Histol Histopath (1987) 2: 57-66

Histology and Histopathology

Purpura cerebri in Gram-negative septicaemia. A histological and immunohistochemical study

Jutta Schwenk and Georg Gosztonyi
Institute of Neuropathology, Free University Berlin, Hindenburgdamm 30, 1000 Berlin 45, FRG

Summary. Two cases with brain purpura following Gram-negative septicaemia were examined morphologically and immunohistochemically.

The brain lesions, including ball and ring haemorrhages, a few days old, with some microglial cells accumulated around the older foci, were restricted to the white matter.

Immunohistochemically, scanty deposits of IgG, IgA and IgM mainly in the macrophages in brain, kidneys and lungs were found, whereas staining with antibodies directed against IgE and complement (C3, C4) remained negative. In the brain, immunoglobulin deposits were located mainly in the macrophages, furthermore, in and around the walls of a few intact (non-haemorrhagic) vessels; within the perivascular haemorrhagic foci no deposits could be demonstrated. The relevance of these observations to the pathogenesis of brain purpura is discussed.

Key words: Acute haemorrhagic leukoencephalitis - Brain purpura - Arthus reaction - Gram-negative septicaemia - Immune complexes - Schwartzmann phenomenon

Introduction

Acute disseminated encephalomyelitis (ADEM), acute haemorrhagic leukoencephalitis (AHLE) and brain purpura (BP) constitute a triad of closely related, severe neurological diseases. The clinical and pathological findings are similar in these diseases but their course is different and the aetiology and pathogenesis are still insufficiently elucidated. AHLE and BP have a hyperacute course; their clinical picture is marked by pyrexia, nuchal rigidity, disturbance of consciousness mostly passing into coma, and by focal neurological signs.

Histopathologically, ADEM, AHLE and BP present three major features, whose ratio and intensity are proportional to the acuity of the condition and are critical for the morphological classification of the individual case (Gosztonyi, 1973, 1978): 1) Multiple ball and ring haemorrhages with a perivascular area of necrotic tissue and a central capillary or vein, the vessel wall of which is more or less damaged and impregnated with fibrin exudation. 2) Perivenous demyelination with proliferation of microglial cells. 3) Inflammatory infiltration, consisting predominantly of polymorphonuclear leukocytes, lymphocytes and monocytes. These morphological features suggested a basically similar pathogenesis; therefore, ADEM, AHLE and BP were regarded as a nosological entity (Mac Ardle et al., 1949; Greenfield, 1950; Környey, 1952; Csermely and Haberland, 1954; Russell, 1955; Gosztonyi, 1978). AHLE and BP are known to arise as complications of acute viral infections and/or drug hypersensitivity; therefore, it seemed to be less probable that bacterial infections might be related to these conditions. Nevertheless, a total of seven cases of AHLE, following Gram-negative septicaemia have been reported by Masland and Barrows (1962) and by Graham et al. (1979). The authors postulated that the condition corresponded to the generalized Schwartzmann phenomenon, in the course of which an antigen-antibody reaction activated the complement system by the alternative (properdin) pathway which, in turn, led to vessel wall damage.

Although it has been presumed that these haemorrhagic-demyelinating conditions develop on the basis of an immunological abnormality resembling the Arthus reaction, except for a short communication (Chou, 1982), no immunohistochemical examinations have been performed on human autopsy material.

Offprint requests to: Jurtta Schwenk, Institute of Neuropathology, Free University Berlin, Hindenburgdamm 30, 1000 Berlin 45, FRG

We present two cases of BP which occurred in Gram-negative septicaemia due to *Pseudomonas aeruginosa.* These cases gave us an opportunity to review the role of humoral immune mechanisms in the development of this condition.

Materials and methods

Light microscopy

Specimens of various regions of the brains, fixed in 10% formalin, were embedded in paraffin and stained with haematoxylin and eosin (H&E), Nissl, periodic acid Schiff (PAS), Mallory, Sudan black B for myelin, Prussian blue for iron and PTAH for fibrin. Silver impregnations for microglial cells, astrocytes and axons were performed according to Gallyas (1981 a, b; 1985). Frozen sections of the centrum ovale were stained with Sudan IV for fat. In addition, four complete coronal slices of each brain were embedded in celloidin and stained with the H&E, Mallory, Nissl and Heidenhain techniques.

Immunohistochemical examinations

In each case, paraffin sections of brain, lungs, liver, spleen, heart and kidneys were stained by the direct immunofluorescence technique with FITC-labelled specific rabbit anti-human-antibodies (Behring) against the immunoglobulins IgG, IgA, IgM, IgE, against the complement factors C3 and C4, and against albumin (Dilution: 1:20). The paraffin sections were pretreated with protease for 10 min. In Case 2, additional cryostat sections of snap-frozen tissue specimens of brain, lung, liver, skeletal muscle, heart and kidney were stained by the same immunohistochemical methods. Paraffin sections from selected blocks were stained with a monoclonal antibody (Serotec) against myelin basic protein (MBP) with the alkaline phosphatase-anti-alkaline phosphatase (APAAP) tecnique. Monocytes and macrophages were demonstrated on selected sections by a polyclonal antibody to human lysozyme (DAKO) with the biotin-avidin-peroxidase technique.

Results

Case reports

Case 1

Clinical history: A 63-year-old woman (A.B.) was admitted to hospital with severe inflammation of the right hip joint following intra-articular cortisone injection. She developed septic temperatures, high erythrocyte sedimentation rate, leukocytosis and left shift in the differential count. Blood cultures yielded excessive growth of *Pseudomonas aeruginosa.* In spite of antibiotic treatment the sepsis progressed, she soon showed signs of renal failure, deterioration of electrolytic and blood coagulation parameters (thrombocytopenia and decreased fibrinogen levels), metabolic acidosis, hypotension and respiratory insufficiency. Four days prior to death, she became comatose and had a generalized seizure. CCT showed extensive parenchymal lesions and disseminated focal haemorrhages (Fig. 1). She died due to the severe haemorrhagic cerebral lesions and brain oedema on the 10th day of hospitalization, 4 days after the appearance of neurological signs.

General necropsy findings: At necropsy, there was evidence of right suppurative and fibrinous coxitis. The lungs were heavy and firm. A fibrinous pleuritis and 500 ml of serosanguineous pleural fluid were found on each side. Oedema of all parenchymal organs reflected the underlying circulatory insufficiency. Pyelon, bladder, rectal mucosa, pleura, larynx and lungs showed a few ecchymoses. Numerous thrombi were found in the peripheral veins and arteries and in the right cardiac atrium. The kidneys were enlarged and weighed 200g, resp. 250g. The liver showed fatty changes. Histologically, intra-alveolar haemorrhages were seen in the lungs. The kidneys showed markedly dilated tubuli, flattened tubular epithelial cells, intratubular protein and acute bilateral tubular necrosis. Inflammatory mononuclear infiltrates were present, suggestive of an interstitial nephritis (Fig. 5). A fresh ulcer was found in the rectal mucosa. The red pulp of the spleen was hypertrophic and activated.

Gross neuropathological findings: The brain weighed 1155 g. Some speckled subarachnoid haemorrhages were present on the surface of both frontal lobes. There were marked bilateral tentorial and slight tonsillar herniations. On cut surfaces, the ventricles were narrowed; in the mid-brain and in the upper part of the pons, confluent streaky secondary haemorrhages were present.

The white matter of both hemispheres displayed numerous petechial haemorrhages. The bulk of the petechiae was situated predominantly in the subcortical zones of the centrum semiovale of the hemispheres, but similar lesions were present also in the internal and external capsules, in the cerebral peduncles, the pons and the upper segments of the medulla oblongata. Infrequently, the petechiae merged into larger haemorrhages, the biggest of which, in the right frontal lobe, measured 40 x 22 mm in diameter. With the exception of a few punctate haemorrhages in the putamen, the grey matter was not involved. No petechiae were seen in either the frontal pole, the corpus callosum, the cerebellum or in the lower medulla. The spinal cord was not examined.

Case 2

Clinical history: A 47-year-old man (N.V.) with a history of recurrent gastric and duodenal ulcers underwent Billroth-II-operation and proximal selective vagotomy. After surgery, he continued to bleed, lapsed into shock and had a short episode of cardiac arrest. He then developed bilateral pneumonia and severe peritonitis necessitating relaparotomy. Insufficiency of the gastroenterostomy suture was found. During the following days, respiratory parameters, red and white blood cell counts further deteriorated, necessitating blood transfusions. Additionally, renal failure developed and haemodialysis was initiated. The

patient had septic temperatures and, for the second time, developed signs of peritonitis. Blood cultures remained sterile. Another relaparotomy was performed on the 14th day of hospitalization, leading to a further increase in blood urea, persistent septic temperatures and further blood loss. Six days before death, the patient became comatose, general muscle fasciculations were noted and he expired 20 days after admission and 6 days after the appearance of neurological signs.

General necropsy findings: The principal findings at necropsy were bilateral bronchopneumonia and peritonitis. 300 ml of fibrino-purulent exudation was found in the abdominal cavity. In the liver focal necrosis and diffuse fatty changes were noted. There was oedema of all parenchymal organs, especially of the lungs and the intestinal tract. The kidneys were congested and cyanotic and weighed 150 g, resp. 180 g. Small haemorrhages were found in the pyelon, bladder and mitral valve. There was moderate hyperplasia of the red pulp of the spleen.

Histologically, the kidneys had markedly dilated tubuli with necrosis of some tubular cells and oedema of the proximal parts of the tubuli. There were fresh and older erythrocyte cylinders in the lumina, thus reflecting a toxic damage to the basement membrane. The liver showed toxic fat accumulation and centrilobular necrosis. Post-mortem cultures of autopsy blood and tissue specimens had a high amount of *Pseudomonas aeruginosa.*

Gross neuropathological findings: The brain weighed 1268 g. It was symmetrically swollen with moderate uncal and tonsillar herniations. On cut surfaces the ventricles were markedly narrowed. Numerous petechial haemorrhages were scattered in the centrum semiovale of both hemispheres, in the cerebral peduncles, the pons, the upper parts of the medulla oblongata, the cerebellum and in the cerebellar peduncles. No petechiae were seen in the frontal poles, corpus callosum, internal and external capsules and in the lower medulla. In the cerebral hemispheres the lesions were restricted exclusively to the white matter and were more strictly localized to the subcortical zones of the centrum semiovale than in Case 1. The diameter of the haemorrhages varied from pinpoint-size to a maximum of 6 x 3 mm.

The spinal cord was not examined.

Microscopic findings in Cases 1 and 2

The microscopic appearance of the lesions in both cases was that of ball and ring haemorrhages, in the centre of which sometimes a capillary or venule could be found (Figs. 2, 4 a, b). The walls of the central vessels in the ring haemorrhages were more or less necrotic and impregnated with a fibrinous PAS- and PTAH-positive exudate also extending into the perivascular aera (Figs. 4 a, b). The tissue in the centre of the ring haemorrhages was usually necrotic. There, the myelin staining was markedly reduced, although complete demyelination could not be seen. The loss of myelin sheaths in the centre of the ring haemorrhages could be explained by the necrosis, and in the periphery by the mechanical damage exerted by the extravasated erythrocytes. A true primary demyelination could not be established. The axis cylinders within the haemorrhagic foci were mostly intact, sometimes tortuous and swollen.

The ring and ball haemorrhages formed by extravasated red blood cells were of different ages. In both cases, older and recent petechiae were present and even haemorrhages with faint as well as fresh erythrocytes could be seen (Figs. 3, 4 a, b). In Case 1, the majority of the lesions were of older date (Fig. 3). In contrast, in Case 2 the vast majority of the lesions proved to be recent. Microglial cells were accumulated in the outer zones of the necrotic perivascular areas of older ring and ball haemorrhages (Figs. 4 c, d).

"Non-haemorrhagic" foci, i.e. perivascular demyelinating lesions without haemorrhages, could not be observed in either case.

The lumina of the central vessels in both cases were patent except for some solitary erythrocytes; especially no hyaline thrombi could be found. Fibrin thrombi were absent in the brain and also in the other organs. With Sudan-IV staining fat embolism, known as a frequent causative agent of brain purpura, could be excluded.

It should be noted that there was no evidence of perifocal inflammatory infiltration of polymorphonuclear leukocytes and lymphocytes in either case, which otherwise is a frequent finding in haemorrhagic encephalitis.

Immunofluorescence findings in brain tissue

Immunohistochemical examination of paraffin sections of the brain showed no extracellular immunoglobulin (IgG, IgA, IgM, IgE) or complement deposits (C3, C4) in either case in the haemorrhagic foci. In the cross-sections of a few small veins a faint imbibition of the vessel wall and perivascular area could be found by IgG and albumin. This change, however, is more likely to be related to a permeability disturbance than to a specific immune reaction. A few macrophages contained IgG and IgA deposits.

In the cryostat sections of the brain of Case 2, homogenous immunofluorescent deposits of IgA and, to a lesser degree, of IgG were present in a few haematogenous cells accumulated around unaffected capillaries. No specific immunofluorescence was found in the haemorrhagic lesions with the exception of two foci, where a few IgG positive macrophages were seen at the periphery.

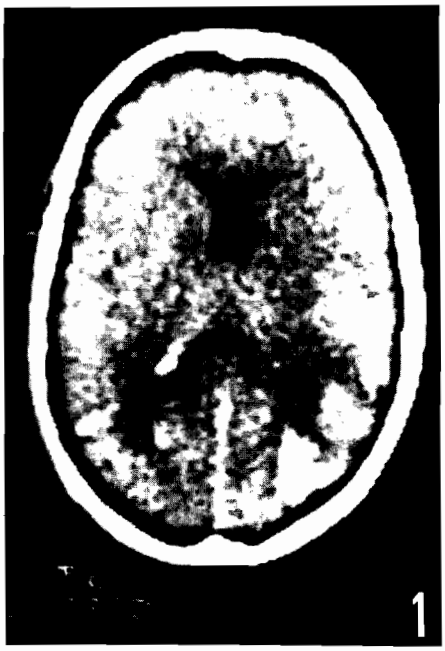
Neither case had deposits of the complement factors C3 and C4.

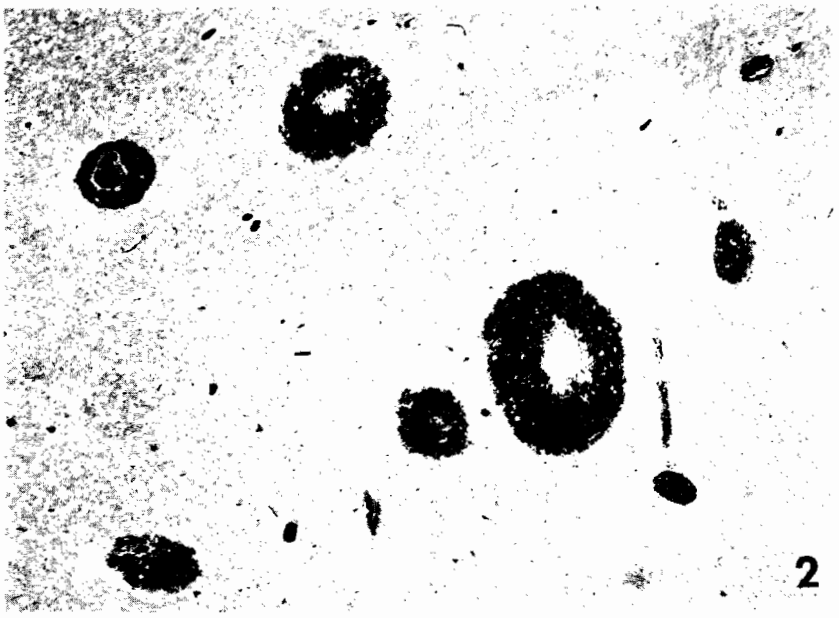
Immunofluorescence findings in the visceral organs

a) Paraffin sections

Immunofluorescence in paraffin sections of the heart showed no deposits of immunoglobulins or of complement in either case.

In the lungs of both cases, a moderate diffuse positivity of IgG, IgA and IgM was seen in some alveolar lumina and in the interstitial tissue in the cytoplasm of infiltrating cells, most probably macrophages.





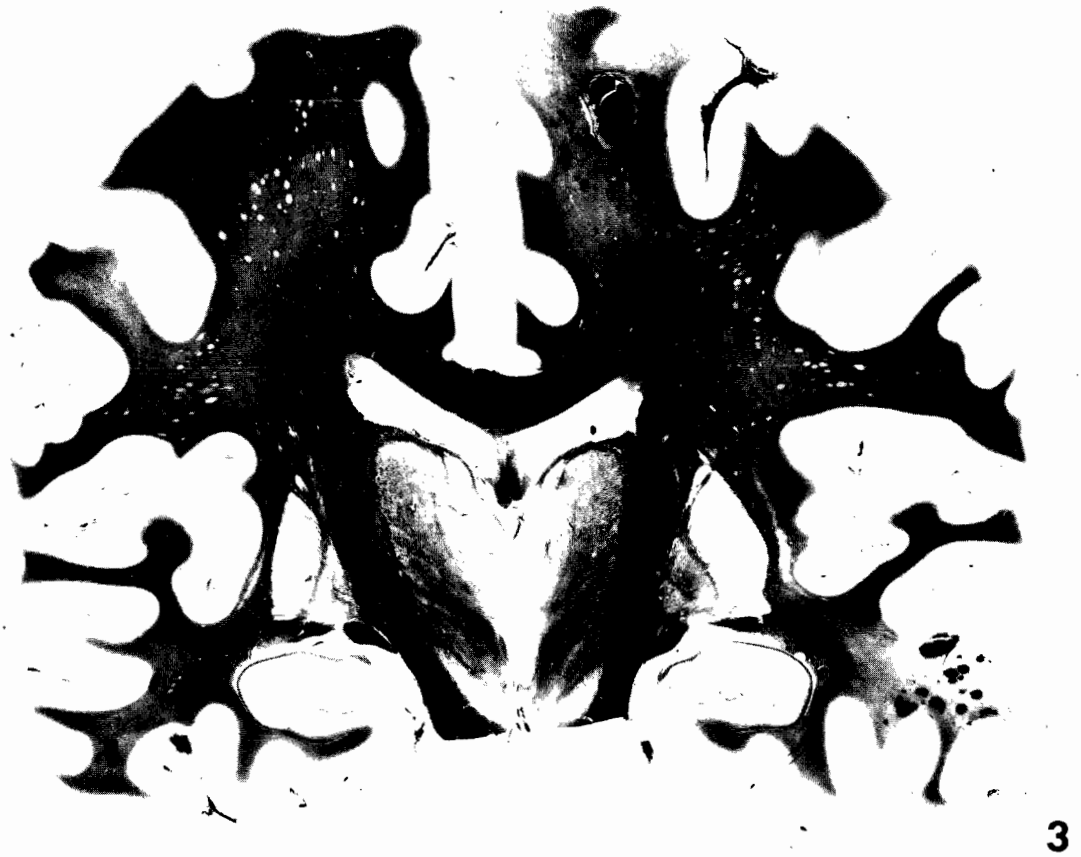


Fig. 1. CT picture with several high density spots in the subcortical white matter. Case 1.

Fig. 2. Frontal white matter. Several ball and ring haemorrhages with recently extravasated erythocytes. Case 2. Mallory stain. x 27

Fig. 3. Coronal section of the cerebral hemispheres. The white matter of the parasagittal convolutions and of the temporal lobes contains fresh haemorrhages (dark spots); the remaining parts of the subcortical white matter and the internal capsules are speckled with older haemorrhages (light spots). The corpus callosum and the central parts of the centrum ovale are conspicuously spared. Case 1. Celloidin, Heidenhain's myelin stain. x 1.4

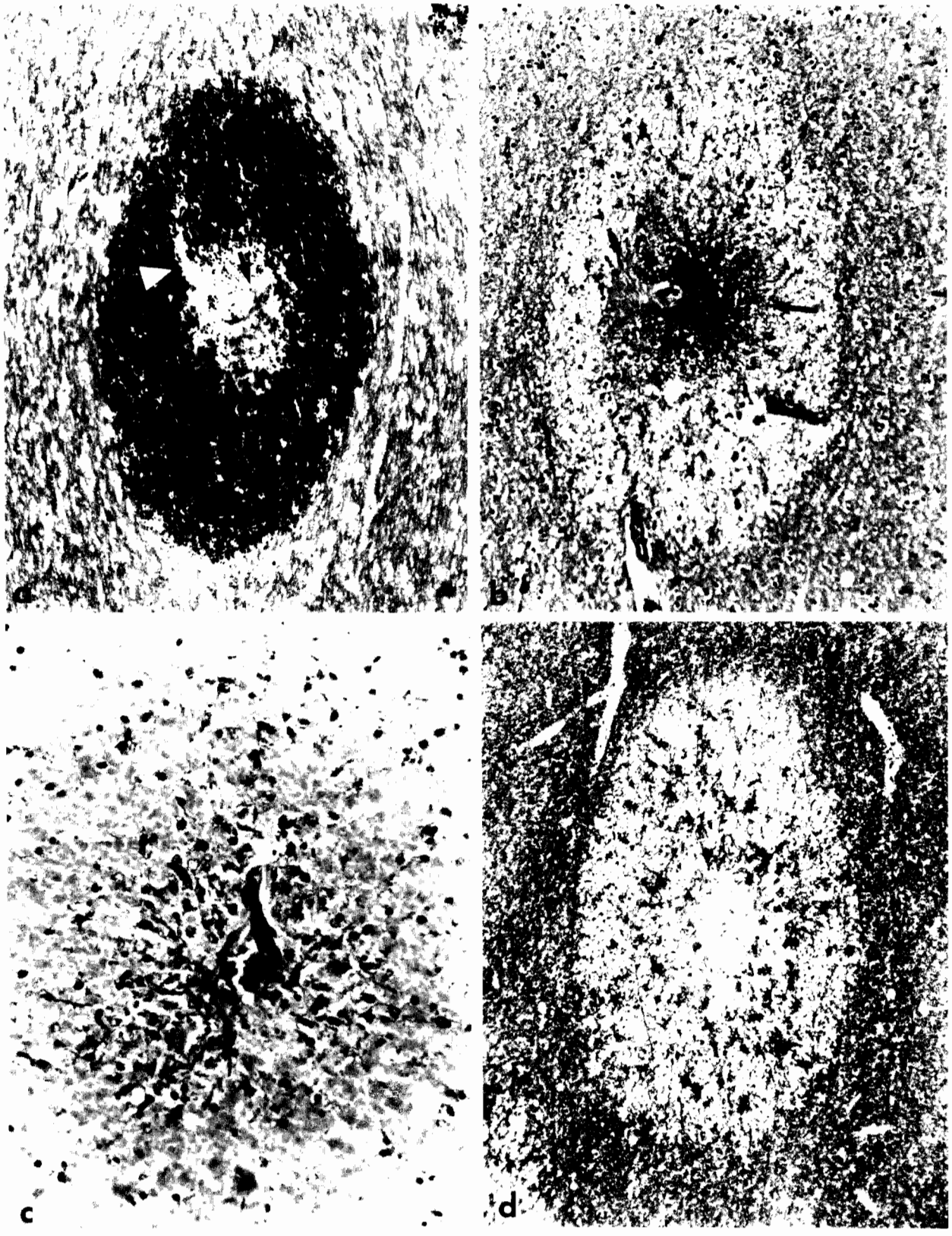


Fig. 4. a) Fresh ring haemorrhage with a tangentially cut central vessel (arrowhead). Slight perivascular fibrin exudation (arrow). Case 2. Mallory stain. x 71. **b)** Older ring haemorrhage with central necrosis and massive perivascular fibrin exudation (arrow). The blood extravasation dates back several days, which explains the faint staining of the erythrocytes that form a light ring around the vascular necrosis. Case 1. PTAH. x 134. **c)** Loose perivascular accumulation of macrophages in the centre of an older ring haemorrhage. The whole field is covered with lightly stained erythrocytes. Case 2. Nissl stain. x 174. **d)** Microglial cells infiltrating the entire extension of a ring haemorrhage. Case 1. Gallyas' silver stain for microglia. x 108.

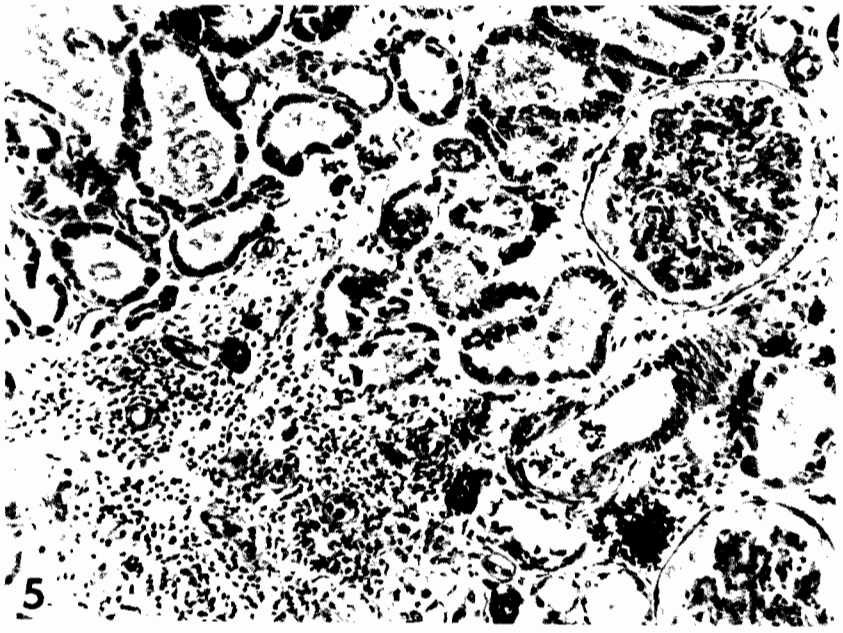


Fig. 5. Perivascular infiltration of mononuclear cells and partial necrosis of the tubular epithelium in the renal cortex. Case 1. H & E. x 142

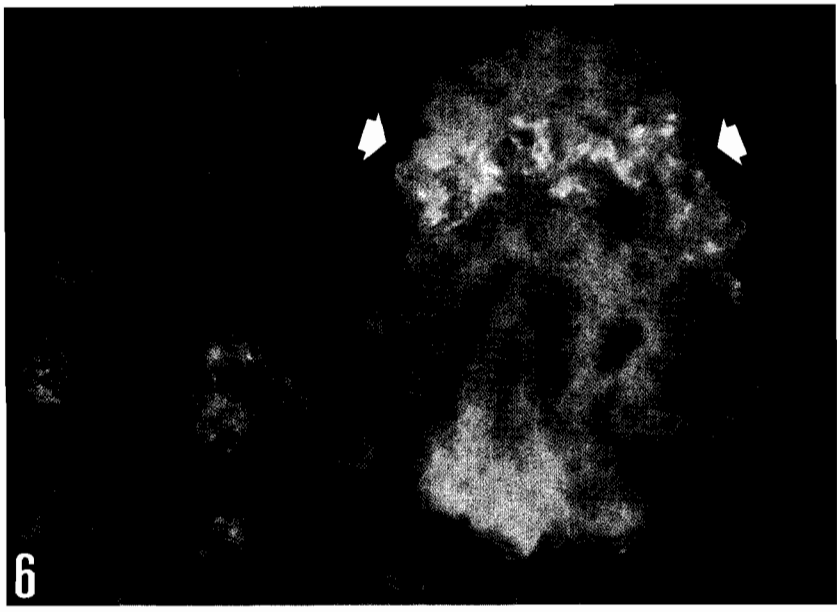


Fig. 6. Deposition of IgG in the vessel walls of the upper part of the renal glomerulus (arrows). Case 2. Direct immunofluorescence. x 190

In the liver of Case 1, an intensive positivity of IgA and a moderate immunofluorescence of IgG and IgM was seen in the cells of some interstitial haematogenous infiltrates.

In the spleen of both cases, marked cytoplasmic deposits of IgA and moderate amounts of IgG and IgM were found in a large number of lymphocytes and macrophages.

The kidneys of both cases showed cytoplasmic fluorescence of IgG and IgA in a number of interstitial haematogenous cells. Distinct deposits of IgA (Case 1) and IgG (Case 2) in the capillary walls of a few glomerula were most conspicuous (Fig. 6). Sporadically slight positivity for IgG was seen in tubular epithelial cells and in tubular lumina. Very often erythrocytes were seen in such tubuli.

It was remarkable that deposits of IgE and complement (C3, C4) could not be found in either case.

b) Crostat sections

Immunohistochemical staining of visceral organs in cryostat sections of Case 2 yielded similar results.

In the liver, small amounts of IgG and IgA were seen in perivascular macrophages. Some deposits were found in the interstitium and in the parenchyma.

The kidneys showed finely granular deposits of IgA in some tubular epithelial cells.

No deposits were found in the heart, skeletal muscle and lungs. None of the organs gave a positive staining for complement factores C3 and C4.

Discussion

This communication presents the findings of two cases of brain purpura which evolved in the course of septicaemia caused by Gram-nmegative bacteria. Our observations follow similar studies published by Masland and Barrows (1962) and Graham et al. (1979). In the case of Masland and Barrows (1962), the septicaemia arose from urinary infection by *Escherichia coli.* Of the 6 observations by Graham et al. (1979), *Pseudomonas pyocyanea* was isolated from their Case 2 and *Staphylococcus aureus,* a Gram-positive microorganism, from their Case 5. No bacteriological findings were a available in their remaining four cases. Case 1 in a report of Burger and Vogel (1977) may be regarded as the victim of a similar pathomechanism as the patient developed Pseudomonas pneumonia and progressive focal neurologic signs 12 days prior to death. At autopsy acute tubular necrosis and confluent cerebral petechiae, restricted to the white matter and sparing the corpus callosum, were found. The assumption of Masland and Barrows (1962) and Graham et al. (1979) that this severe condition was identical with the generalized Schwartzmann phenomenon and that it was elicited by endotoxin shock was based mainly on the finding of a renal tubular necrosis and the presence of fibrin thrombi in many vessels in the majority of their cases. They postulated that in the course of the Schwartzmann reaction complement will be activated thus producing endothelial damage. Because of the hyperacute course of this disease, a detailed clinicochemical study of complement components and haemorrheological parameters was not possible either in our cases or in those of the above authors. Therefore, we must rely on the assessments of experimental pathophysiology to understand the chain of events during endotoxin shock.

Endotoxaemia activates complement by formation of immune complexes which will be deposited in various organs, preferentially in the glomerular capillaries of the kidney. Complement activation leads to endothelial damage giving opportunity to the formation of multiple fibrin thrombi, since endotoxaemia, at the same time, triggers a series of abnormalities in the blood coagulation system (Bick, 1983) resulting in disseminated intravascular coagulation (DIC). Occlusion of the glomerular capillaries leads to bilateral tubular necrosis. Intravascular coagulation in other organs, first of all in the lungs, results in shock aggravated by the C3- induced activation of histamine and other mediators. The fibrin thrombi in the vessels can result in multiple haemorrhagic necroses with profuse diapedesis of granulocytes in various organs.

In the two cases presented here, these events were reflected by both the deposition of immunoglobulins in the glomerular capillaries and the consecutive renal cortical damage.

The clinical and pathological findings of our two cases leave little doubt that endotoxin shock due to *Pseudomonas aeruginosa* infection was the reason for this condition. Since endotoxin shock is frequent, but its combination with brain purpura is rather exceptional, we found it rewarding to elucidate the nature and mechanism of brain damage.

The neuropathological findings included numerous ring and ball haemorrhages predominantly in the subcortical white matter of both hemispheres, resembling closely the typical picture of AHLE, first described by W. Hurst (1941). Histologically, focal perivascular necrosis with fibrin exudation and destruction of myelin sheaths, surrounded by microglia cells were found. In contrast to the reports of Masland and Barrows (1962) and Graham et al. (1979), there was a striking lack of inflammatory cellular infiltrates in these two brains. Our patients - with 29 000 resp. 4 000 leukocytes per mm^3 - showed no critical leukopenia (Humphrey, 1955; Stetson, 1951). These, however, were initial values that might have changed thereafter. In the Schwartzmann phenomenon, the i.v. challenging endotoxin injection results in the clumping of platelets and granulocytes into aggregates, to be removed later from the circulation by sequestration into the capillaries of the lungs and the skin (Stetson, 1951). If brain damage is a late complication, the supply of granulocytes might by then be rather scarce. It seems, therefore, reasonable to replace in our cases the diagnosis of "AHLE" by "brain purpura", in which case leukocytic infliltration is a less prominent histological feature. The fact that the haemorrhages are restricted to the white matter also stresses the close relationship between this condition and AHLE.

On the other hand, brain purpura has a much more acute clinical course (1 to 2 hours, 48 hours at the most) than AHLE (death within 1 or 2 days up to even 2 weeks). In this regard AHLE would be the more appropriate diagnosis.

Comparing the histological picture of our cases with the 7 cases of endotoxin shock reported by Masland and Barrows (1962) and Graham et al. (1979), it has to be noted that the authors found focal haemorrhages also in the grey matter in 3 of their 7 cases. This is in contrast to our 2 cases with the elective involvement of the white matter. Furthermore, the corpus callosum, almost invariably affected by AHLE, was completely intact in both of our cases just as in Case 1 of Burger and Vogel (1977).

Immunohistologically, we found fluorescent deposits of IgG, IgA and, exceptionally, also IgM in brain, liver, kidneys, lungs and spleen of both patients. This positivity was almost completely restricted to the cytoplasm of macrophages. Staining for albumin showed an unspecific diffuse imbibition of the walls of a few vessels in all examined organs. IgE and complement (C3, C4) deposits could not be found. Staining for IgG and IgA gave brighter immunofluorescence in all sections than for IgM. In the brains of both cases, a slight and non-specific IgG and IgA

impregnation of some morphologically unaltered venous vessel walls was found in paraffin sections. Apart from two isolated haemorrhfagic foci in Case 1, where a few positive staining macrophages could be seen, all the haemorrhagic foci stained completely negative for immunoglobulins and complement factors. In the cryostat sections of Case 2, however, there was a more pronounced IgG and IgA immunofluorescence located as granular clumps in haematogenous cells, most probably macrophages.

The scarcity of immunoglobulin deposits was against our expectations. AHLE and BP belong to the demyelinating diseases and can be regarded as the hyperacute form of ADEM. In this form, an Arthus-reaction-like humoral immune mechanism was regarded to be the basic pathological event. The antigen is located in the white matter of the brain, which will be reached by circulating humoral antibodies. Antigen-antibody interation takes place in and around the thin walls of postcapillary venules with increased permeability. A deposition of immunoglobulins and complement has been demonstrated at these points in ordinary and, especially in hyperacute experimental allergic encephalomyelitis (EAE) (Grundke-Iqbal et al., 1980; Traugott et al., 1982) and experimental Arthus reaction (Cream et al., 1971). Perivascular deposition of immunoglobulins and complement was described recently in a short report (Chou, 1982) in two human cases of AHLE. We have not found, however, data in the literature on the demonstration of immunoglobulins and complement in human AHLE viz. BP complicating septic shock. In the two cases presented here, immunoglobulins were present in the brain only in scattered macrophages; extracellular deposits of immunoglobulins in the haemorrhagic foci could not be demonstrated. Theoretically, there are two possibilities for the explanation of the lack of extracellular deposits: it may be that an antigen-antibody complex does not play any role in the formation of the lesions and the petechial haemorrhages are merely the consequences of haemodynamic disturbances (Burger and Vogel, 1977). Such an interpretation, however, would contradict almost all our current considerations on the pathogenesis of demyelinating diseases. It seems to be more probable that immune complexes were first formed in the brain by some kind of a CNS antigen, specific antibody and complement, and these complexes initiated the damage to the vessel wall but were subsequently removed by sequestration into phagocytic cells. Experimental data indicate that immune complexes do not stay for a long time at the site of their formation, their demonstrability is strictly limited in time. Cream et al. (1971) reported that in the Arthus reaction gammaglobulin and complement deposits first appear 20 min after the second (provocative) injection. First they outline the vessels, then surround them with shrunken deposits; after 8 h they disperse into the tissue to disappear completely after 16 h, so that the immunofluorescence is seen most clearly at the time before the Arthus reaction has reached its macroscopic peak and before haemorrhage is present. Cochrane et al. (1959), in another immunofluorescence study on antigens in Arthus vasculitis, report that the majority of the visible antigens is held in the leukocytes as early as 7 h after injection and that in cases with mononuclear cell predominance, the burden of antigen-antibody catabolism falls upon the macrophages.

If the formation of Arthus-like foci and the consequent damage to the vessel wall occurs at random in time, the vascular foci are in various phases of development so that there is a chance to find immunoglobulin and complement deposits in the brain. In the majority of cases of AHLE and BP, however, the vascular damage at multiple sites is a dramatic, unique event which is limited in time. Afterwards, most probably only a few, single foci will be formed.

As in our cases the interval between the appearance of the lesions (i.e. development of neurological signs) and death was 4 resp. 6 days, the immunoglobulin and complement deposits had already disappeared from the haemorrhagic foci. We have to presume that the very faint IgG and IgA deposits in our cases appearing around morphologically normal vessels were not older than 18 h and that the few vessels showing positive immunofluorescence were just about to undergo vessel wall damage. This sequence of disappearance of the immune complexes in the Arthus reaction may also explain the striking discrepancy between the microglial accumulation around the haemorrhagic lesions and our sparse immunofluorescence findings.

In recent years, an important role has been attributed to circulating immune complexes in the pathogenesis of autoimmune diseases. Such complexes are formed in the blood in case of antigen excess by a circulating antigen and antibody. These complexes are deposited preferentially in organs with high blood flow and highly permeable vessels, e.g. kidneys, skeletal muscles. The binding of complement to the deposited complexes leads subsequently to the damge of the vessel wall by activating vasoactive mediators. This passive trapping of circulating immune complexes is opposed to the local formation of complexes in the vessel walls of the target organ by a tissue antigen and circulating antibodies. Reik (1980) postulated that a deposition of circulating immune complexes could explain, on the basis of a small vessel vasculopathy, the myelin damage in demyelinating diseases (''disseminated vasculo-myelinopathy'').

In our two cases the deposition of circulating immune complexes in various regions seems probable. The demonstration of IgG, IgA and IgM deposits in the wall of glomerular capillaries and in the macrophages of the kidneys, lungs, liver and pancreas may represent immune complexes extracellularly in the vessel walls or already sequestered in phagocytes.

Reik's assumption, however, appears to us insufficient for the explanation of the haemorrhagic-demyelinating lesions in these cases. In experimental models (Tsukuda et al., 1982) and in human cases with circulating immune complexes, these were demonstrable within the CNS in the choroid plexus, subependymal regions and meninges, and not at the preferential sites of the demyelinating lesions of ADEM and related conditions.

There is no satisfactory explanation for the complete lack of complement deposits in all tissue specimens of our two cases.Cream et al. (1971) report on the same sequence in appearance and disappearance of complement factors in Arthus reaction as for immunoglobulins. Greenwood et al. (1973) found C3 by direct immunofluorescence in snap-

frozen skin and synovial biopsy specimens of patients suffering from meningococcal meningitis, but the lesions were not older than 24 h; the authors explained the presence of immune complexes at these sites by the Arthus phenomenon. Other authors (Wemambu et al., 1969; Davis and Peters, 1976; Gonzalo et al., 1981) report similar findings. It can, therefore, be presumed that in our cases, the excessive consumption of complement factors resulted in a complete C3 and C4 depletion. Masland and Barrows (1962) as well as Graham et al. (1979) postulated that AHLE, complicating Gran negative septicaemia, developed in 7 cases because the endotoxin shock produced a Schwartzmann reaction, activated complement and produced endothelial damage. Endotoxin shock and Schwartzmann reaction, however, do not give a sufficient explanation for the brain damage. Endotoxin shock occurs frequently, but its combination with AHLE or BP is quite exceptional. BP does not belong to the pathological picture of the experimental Schwartzmann reaction either. A complement-dependent endothelial damage does not explain why the lesions are limited to the white matter. Furthermore, an essential feature of the tissue lesions of the Schwartzmann phenomenon is the local accumulation of polymorphonuclear leukocytes. Leukopenia induced by nitrogen mustard inhibits the development of the Schwartzmann phenomenon; the haemorrhagic-necrotic lesions do not ensue (Stetson and Good, 1951). In the brain lesions of our two cases, polymorphonuclear leukocytes failed remarkably.

Nevertheless, endotoxin shock certainly has a crucial role in initiating the events leading to brain damage. Derangement of blood-brain-barrier (BBB) functions has been demonstrated in sepsis (Jeppsson et al., 1981); increased permeability establishes the conditions for an antigen-antibody reaction in the wall of cerebral vessels, where the antigen is a kind of myelin constituent which reacts with circulating antibodies. The liability to develop an autoimmune reaction against myelin is a matter of genetic predisposition (Wentzel et al., 1984); this explains the low incidence of such complications.

Besides genetic determination, there is another factor in endotoxin shock which facilitates white matter damage. Levine and Wenk (1965) elaborated a model for human AHLE from the classic EAE model, the "hyperacute experimental allergic encephalomyelitis". The crucial moment in the production of this model was to change the adjuvant in EAE, the tubercle bacilli in mineral oil ("complete Freund's adjuvant") to aqueous pertussis vaccine when injecting the spinal cord homogenate. When the genetic factor was also considered, by using the appropriate rat strain, hyperacute EAE could be elicited by this mixture with great regularity.

Bacterium pertussis is also a Gram-negative microorganism which produces an endotoxin. An observation of AHLE following pertussis vaccination in man (Moossy et al., 1954, Case 2) corroborates the validity of the model of Levine and Wenk.

In summary, we postulate that septic shock due to Gram-negative bacteria leads to endothelial damage in the cerebral vessels by complement activation. In individuals with genetically determined predisposition to demyelinating diseases, an Arthus-like anaphylactic reaction takes place in the wall of the venules of the white matter with immune complex formation. In this process, Gram-negative bacteria and their endotoxin play a crucial but at present only incompletely understood adjuvant role.

References

Bick R.L. (1984). Disseminated intravascular coagulation and related syndromes. CRC Press, Inc. Boca Raton. Florida.

Burger P.C. and Vogel F.S. (1977). Hemorrhagic white matter infarction in three critically ill patients. Human Pathology 8, 121-132.

Chou S.M. (1982). Acute hemorrhagic leucoencephalitis as a disseminated vasculomyelinopathy: Immunoperoxidase study. Abstract. J. Neuropath. Exp. Neurol. 41, 357.

Cochrane C.G., Weigle W.O. and Dixon F.J. (1959). The role of polymorphonuclear leukocytes in the initiation and cessation of the Arthus vasculitis. J. Exper. Med. 110, 481-494.

Cream J.J., Bryceson A.D.M. and Ryder G. (1971). Disappearance of immunoglobulin and complement from the Arthus reaction and its relevance to studies of vasculitis in man. Br. J. Derm. 84, 106-109.

Csermely H. and Haberland K. (1954). Brain purpura and haemorrhagic leucoencephalitis. Acta Morph. Acad. Sci. Hung. 4, 217-226.

Davis J.A. and Peters N. (1976). Circulating immune complexes in a patient with meningococcal disease. Brit. Med. J. 2, 1445-1446.

Gallyas F. (1981a). An argyrophil III method for the demonstration of microglia and oligodendroglia. Acta Morphologica Acad. Sci. Hung. 29, 177-183.

Gallyas F. (1981b). An argyrophil III method for the demonstration of fibrous neuroglia. Acta Morphologica Acad. Sci. Hung. 29, 185-193.

Gallyas F. (1985). Versilberungsverfahren mittels physikalischer Entwicklung für den Nachweis der Achsenzylinder an Gefrier- und Paraffinschnitten. Ideggyógy. Szemle 38, 283-287.

Gonzalo A., Mampaso F., Gallego N., Bellas C., Segui J. and Ortuno J. (1981). Hemolytic uremic syndrome with hypocomplementemia and deposits of IgM and C3 in the involved renal tissue. Clinical Nephrology 16, 193-199.

Gosztonyi G. (1973). Acute haemorrhagic leucoencephalitis. Report of three cases. Z. Neur. 204, 43-66.

Gosztonyi G. (1978). Acute haemorrhagic leucoencephalitis (Hurst's disease). In: Handbook of Clinical Neurology, Vol. 34. Infections of the Nervous System, Part II. Vinken P.J. and Bruyn G.W (eds). North Holland. Amsterdam. pp 587-604.

Graham J., Behan P.O. and More J.A.R. (1979). Brain damage complicating septic shock. Acute haemorrhagic leucoencephalitis as a complication of the generalized Shwartzman reaction. J. Neurol., Neurosurg., Psychiat. 42, 19-28.

Greenfield J.G. (1950). Encephalitis and encephalomyelitis in England and Wales during the last decade. Brain 73, 141-166.

Greenwood B.M., Whittle H.C. and Bryceson A.D.M. (1973). Allergic complications of meningococcal disease - Immunological investigations. Brit. Med. J. 2, 737-740.

Grundke-Iqbal I., Lassmann H. and Wisniewski H.M. (1980). Chronic relapsing experimental allergic encephalomyelitis. Immunohistochemical studies. Arch. Neurol. 37, 651-656.

Humphrey J.H. (1955). The mechanism of Arthus reactions. The role of polymorphonuclear leucocytes and other factors

in reversed passive Arthus reaction in rabbits. Brit. J. Exp. Path. 36, 268-282.

Hurst E.W. (1941). Acute hemorrhagic leucoencephalitis: a previously undefined entity. Med. J. Aust. 28, 1-6.

Jeppson B., Freund H.R., Gimmon Z., James J.H., von Meyenfeldt M.F. and Fischer J.E. (1981). Blood-brain barrier derangement in sepsis: cause of septic encephalopathy? Am. J. Surg. 141, 136-142.

Környey St. (1952). Die Entmarkungsencephalomyelitide. Fortschr. Neurol. Psychiat. 20, 1-24.

Levine S. and Wenk E.J. (1965). A hyperacute form of allergic encephalomyelitis. Amer. J. Path. 47, 61-88.

Masland W.S. and Barrows L.J. (1962). A case of generalized Shwartzman phenomenon in the human. Arch. Neurol. (Chicago) 7, 64-73.

McArdle J., Van Bogaert L. and Lhermitte F. (1969). La leuco-encéphalite hémorrhagique aigue (Hurst). Rev. neurol. 81, 709-739.

Moossy J., Wolf A. and Cowen D. (1954). Acute hemorrhagic leukoencephalitis. Its relationship to demyelinating disease. Am. J. Pathol. 30, 642-643.

Reik L.J. (1980). Disseminated vasculomyelinopathy: an immune complex disease. Ann. Neurol. 7, 291-296.

Russell D.S. (1955). The nosological unity of acute haemorrhagic leucoencephalitis and acute disseminated encephalomyelitis. Brain 78, 369-376.

Stetson C.A. and Good R.A. (1951). Studies on the mechanism of the Shwartzman phenomenon. J. Exp. Med. 93, 49-64.

Stetson C.A. (1951) Similarities in the mechanisms determining the Arthus reaction and Shwartzman phenomenon. J. Exp. Med. 94, 347-357.

Traugott U., Shevach E., Chiba J., Stone S.H. and Raine C.S. (1982). Chronic relapsing experimental allergic encephalomyelitis: identification and dynamics of T and B cells within the central nervous system. Cell Immunol. 68, 261-275.

Tsukuda N., Koh Ch-S., Yanafwisawa N. and Tsukafoshi H. (1982). Nervous tissue injury induced by immune complexes. Acta Neuropathol. (Berl). 56, 279-284.

Wemambu S.N.C., Turu J.L., Waters M.F.R. and Rees R.J.W. (1969). Erythema nodosum leprosum: a clinical manifestation of the Arthus phenomenon. Lancet I, 933-935.

Wentzel J., Roberts D.F. and Bates D. (1984). Multiple sclerosis, HLA, and lymphocyte surface markers. Acta Neurol. Scand. 69, 65-73.

Accepted October 6, 1986