed by proteolytic enzymes, phospholipase and lipid solvents, establishing its protein and lipid composition.

On the other hand, very few detailed reports of the neuropathological alterations associated with thermal injury are found in the literature. Internal hydrocephalus, cortical atrophy and gliosis were described by Ule and Doose⁵ in a child who died three

years after burn encephalopathy. "Toxic degeneration" of the ganglion cells was described in six patients by Walker and Shenkin in 1945.⁶ Perivascular demyelination was first reported in 1936 by Globus and Bender.⁷ In 1954, Madow and Alpers⁸ reported similar changes associated with diffuse perivascular haemorrhage in two other patients and felt that these were due to a toxic agent formed in the burned tissue. Since then, no other good neuropathological studies have been reported. The purpose of this communication is to describe in detail the neuropathological alterations that were seen in two patients with severe burns and to postulate the toxic nature of burn encephalopathy.

Case reports

CASE I

Clinical history

This 19-month-old white boy sustained 55% second and third degree burns after accidentally falling into a vat of boiling tomato juice that was being prepared for home-canning. Upon admission to the hospital, he was alert and responsive without any gross neurological deficit or evidence of respiratory distress. Initial laboratory data included normal complete blood count and serum electrolyte levels. On the 6th hospital day, he developed spiking temperatures and became intermittently lethargic. Peripheral blood smear showed toxic granulations. Wound culture grew moderate colonies of *E. coli*. Chest radiograph showed an infiltrate in the middle lobe of the right lung. Antibiotics were started. He then developed increasing abdominal distension, diarrhoea, oliguria, episodes of bradycardia and hypotension. Subsequent laboratory findings showed marked pancytopenia and thrombocytopenia (platelet count 4000/cumm.). Fibrinogen level was normal. Fibrin split products were negative. He

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developed several episodes of cardiac arrest and expired on the 11th hospital day.

General necropsy findings

The heart was unremarkable except for some foci of recent interstitial haemorrhage. The lungs showed diffuse and extensive intra-alveolar haemorrhage, patchy interstitial haemorrhage and foci of acute inflammatory cell infiltration. Severe ischaemic enterocolitis was noted in the ileum and colon. No thrombosed or necrotic vessels were identified. The liver showed diffuse coarse fatty change. The spleen was markedly congested. There was marked lipid depletion and cortico-medullary congestion of both adrenal glands. The kidney showed severe medullary congestion but there was no evidence of acute tubular necrosis or fibrin thrombi. The bone marrow was hypercellular with marked shift to the left of the myeloid elements.

Gross neuropathological findings

The brain weighed 1050g. The meninges were thin, translucent and congested. The gyri appeared full although there was no gross evidence of uncal, cingulate or tentorial herniation. A localised subarachnoid haemorrhage was noted over the convexity of the left fronto-parietal lobe. The spinal cord showed petechial haemorrhages in the lumbosacral region and cauda equina. Multiple petechial haemorrhages became more apparent after fixation in 20% formalin. These were bilateral, symmetrical in distribution and most prominent over the cerebellar hemispheres which had a generalised dusky discoloration. In the cerebral hemispheres, they were distributed mainly along the deeper layers of the cortex, at the junction of gray and white matter and sometimes scattered throughout centrum semiovale (fig 1). Petechial haemorrhages were also seen in the lenticular nucleus, thalamus and throughout the entire length of the corpus callosum, producing a peppery or stippled appearance. The punctate haemorrhages were most numerous along the dusky cortex of the cerebellum, curiously sparing the white matter so that the cortical outlines stood out prominently. Petechial haemorrhages were noted in the cerebral peduncles, colliculi and brainstem nuclei although to a less degree than those seen in cerebral and cerebellar hemispheres. Scattered haemorrhages were present in the lumbosacral segments of the spinal cord, occasionally involving the gray matter but most prominent in the spinal roots and ganglia.

Microscopic findings

A large focus of subarachnoid haemorrhage was present in the left frontoparietal lobe. Within and around this region, confluent bacterial colonies were seen particularly within the vessel lumen, admixed with some acute inflammatory cells and occasional macrophages. Along the base of the brain, the meninges were thickened and mildly infiltrated by mononuclear cells. In the cerebral cortex, there was moderate to marked hyperplasia of protoplasmic astrocytes, many of which had large irregular and vesicular nuclei. Many petechial and ring-type haemorrhages were seen, most confluent in the upper cortical layers, at the junction of gray and white matter and in the centrum semiovale. Many ring haemorrhages contained a central

Fig 1 Coronal section of the cerebral hemispheres showing diffusely scattered petechial haemorrhages predominantly involving the junction of gray and white matter. A localised subarachnoid haemorrhage is also seen in the left fronto-parietal region. Case 1.

core of fibrinoid material associated with occasional collections of mononuclear cells, macrophages and rare polymorphonuclear leukocytes. In others, a faint outline of fragmented thin vessel wall mostly of venules and capillaries were seen. There was no associated endothelial hyperplasia. Bacterial colonies were seen filling up small vascular lumens but did not have any associated cellular reaction nor did they appear to be especially related to the haemorrhagic areas. Multiple scattered petechial and ring haemorrhages were present in the anterior commissure, claustrum, internal and external capsules, caudate nucleus, putamen, globus pallidus, optic chiasm, hippocampus, supraoptic nuclei, mamillary bodies, mamillothalamic tracts, corona radiata and thalamus. Occasional eosinophilic neurons were seen in Ammon's horn. Otherwise, the neurons and ganglionic cells appeared

unremarkable. Many small and confluent areas of haemorrhage were noted throughout the cerebellum, mostly oriented perpendicular to the surface. The ring haemorrhages were concentrated mainly in the molecular and granular layers although sometimes also involving the junction of gray and white matter. Petechial and ring haemorrhages were present in the cerebral peduncles, superior and inferior colliculi, red nucleus, substantia nigra and restiform body. In the pons, haemorrhages were seen in the tegmentum, medial longitudinal fasciculus, corticopontine and corticospinal tracts, cerebellar peduncles and occasionally in the periaqueductal gray matter and trigeminal nerve nuclei. In the medulla, some haemorrhages were noted in the cranial nerve nuclei, inferior olives and occasionally in the pyramidal tracts. Foci of haemorrhage were seen in the anterior horn at the thoracic and lumbar cord segments on one side, in the anterior and posterior horns at S₁ level, and focally in the corticospinal tracts. The haemorrhages were more prominent and confluent in the spinal roots, dorsal ganglia and cauda equina. Small petechial haemorrhages were also present in the infundibulum and posterior lobe of the pituitary gland.

Myelin stains showed minute discrete foci of pallor and demyelination of cerebral and cerebellar white matter which were usually oriented around small blood vessels and surrounded by haemorrhage although sometimes also occurring in the non-haemorrhagic white matter perenchyma itself. Luxol Fast Blue and Periodic Acid-Schiff (PAS) stains showed PAS-positive central fibrinoid material within the haemorrhages surrounded by pale demyelinated zone and more peripherally by a ring-like collection of red blood cells (fig 2).

CASE II

Clinical history

This 17-year-old white male sustained 58% second and third degree burns following an explosion while he was driving a fork lift at work. He did not lose consciousness and he understood the events of the accident although he "possibly sustained some injury to his head by falling off the fork lift". The extent of injury was not known. On admission, his vital signs were stable. He was alert and fully oriented. His heart and lungs were normal. No neurologic deficit was noted. Serum electrolyte levels were normal. On the 4th hospital day, he became hypotensive and oliguric. He was noted to be restless and slow to respond. He developed intermittent episodes of confusion, disorientation, lethargy, hypotension and anuria following debridement and tub treatments. He then developed respiratory insufficiency and metabolic acidosis. Persistent hyperglycaemia was noted in spite of insulin therapy. Sputum cultures later yielded *Escherichia coli* and *Pseudomonas* organisms. Blood and urine cultures grew *Candida albicans*. Antibiotics were started. Peritoneal dialysis was given because of increasing blood urea nitrogen and creatinine levels. He developed right-sided focal seizures and later became progressively comatose. He expired on the 21st day of hospitalisation following several episodes of cardio-respiratory arrests.

General necropsy findings

Both lungs showed massive acute bronchopneumonia and thromboemboli within small pulmonary vessels associated with focal acute pulmonary infarcts. The heart was congested but was otherwise unremarkable. There was severe congestion of the liver with fine vacuolar lipid

Fig 2 Luxol Fast Blue-Periodic Acid Schiff stain emphasising the central fibrinoid material surrounded by a pale zone of demyelination and more peripherally by a ring-like collection of red blood cells. Case I ($\times 270$ magnification)

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droplets within centrilobular hepatocytes. There was bilateral atrophy of adrenal glands. The spleen was congested. There was mild acute and chronic pancreatitis. Acute renal tubular necrosis and focal acute pyelonephritis were noted. No fibrin thrombi were seen.

Gross neuropathological findings

The brain weighed 1590g. The gyri appeared full. There was generalised congestion of the meningeal vessels. Bilateral temporal, uncus and cerebellar tonsillar herniations were noted. There was no external evidence of bleeding. The circle of Willis was normal. The spinal cord was grossly normal. Sections of the brain after fixation in 20% buffered formalin showed congestion of the vessels in cerebral cortex and subcortical white matter with poor delineation between gray and white matter. Petechial haemorrhages were seen in the right posterior aspect of the corpus callosum. There was a focus of haemorrhage in the medial aspect of the right parieto-occipital lobe. Along the deep white matter, superior and lateral to the frontal and temporal horns of the lateral ventricles, there were bilateral ill-defined elevated zones alternating with tiny-pitted or depressed areas which were slightly soft to touch (fig 3). These zones were symmetrical and extended posteriorly to the level of the posterior thalamus and pulvinar, concentrated mostly along the periventricular areas. Haemorrhagic necrosis was noted along the superior aspect of the cerebellar vermis extending symmetrically into both cerebellar hemispheres. Petechial haemorrhages were also seen in the white matter of the left cerebellar hemisphere superior to the dentate nucleus.

Microscopic findings

The meninges were thickened and showed focal perivascular collections of mononuclear cells and macrophages. Extravasated red blood cells were seen in the subarachnoid space overlying the right temporal lobe. Within the cerebral

hemispheres, there was diffuse subcortical pallor with focal loss of neurons in the deep cortical layers. Hypertrophic astrocytes with large vesicular nuclei were scattered in the white matter. Eosinophilic and degenerating neurons were seen in the hippocampus, most prominent in the Sommers' sector where microglial reaction and abnormally large astrocytes were abundant and macrophages were occasionally seen. Bacterial colonies were present within some small blood vessels but were not accompanied by significant inflammatory cell reaction. Discrete zones of necrosis were seen in white matter. These were mostly periventricular but sometimes appeared confluent and were associated with swollen astrocytes and oligodendroglial cells. Many astrocytes were irregular and hypertrophic with lobulated, vesicular and sometimes vacuolated nuclei. The necrotic zones in white matter were seen bilaterally and symmetrically in the frontal, parietal and occipital lobes, usually in periventricular distribution. Symmetrical zones of pallor were also noted in the lateral aspects of the corpus callosum with disruption of fibres and scattered large astrocytes. Bodian and myelin stains showed concomitant loss of both myelin and axis cylinders within the pale zones. There was no associated inflammatory cell reaction. A large area of haemorrhage was seen within the subcortical and deep white matter of the right parieto-occipital lobe associated with peripheral layering of leukocytes surrounded by a zone of necrosis. Microcystic degeneration was present in the periphery of the lesion with reactive gemistocytic astrocytes, microglial cells, perivascular exudation of polymorphonuclear leukocytes and acute degeneration of the neurons in the overlying cortex. Away from the major haemorrhage, ring haemorrhages were seen in the cortex associated with capillary endothelial hyperplasia. Foci of ischaemic necrosis characterised by pallor, neuronal cell loss, eosinophilic neurons and microglial reaction were seen in the putamen and globus

Fig 3 Coronal section of the cerebral hemispheres showing bilateral ill-defined elevated areas alternating with tiny pitted depressions in the periventricular zone. Case II.

Fig 4 Section through the medulla showing perivascular zones of white matter necrosis with relative sparing of the inferior olives (arrow). Case II. H & E stain, $\times 70$ magnification.

pallidus. There was a large zone of haemorrhagic necrosis in the cerebellar vermis and hemispheres with occlusion of the overlying veins by fibrin thrombi and focal subarachnoid pooling of blood. The dentate nuclei showed prominent degenerative changes with glial cell reaction. Discrete microscopic areas of necrosis were also seen in cerebellar white matter but were most prominent and extensive in the perivascular zones. Multiple scattered areas of pallor and necrosis were seen in the brainstem, mainly in white matter, and involved the corticospinal tracts, corticopontine fibres and middle cerebellar peduncles. There was a relatively symmetrical zone of pallor with spongy degeneration and necrosis of white matter of the medulla, surrounding but curiously sparing the inferior olivary nuclei (fig 4). These changes were more prominently seen with myelin and Bodian stains which showed a parallel loss of myelin and axis cylinders. Although occasional neurons showed evidence of degeneration, the gray matter did not seem to be as severely involved as the white matter.

Discussion

Clinically, both patients sustained extensive burns, developed metabolic acidosis, sepsis, disturbance in consciousness and multiple episodes of cardio-respiratory arrest prior to death. The basic neuropathological changes consisted of widespread perivascular areas of demyelination distributed symmetrically in the brain and affecting the white matter predominantly.

The extensive petechial and ring haemorrhages with foci of perivascular demyelination in Case I bear a superficial resemblance to acute necrotising haemorrhagic leukoencephalitis first described by

Hurst in 1941.⁹ However, the clinical picture presented by the patient was clearly *not* the same as the clinical presentation of acute necrotising haemorrhagic leukoencephalitis which typically follows a mild respiratory infection with subsequent rapid evolution of neurologic signs progressing usually to coma and death within a few days to several weeks.

Case I fits better the diagnosis of brain purpura, sometimes confused with acute necrotising haemorrhagic leukoencephalitis and characterised by minute pericapillary haemorrhages confined to white matter and associated with destruction of both myelin and axis cylinders. Cerebral purpura has been reported in association with disseminated thrombocytic thrombosis,^{10–12} fat embolisation,¹³ viral infection,^{14–15} pertussis vaccination,¹⁶ drug intoxication with arsenic,^{17–20} streptomycin and para-aminosalicylic acid,²¹ sulfamethylthiazole,²² nitrore gas,²³ and paraquat.²⁴ Haemorrhagic and non-haemorrhagic perivenous demyelinating lesions have also been observed in post-anti-rabies vaccine encephalomyelitis.²⁵ The patient had marked thrombocytopenia which is known to occur in disseminated intravascular coagulation and which may be triggered by bacterial or viral sepsis. In our case, disseminated intravascular coagulation was ruled out by the normal fibrinogen level and negative fibrin-split products. Central cores of fibrinoid necrosis were seen within the ring haemorrhages with fragmentation of thin vessel walls but no associated endothelial hyperplasia or occlusion of the vessels by

fibrin thrombi. The parenchymal haemorrhages were greater in comparison with the tissue necrosis or vascular damage. Although both gray and white matter were involved by the bleeding, the areas of demyelination were predominantly seen in white matter. Also, the demyelinated foci were not always intimately related to the areas of haemorrhage, suggesting that the two processes, although probably occurring simultaneously, might actually be manifestations of two related by independent processes. The foci of demyelination may be secondary to some reaction of the white matter substance to toxic factors presumably circulating within the blood, causing the same widespread foci of perivascular softening and demyelination sometimes associated with destruction of capillary and precapillary arterioles which have been observed with drug intoxication or septic shock.²⁶ The severity of the haemorrhagic diathesis in Case I is most probably related to the severe depletion of platelets consequent to his toxic metabolic state.

In Case II, the most impressive alteration was the presence of bilateral symmetrical foci of white matter necrosis with almost parallel destruction of myelin and axis cylinders but without associated inflammatory reaction. Similar changes were described in 1936 by Globus and Bender⁷ in an 8-year-old boy who died six months after extensive burns complicated by sepsis, and thought to be due to a toxic agent formed in the disintegrating burned tissue.

Diffuse degeneration of cerebral white matter was reported by Strich²⁷ in five patients who had prolonged coma following closed head injury, and was presumed to be due to stretching and tearing of the nerve fibres following trauma. Although our patient "possibly sustained some injury to his head", he did not lose consciousness and did not fit the clinical picture presented by the patients with post-traumatic injury. Plum, Posner and Hain²⁸ described five patients who regained consciousness following an anoxic episode and later developed extensive cerebral hemispheric demyelination with no predilection for perivascular regions. White matter degeneration secondary to anoxia has also been described following carbon monoxide poisoning²⁹⁻³¹ and after administration of potassium cyanide.³²⁻³³

Case II does not fit the picture of post-anoxic encephalopathy. The patient developed intermittent confusion, lethargy and mental deterioration even before he had any significant anoxic episode. The areas of demyelination although predominantly involving the deep cerebral white matter, were also seen in cerebellar and brainstem white matter, cerebral and cerebellar peduncles, corticospinal tracts and transverse pontine fibres. The lesions were therefore more extensive than those seen with

delayed anoxic changes. The foci of demyelination were mostly perivascular and associated with swollen astrocytes and oligodendroglial cells as well as axonal loss but was not accompanied by significant inflammatory reaction. It is possible that, as in the first case, the degenerative changes may have been related to the direct action of or to sensitivity of the brain tissue to a circulating toxin rather than being purely secondary to anoxia, hypoxia or ischaemia. However, anoxic changes, as evidenced by degenerating neurons in the hippocampus, could also conceivably have played a contributing role.

The evidence for the presence of a burn toxin has been established experimentally although the exact mechanism by which it causes neurologic abnormality is still not defined. It is possible that such a neurotoxic substance might have been circulating in the two patients we have just described, and that such substance preferentially acted against myelin or axis cylinders or both, and involved the perivascular zones as it diffused out into the neural tissue from the bloodstream where it circulated. The concomitant low platelet count might have further complicated the case and caused the increased bleeding tendency and consequent haemorrhagic diathesis within the brain parenchyma. A toxic metabolic state related to a possible circulating burn toxin, either derived from the degenerating tissue or from a gram-negative organism, is postulated as the major pathogenetic factor in the development of the neurologic symptoms and the patients' demise.

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