BRAIN OEDEMA: INFLUENCE OF THERAPY

1.0450 Normal
475 - 400 Slight
472 - 350 Medium
465 - 300 Severe

FIG. 1. Twenty-four-hour-old cold lesion in the cat. The Evans Blue discoloration outlines preferential spreading of oedema in the white matter. The numbers point to the location of 1-mm diameter samples in the brain tissue. The specific gravity values less than 1.0450 are classified arbitrarily into slight, medium and severe degrees of oedema intensity. The measurements show a gradient in intensity of oedema diminishing from the site of cryogenic injury. A slight oedema is also present in the cerebral cortex of the injured gyrus and of the immediately adjacent portions of the neighbouring gyri. (From: Klatzo et al., 1984.)

white matter, where the BBB to proteins remains intact, the $L_p$ and $\sigma$ (osmotic reflection coefficient) remain as in the normal brain tissue and the flow of fluid ($J_f$) across the vascular wall becomes influenced by the difference in osmotic pressures between plasma ($\Pi_{\text{plasma}}$) and oedematous tissue ($\Pi_{\text{tissue}}$). Since the preserved BBB impedes the re-entry of extravasated proteins into the vascular lumen, the proteins are trapped for some time in the extracellular spaces, exerting their colloidal-osmotic pressure and retarding the movement of water into the vessels. In this respect, the osmotic pressure of proteins (which is considered to be rather low) may increase considerably in the area of oedema by fractionation into various smaller units (Rasmussen and Klatzo, 1969); also, a significant water binding capacity of proteins was reported in the recent studies on free and bound water in various brain disorders (Furuse et al., 1984; Kuchiwaki et al., 1984).

From the sites of increased cerebrovascular permeability, oedema fluid overcomes resistance of cellular structures of the brain tissue and spreads by bulk flow propelled by hydrostatic forces. This results in increasing interstitial fluid pressure and the development of pressure gradients which determine the driving force of the oedema fluid. As the resistance of the tissue is overcome, there is initially a rather steep increase in interstitial tissue pressure required to separate densely packed cellular structures and thus dilate the extracellular spaces. This may provide a "safety factor" in protecting the brain tissue from oedema of lesser intensity (Reulen et al., 1976). The preferential spread of VBO through the white matter is related presumably to the structural features of the tissue. Ultrastructurally, the grey matter resembles a dense jungle of tangled cellular structures, whereas the white matter consists of rather straight and orderly arrangement of extracellular channels, thus providing less resistance to the flow of oedema fluid.

Theoretically, the clearance of vasogenic oedema fluid may proceed by several routes: CSF, blood or lymphatic channels (Marmarou et al., 1984). Reulen and colleagues (1976) postulated that oedema fluid follows a downhill pressure gradient and it is cleared through the ventricular wall into the CSF. Klatzo and others (1980) indicated that intracellular uptake of serum proteins by the glial elements may constitute a major mechanism for resolution of VBO. In their quantitative studies, Marmarou and others (1984) examined the relative involvement of various routes and concluded that the clearance of oedema by bulk flow into the CSF is restricted to the early phase of the oedema and, following this stage, the loss of water from the tissue is associated closely with the dynamics of protein clearance. These studies also indicated that the clearance by the vascular route was considerably less than by CSF, whereas the lymphatic route proved to be rather insignificant.

**Cytotoxic brain oedema (CBO)**

The main event is the swelling of cellular elements of brain parenchyma by the effect of some cytotoxic agents which may selectively affect various cellular types and structures. The most common CBO occurs in hypoxic and ischaemic conditions and is related to interference with cellular osmoregulation which relies on energy-dependent function of ionic pumps. Other forms of CBO related to various toxic agents have been described, such as that caused by triethyltin and hexachlorophene intoxication producing splitting of the intraperiod line of myelin sheaths and accumulation of water in intramyelinic clefts (Aleu, Katzman and Terry, 1963); hydrogen cyanide intoxication resulting in selective swelling of (predominantly) axons (Hirano, Levine and Zimmerman, 1967); and by kainic acid which may pro-
duce a selective swelling of astrocytes (Seitelberger et al., 1984). The BBB permeability to serum proteins in a pure form of CBO remains basically intact, whereas an increased entry of water into brain parenchyma is related primarily to osmotic gradients which develop from interference with cellular osmoregulation.

Pathophysiology of ischaemic injury

As noted above, ischaemic brain oedema (IBO) has elements of both VBO and CBO and the assessment of their relative involvement is important in the elucidation of the pathophysiology of ischaemic injury.

Cytotoxic intracellular accumulation of water dominates the initial stages of IBO and it is related to an acute tissue deprivation of glucose and oxygen. The main event here is a disturbance of cellular osmoregulation, which depends primarily on the Na⁺-K⁺ exchange pump, with ATP as the energy source. In global ischaemia, with total cessation of blood flow and before recirculation, there is no oedema (which, according to definition, must be associated with a volumetric increase of tissue), since the ischaemic swelling of cellular elements is related merely to the shift of water from extra- to intracellular compartment and because only the systemic circulation may provide water for a net volumetric increase.

In the regional ischaemia produced by occlusion of a major artery, the increase in water content of the tissue may be demonstrated within 5 min, using the sensitive gravimetric method (Fujimoto et al., 1976); otherwise, electrical impedance measurements indicate, within a few minutes, reduction of extracellular spaces by cellular swelling. Generally, the vulnerability of brain tissue to ischaemia is related to discrepancy between energy demand and supply. Thus, the grey matter appears to be more sensitive to ischaemic injury than the white matter and the cytotoxic oedema is initially more pronounced in grey than white matter.

In recent years, concepts of thresholds and of selective vulnerability proved useful in the interpretation of some aspects of the pathophysiology of cerebral ischaemia. Thus, it was shown that the onset of cytotoxicity occurs at a certain threshold of cerebral blood flow (CBF) reduction (<20 ml min⁻¹/100 g) (Symon, Branston and Chikovani, 1979) and the recent observations on selective vulnerability indicate that the thresholds to ischaemic injury vary in different brain regions. Thus, at similar values of reduction in CBF, certain regions develop severe ischaemic injury and oedema, whereas the other regions do not (Klatzo, 1984). Also, differences in ischaemic injury and oedema appear to be age-dependent, as has been noted in most recent comparative studies on effects of ischaemia in 3-week-old and adult gerbils (Martinez et al., 1984).

The opening of the BBB to proteins in cerebral ischaemia introduces the element of VBO. This may occur in two separate phases following release of arterial occlusion (Kuroiwa et al., 1982). The first opening of the BBB does occur promptly after release of occlusion when, during the ischaemia, the CBF reduction is below certain threshold values. This is followed by an acute reactive hyperaemia, which induces a barrier opening by the haemodynamic effect of greatly increased intraluminal pressure in blood vessels, maximally dilated as a result of loss of autoregulation. The important factors in this haemodynamic opening are the intensity of preceding ischaemia and the amplitude and rapidity in the development of reactive hyperaemia.

The second opening of the BBB occurs after considerable delay (Suzuki et al., 1983), and it appears to be related clearly to factors deriving from the severely damaged ischaemic tissue. The breakdown of the BBB to proteins in the permanent arterial occlusion is of a similar nature and this takes place usually after some hours in instances when the intensity of ischaemia is below certain threshold values (<12 ml min⁻¹/100 g) (Wagner et al., 1983).

The leakage of serum proteins into brain tissue undoubtedly aggravates the existing cytotoxic oedema. It was shown (Klatzo et al., 1984) that areas with protein extravasation reveal, as a rule, a significantly higher water increase than areas with cytotoxic oedema. With further progression of ischaemic injury and onset of necrotic changes, the extracellular compartment enlarges rapidly as a result of rupture of membranes of dying cells, the contents of which are spilled out into extracellular spaces. All this leads to a considerable increase in osmolality by accumulation of catabolic products of cellular disintegration and a further significant increase in water content. In such severely injured oedematous foci, the resulting marked increase in tissue pressure affects significantly the surrounding regions of penumbra, where it is likely to produce depression of regional blood flow below the critical thresholds of viability and to a further extension of territory with an irreversible tissue damage (fig. 2). This may be compared to a forest fire spreading by
BRAIN OEDEMA: INFLUENCE OF THERAPY

engulfing the adjacent areas. The final outcome of an ischaemic insult and oedema is decided ultimately by the battle between the forces involved in self-propagation of the lesion based on progressive increase in tissue pressure interfering with microcirculation, and the forces engaged in healing and resolution of the ischaemic lesion. The latter are related to the most vigorous intracellular uptake of cellular debris and of extravasated proteins by predominantly macrophagic cells, and by formation of a dense mesodermal and glial scar tissue.

There is increasing evidence that the ischaemically injured neurones have a considerable capacity for recovery. This assumption accords with observations of Symon (1985) indicating different CBF thresholds for EEG changes, onset of oedema, interference with ionic pumps and irreversible neuronal destruction. It is therefore possible that most of the regions of penumbra can recover fully, and this should provide a stimulus to concentrated research on factors which may influence recovery after ischaemia. Unquestionably, the mechanisms related to development and dynamics of ischaemic oedema should be the main focus of attention.

Regional ischaemia and oedema

Infarction and regional increase in osmolarity → Progressive peripheral expansion of infarcted areas

Interference with microcirculation in the adjacent areas of penumbra

Space-occupying lesion and increased tissue pressure

Fig. 2. Diagram indicating a sequence of events in the progressive development of ischaemic lesions.

Therapeutic considerations

The recognition of the major mechanisms involved in various phases of IBO provides guidance in the search for rational therapeutic measures.

With regard to CBO, attempts may be made to influence the primary injury responsible for induction of cytotoxic swelling. In this respect, it was shown that early application of hypothermia, phenobarbitone or other metabolism-reducing agents, may dramatically reduce the intensity of ischaemic injury and associated oedema. Otherwise, the application of hyperosmotic therapy, using mannitol, glycerol, etc., appears to be indicated primarily in CBO, since in the vasogenic type of oedema in areas with increased BBB permeability, the influx of hyperosmotic fluid may further increase water content. Nevertheless, in critical situations, prompt application of osmotically active agents or surgical decompression may be required to break a "vicious circle" which may become established when a further increase in intracranial pressure leads to impairment of the microcirculation, which in turn increases ischaemic oedema and further increases intracranial pressure.

With regard to VBO, the "tightening" of the BBB to prevent leakage of serum proteins would be important. So far, the search for agents inhibiting opening of the barrier has not been very successful. The mode of action of steroids still remains obscure, although dexamethasone has proved to be most effective in vasogenic oedema associated with brain tumours and abscesses. According to assumptions in the studies of Reulen and colleagues (1976), reduction of CSF pressure may increase clearance of oedema fluid into ventricles, and this may also be accomplished by curtailing CSF production with some diuretic drugs, such as furosemide and acetazolamide. Effective application of these drugs in combination with dexamethasone in cold injury oedema was demonstrated by Long, Maxwell and Choi (1976).

In recent years, there have been suggestions that, in various forms of brain injury, release of certain compounds from the damaged tissue may be responsible for increase in cerebrovascular permeability, thereby promoting the development of oedema. Thus fatty acids, especially arachidonic acid, or peptides, such as kinins, have been implicated as possible oedema activators (Baethmann 1978). Also, some studies have suggested that the release of serotonin, which was reported to increase cerebrovascular permeability (Westergaard, 1980) and prostaglandins, synthesized in the area of lesion, may affect the dynamics of oedema. It can be assumed that the synthesis of appropriate inhibitors will probably result in agents with some beneficial effects in the treatment of oedema.

In general, treatment of IBO should be flexible, adjusted to the predominant pathological mechanism in a particular phase of oedema and it should be directed also to regulation of various extracerebral parameters. Thus, control of systemic arterial pressure within normal limits is of great importance, since increased arterial pressure was shown to accelerate greatly the spreading of VBO (Klatzo et al., 1967), and to increase an ischaemic...
injury (Ito et al., 1978). In contrast, reduction in arterial pressure may intensify interference with CBF in the ischaemic regions. Based on meticulous control and adjustment of various extracerebral parameters, Hossman (1984) recently reported a successful restitution of various brain functions in cats subjected to 1 h of complete, global ischaemia. Such observations should provide a further stimulus in our search for measures which may effectively ameliorate or prevent brain damage induced by cerebral ischaemia.

ACKNOWLEDGEMENT

Meticulous editorial work on this manuscript by Mrs H.C. Mittelman and Mrs B.T. Riley is greatly appreciated.

REFERENCES


