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LEADING ARTICLE

Non-atheromatous causes of cerebral infarction

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Introduction

The 600-fold increase in the incidence of stroke with advancing age, from 10 per 100,000 below 35 years of age to 6,000 per 100,000 over 75 years (Kurtzke, 1976), is related in the main to the creeping peril of atherosclerosis. However, only a minority of strokes before middle-age can be ascribed to atheroma and in every age-group non-atheromatous causes of cerebral infarction account for a small but significant proportion of vascular lesions. Two fascinating reports, presented in this issue of the *Postgraduate Medical Journal* by Salanova and Taubner and by Monton *et al.*, provide a reminder that extraordinary and preventable aetiological factors may precipitate sudden hemiplegia. The diversity of aetiologies of cerebral infarction reflects the changing patterns of modern civilization: our life-style includes many hazardous occupations and leisure pursuits, the excesses of society range from drug abuse to fitness fanaticism, and medical survival is achieved at the cost of occasional but unanticipated side effects of yet more potent therapeutic agents (Chambers *et al.*, 1981). One result has been an increase in the incidence of non-fatal strokes in the decade 1970–9 (Lindstrom, Soderström and Mettinger, 1982).

Age-related factors

The major causes of cerebral infarction in paediatric practice provide a spectrum of disease from infancy to adolescence (Brett, 1983; Russell, 1983). Even the fetus can be subject to strokes detectable by intrauterine ultrasonography (Ong, Ellison and Browning, 1982). Hemiplegia in early childhood may be produced by systemic infection often complicated by dehydration and malnutrition leading to cortical venous thromboses or pyogenic thrombosis of the carotid artery. Cyanotic heart disease may result in septic or thrombotic cerebral embolism or venous and arterial thrombotic lesions due to the associated polycythaemia. Congenital vascular malformations commonly present with symptoms in childhood. Arterio-venous malformations are most commonly seen in middle cerebral territory where they are liable to produce spontaneous intracranial haemorrhage or wedge-shaped infarction from the surface of the brain to the lateral ventricle. Arterial dissection can arise from Marfan's syndrome or homocystinuria; and Moya-moya disease is essentially a progressive cerebral arterial occlusive disorder of unknown pathology in children and young adults: 40% are under 10 years and 70% under 20 years. Traumatic hemiplegia can occur at all ages: from baby battering, from penetrating injury to the tonsillar fossa thrombosing the carotid artery as when a child falls with a pencil in its mouth, or due to gymnastic exertion with over-extension of the neck, rotation of the head and stretching of the vertebral artery. Hemiplegia following trauma to the carotid or vertebral arteries may be delayed until a thrombotic or embolic event occurs 24 hr after the initial insult. Among the haematological causes of infarction in childhood are leukaemia, other bleeding diseases, sickle cell disease, cerebral malaria and vascular occlusion from parasitic emboli.

Although the risk of thromboembolic disease from oral contraceptives is well recognized (Vessey and Doll, 1969), the stroke-incidence in the age group 15–45 years is equal in men and women, and the pill has had little impact on the number of stroke fatalities below the age of 45 (Kuller, 1978). Such information is somewhat surprising, for during the child-bearing years females are also at risk from thromboembolism (Cross, Castro and Jennett, 1968) and disseminated intravascular coagulation (Rascol *et al.*, 1980) in pregnancy and the puerperium; the incidence of complicated migraine is higher in females than males, and drugs such as amphetamine and phenylpropanolamine used for dieting have been implicated in cerebrovascular accidents (Johnson,

Etter and Reeves, 1983). However, certain counterbalancing influences explain the approximately equal sex incidence for strokes among young adults. Alcohol consumption is positively associated with cerebrovascular disease (Ashley, 1982), and in the Framingham study of men, aged 35–64 years, the incidence of strokes was directly related to the number of fluid ounces of alcohol imbibed per month (Kannel and Wolf, 1983). Alcohol ingestion decreases fibrinolytic activity, increases the components of factor VIII and shortens the bleeding time thereby predisposing to thrombus formation (Hillbom, Kastaa and Rasi, 1982). Drug abuse, particularly the use of 'hard' drugs, carries a high risk of cerebral infarction (Caplan, Heir and Banks, 1982); thus heroin addiction may result in thromboembolism from endocarditis or injected impurities.

The major source of cerebrovascular accidents among young males is physical, due to exposure to trauma and adverse environmental conditions. Recent reports include hemiparesis in a 14-year-old marathon runner (Phillips *et al.,* 1983) presumably due to dehydration although excessive tissue breakdown with a raised creatine kinase may have been a factor; brain stem ischaemic damage from near-drowning (Beal *et al.,* 1983); strokes and deaths at altitude from mountain sickness in the Himalayas (Ward, 1975; Dickinson *et al.,* 1983). Such events are not exceptional to everyday neurological practice; thus in recent months I have seen a 22-year-old gamekeeper who developed dizziness, neck pains and an unexplained left hemiparesis on the grouse moors, a 38-year-old windsurfer with post-concussive aphasia and a 33-year-old Catholic priest flown home from Jamaica where he had been scuba diving. After diving at 35 ft for approximately 35 min he surfaced rapidly, sustaining a painful perforation of his right eardrum. He went down again and resurfaced more slowly but 2 days later developed a left hemiparesis. After treatment in a decompression chamber to a depth of 165 ft with no change in his symptoms he was transferred to a hospital in Florida. A CT scan showed a low density area consistent with an infarct involving the right globus pallidus. Over the next 6 days his physical state deteriorated with the development of a dense hemiplegia and he became unresponsive with anisocoria. A repeat CT scan showed a massive right hemisphere infarct with oedema, a midline shift and herniation. He responded to hyperventilation, dexamethasone and mannitol. An angiogram performed 2 weeks later revealed an area of dissection of the right internal carotid artery with distal embolization.

Despite the welter of strokes due to atheroma, many kinds of stroke developing in the elderly are eminently treatable. Cranial arteritis is rare before 60 years and is particularly prone to involve the extracranial portions of the vertebral and internal carotid arteries, the ophthalmic artery and central artery of the retina (Wilkinson and Russell, 1972). Visual symptoms occur in 25% of patients; cerebral infarction due to embolism or thrombosis originating in the intra-cranial vertebral or carotid vessels is comparatively unusual. The erythrocyte sedimentation rate and alkaline phosphatase (liver fraction) are raised and the diagnosis may be confirmed by biopsy of a non-pulsatile portion of the superficial temporal artery. Continued treatment with prednisolone or immunosuppressive drugs can prevent progression of the disease (Graham *et al.,* 1981). Tertiary neurosyphilis and meningovascular syphilis may produce a patchy intracranial arteritis afflicting larger vessels. If the endarteritis is incomplete ischaemic or 'congestive' attacks may be precipitated but thrombotic changes can cause hemiplegia due to occlusion of the middle cerebral artery or its branches. The high incidence of vascular disease with diabetes is mostly ascribed to atheroma and hypertension affecting large and medium sized vessels but microangiopathic changes can also result in infarction and haemorrhage. The relationship between strict control of diabetes and the development of vasculitis is still a contentious issue. Cerebral embolism from bacterial endocarditis often remains undiagnosed in life and is progressively becoming a disease of the older age-groups with Gram-negative organisms, *Streptococcus pneumoniae* or *Staphylococcus aureus* as frequently implicated as the more renowned *Streptococcus viridans.* Blood vessels in the elderly tend to be friable especially in the presence of nutritional deficiencies such as scurvy and the sluggish circulation of hyperviscosity syndromes can add to the hazard of venous and arterial thromboses. Diseases especially liable to produce hyperviscosity in the elderly include chronic lymphatic leukaemia, Waldenstrom's macroglobulinaemia, myelomatosis, primary polycythaemia and polycythaemia secondary to hypoxic lung disease (Wade *et al.,* 1981).

Other vascular causes

The frequency and diversity of traumatic injury causing rupture, dissection or thrombosis of the blood vessels of the neck and skull-base needs to be restated. The trauma may be direct or indirect as from penetrating injuries, such as javelin injuries to the carotid, strangulation, atlanto-axial dislocation, cervical manipulation, yoga, whiplash injuries, head banging (Jackson *et al.,* 1983), skiing injuries (Bonneton *et al.,* 1974) and motor cycle accidents (Hughes and Brownell, 1968). Symptoms are particularly liable to develop in the presence of congenital abnormalities. Indeed, loops, kinks and coils, and arterial dysplasia as from pseudoxanthoma elasti-

cum, Ehlers-Danlos syndrome, or fibromuscular dysplasia may predispose to thromboembolism in the absence of trauma or atheroma. Irregular loss of the internal elastic tissue and muscle coat in fibromuscular dysplasia may produce segmental stenosis and ballooning to give a 'string of beads' appearance to the arteries of the neck. Delayed neuronal and vascular necrosis with stenosis and infarction is a very real hazard of irradiation to the head and neck. Any source of infection, usually with coexistent encephalitis, meningitis or cavernous sinus thrombosis, whether viral, Rickettsial, bacterial, spirochaetal or fungal can produce intimal fibrosis and infarction, particularly in states of altered immunity. Tuberculous meningitis and syphilitic infection still remain potent causes of stroke in young people throughout the Third World. Takayashu's disease with stenosis of the arteries of the neck near their origins from the aorta is believed to be due to a low grade arteritis but more widespread arteritis of large and medium sized blood vessels is particularly a feature of collagen vascular disease. The high incidence of cerebral infarction with systemic lupus erythrematosus (S.L.E.) is related not only to direct involvement of cerebral arteries, occasionally presenting with hemiplegia in an otherwise asymptomatic person (Haas, 1982), but also to the presence of an antilipid antibody—the so-called lupus anticoagulant (Hughes, 1983), often associated with a false positive luetic reaction,—and to microemboli arising from verrucous endocarditis. S.L.E. should always be considered in young females suspected of having bacterial endocarditis. In Behçet's disease there is characteristically hyaline degeneration of small arteries often with associated venous and arterial thromboses.

Hypotension and embolism

Hypotension due to disordered heart rate or rhythm is rarely sufficiently severe to produce cerebral infarction in the absence of occlusive vascular disease but the survivors of prolonged, sustained hypotension as from cardiac arrest or blood loss may be left with bilateral watershed infarction usually involving the parieto-occipital regions at the boundary zone between the anterior, middle and posterior cerebral circulations. Watershed infarcts may also be produced by showers of microemboli which tend to lodge in the terminal vascular fields (Torvik and Skullerud, 1982). Thrombotic and other emboli do not necessarily originate from the heart. Emboli can arise distally from kinks, aneurysms or dissection of the aorta, carotid and vertebral arteries and intracranial arteries. Paradoxical emboli from thrombophlebitic veins in the pelvis and legs can reach the brain via a cardiac septal defect without overt evidence of a right-to-left shunt. Infective emboli from the lungs are conveyed by the pulmonary arteries to the left atrium and ventricle, and neoplastic infiltration of blood vessel walls result in the release of metastatic emboli. Showers of fat emboli may be disseminated within a few hours or days of a fracture, producing dyspnoea, tachycardia and precordial pain as they reach the lungs and heart, pyrexia and petechial haemorrhage predominantly over the head and neck, disorientation and delirium as well as cerebral infarction. Droplets of fat may be found in the urine.

The prime source of embolism from the heart is the auricle of the left atrium where dilatation and poor contractility lead to stagnation of blood and thrombus formation; but emboli may also break off from valves roughened by rheumatic infection, calcium deposition, verrucous vegetations or bacterial (subacute and pyogenic) endocarditis, from the walls of the left ventricle damaged by mural infarction, aneurysmal dilatation, neoplasia or cardiomyopathy, and from pedunculated myxomas and ball valve thrombi. Rheumatic heart disease is relatively rare. Even so mitral stenosis, particularly with atrial fibrillation remains the commonest cause of cerebral embolism arising from the heart. Rheumatic mitral regurgitation with embolism is somewhat less frequent. The incidence of non-rheumatic mitral valve prolapse is high in the normal population (5–8%) and is increasingly recognized as a cause of cerebrovascular accidents below the age of 40 (Taylor *et al.*, 1979; Tharakan *et al.*, 1982). Valve prolapse may be inferred from the presence of clicks or gallop rhythms in the absence of other causes of heart disease but even after examination in the upright, lying and left lateral postures only 60% of patients are found to display auscultatory abnormalities. The identification of patients at risk remains uncertain; one factor is a possible association with altered platelet function. The rare occurrence of atrial myxoma, also predominantly in young people, may be suggested clinically by fainting with alterations of posture, variable cardiac murmurs and a raised erythrocyte sedimentation rate. Other causes of embolism, particularly in older patients, are myocardial infarction, atrial fibrillation in the absence of valvular disease and sino-atrial node dysfunction, including the sick sinus syndrome. The hazards of cardiac surgery include the risks of air embolism and the release of calcific, platelet or fibrin emboli. The immediate mortality from heart valve replacement is low. Thereafter mechanical prostheses are more reliable than tissue valve repairs but carry a greater risk of thromboembolism and endocarditis (Oakley, 1982).

Haematological disorders

Although it may be convenient to divide haemato-

logical causes of cerebral infarction into coagulation and bleeding defects, the separation is rarely absolute. The few examples of pure coagulation defects include local carotid thrombosis in the presence of tonsillar sepsis, venous thrombosis with debilitating fevers, such as typhoid and typhus, and thrombophlebitis migrans. Disseminated intravascular coagulation (D.I.C.), the archetypal 'consumption coagulopathy' syndrome with activation of available fibrinogen to form soluble and insoluble fibrin, produces thrombosis, haemorrhage and toxic or anoxic damage to arterioles and capillaries. With the more slowly developing hyperviscosity syndromes the majority of lesions are thrombotic or anoxic but haemorrhage into the nervous system can be an occasional feature. With bleeding diatheses, thrombosis is a secondary event. Purpuric disorders whether congenital, nutritional, drug-induced or allergic necessarily involve endothelial changes as well as platelet function and clotting mechanisms. Few haematological abnormalities which may produce cerebral infarction escape discovery if simple procedures such as a full blood count, platelet counts and examination, bleeding and coagulation screening tests are performed. Their further elucidation to trace the source of the primary malfunction can be highly complex.

Increased resistance to blood flow, common to all hyperviscosity syndromes, predisposes to venous as well as to arterial thromboses. A pathologically elevated haematocrit has long been recognized as a cause of stroke but rheological changes also influence the risk of infarction at the upper limit of the normal range; thus there is a statistical correlation between the incidence of stroke and the antecedent haemoglobin level (Kannel *et al.*, 1972; Toghi *et al.*, 1978). Cigarette smoking has a modest and mainly obscure association with the development of strokes but in one respect it can be shown that where the red cell mass is increased to compensate for 10% or more carboxyhaemoglobin the subsequent packed cell volume (PCV) is a significant factor in the risk of infarction (Smith and Landaw, 1978). Until the present decade, 97% of strokes involving small perforating arteries into the deeper non-cortical parts of the cerebrum and brainstem—lacunar strokes—were associated with hypertension but the proportion has declined to around 70%; the other 30% resulting mainly from thromboembolism or hypoperfusion due to occlusive extracranial vascular disease (Miller, 1983; Critchley, 1983). However, Pearce, Chandrasekeva and Ladasans (1983) have reported that polycythaemia may also produce similar infarction as was the case with a 57-year-old district midwife found to have primary polycythaemia after presenting with headache and a deep venous thrombosis of the calf following a road traffic accident. The initial CT scan showed a large right temporo-parietal infarct. Her response to treatment was interrupted by the development of mild confusion and aphasia with hesitation at the beginning of sentences. A further scan showed an additional lacunar lesion in the left hemisphere in the region of the internal capsule.

Conclusion

The diversity of possible aetiologies of non-atheromatous strokes should appeal to the clinical skills of all those responsible for the care of patients with cerebral infarction. Cardiologist, haematologists, and endocrinologists may find that they have as much to contribute as the pure neurologist. Unfortunately, too few neurologists have detailed knowledge of the use and potentiality of echocardiography and too few general physicians have ready access to CT scanning and neuroradiological services.

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