Dermatological aspects of cerebrovascular diseases

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SUMMARY

Neurological symptoms are sometimes triggered by the same mechanisms as are skin manifestations. They include genetic conditions like the epidermal nevus syndrome, the Sneddon syndrome, Fabry disease and others, as well as certain inflammatory disorders like erythematous lupus, Behcet disease. Basically all conditions giving rise to anticoagulation processes may cause simultaneously neurological and cutaneous manifestations.

Cerebrovascular stroke is the third most common condition of death in the developed world after cancer and ischemic heart disease. The mechanisms responsible for development of skin manifestations in patients afflicted by stroke are shortly reviewed. Stroke may also influence the already existent skin diseases.

KEY WORDS

dermatological symptoms, cerebrovascular diseases, review

Introduction

The affliction known commonly as 'stroke' is the third most common cause of death in the developed world after cancer and ischemic heart disease (1). It is responsible for a large incidence of physical disabilities, and becomes more frequent with advancing age (2). The US annual incidence of acute cerebrovascular disease (CVD) is 700,000. Nearly 5 million stroke survivors are involved in personal health management today. CVD can cause death and disability either by ischemia from occlusion of the blood vessels or hemorrhage due to rupture (3). Acute focal stroke is characterized by the sudden appearance of a focal deficit of brain function, which most commonly lead to hemiplegia with or without signs of focal higher cerebral dysfunction such as aphasia, hemisensory loss, visual field defect or brain-stem deficit.

Intimate mechanisms of dermatological reactions in stroke

Under various experimental conditions normal human skin can produce many neuropeptides (vasointestinal peptide, calcitonin-gene-related peptide, neuropeptide Y, etc.), whose release or blockage may strongly influence the immune system (4). The occurrence of bacterial and fungal infections, eczematous and severe seborrheic dermatitis, benign and malignant tumors shows that the destruction of nerve fibers alters the local immune state and supports the hypothesis that such neurological alteration with associated immunologic symptoms may be considered to be the first step in the pathogenetic mechanism of isotopic response. On the other hand, there are descriptions of unusual presentation of alopecia universalis that spared

the denervated area during lymph node biopsy, and of the healing of chronic atopic dermatitis lesions in skin areas with post-traumatic paraplegia. It has been reported that innervation may promote the growth of supplied tissues. All these facts support the hypothesis of a close relationship between the neuropeptidergic system, the immunologic system, and the trophic attitude of the skin (5, 6). Immune response is the result of a complex set of cellular interactions, each with their own multiple regulatory points. Although the nature of the regulatory factors is not fully known, genetic factors, age, nutrition, psychological status, and circadian rhythm can affect immunocompetence (7). The evidence of afferent and efferent channels of communication between the central nervous system and the immune system has been demonstrated by 3 distinct lines of research (8-12), namely:

1. Compartmentalized innervations with noradrenergic sympathetic nervous fibers that occur within the immunologically active areas of the primary and secondary lymphoid organs. All immunologically active areas within primary and secondary lymphoreticular tissues are potentially responsive to neurological stimulation resulting from cognitive stimuli that activate adrenergic or peptidergic fibers in the central nervous system.

2. Immune cells that express cell membrane receptors for many hormones, neuropepides, and neurotransmitters produced by the brain or peripheral nerves, in response to different stimuli. In particular, receptors for corticosteroids, insulin growth hormones, estradiol, testosterone, arginine-vasopressin and oxytocin, substance P, the vasoactive intestinal peptide, beta-adrenergic agents, acetylcholine, and endorphins have been demonstrated on the surface of immunologically active mononuclear cells.

3. Cytokines that have a neuroendocrine-like activity that can influence peripheral and central nervous functions.

Anti-beta 2 glycoprotein I antibodies (anti-beta 2 GPI antibodies) (13) may be present in patients with ischemic stroke and Sneddon's syndrome. This is a cofactor that increases anticardiolipin antibody adhesion to cardiolipin. The prevalence of anti-beta 2 GPI antibodies is not high in young patients with either livedo reticularis or ischemic stroke. Factor V Leiden is a common mutation known to cause congenital hypercoagulable disorder (14). Cutis marmorata telangiectatica is typified by persistent cutis marmorata and progressive neurological complications. Moyamoya-like vascular abnormalities have been demonstrated in addition to factor V Leiden mutation in this congenital hypercoagulable disorder. For these reasons we can emphasize the importance of evaluating children with stroke for congenital thrombophilic disorders. Symptomatic hereditary type 1 protein C deficiency, antithrombin III deficiency and antiphospholipid syndrome are also symptomatic in patients with livedo reticularis (15, 16). Therefore, a thrombophilia screen is recommended as a means to establish the diagnosis of a patient with an otherwise unexplained livedo, particularly if there is a personal or a family history of thromboembolism.

Skin diseases causing or associated with stroke

Basically any skin diseases that cause vasculitis and vasculopathy or those with infiltrative natures might involve both skin and the central nervous system.But as a rule, primary skin lesions do not cause cerebrovascular involvement. They may however run a parallel course. This can be the case in certain systemic and genetic disorders. Occurrence of stroke in epidermal nevus syndrome (17) is suggested to be caused by arterial occlusion of a dysplastic artery. Chronic mucocutaneous candidiasis (18) can be associated with intracranial aneurysm and complicated by cerebral infarction. Intravascular malignant lymphomatosis (19) may initially cause the dizziness, confusion, and hemiparesis that precede the development of a generalized telangiectasia. The diagnosis, however, is most often established through the subsequent skin biopsy. Sneddon's syndrome (20-23) is a rare neurocutaneous disorder of unknown origin characterized by generalized livedo reticularis (livedo racemosa) and cerebrovascular disorders. It has been the subject of much controversy. Skin biopsy findings in these cases show inflamed "endothelitis" of small to medium-sized arteries followed by subendothelial proliferation and fibrosis. Cerebral venous thrombosis and hemiplegia may occur in Behcet disease (24, 25) one to ten years after its initial presentation. The mortality of a number of patients has been ascribed to intracranial hemorrhage and cerebral aneurysm. Basically, all the defects that give rise to anticoagulation (protein C deficiency, coumadin necrosis, purpura fulminans, hereditary protein C/S deficiency, calciphylaxis), fibrinolytic disorders (26) (antithrombin III deficiency, disseminated intravascular coagulopathy), platelet abnormalities (abnormal structure or function, heparin necrosis, drug induced platelet dysfunction, cryoglobulinemia), endothelial cell injury (27), antibodies to endothelial cells in connective tissue diseases, Degos' disease, lupus anticoagulant, thrombotic thrombocytopenic purpura, cholesterol emboli, septic emboli), and states of hyperviscosity (28) (cryogloubulinemias, cryofibrinogenemias, cold agglutinins, hypergammaglobulinemia) may lead to both skin and neural involvement. In Fabry disease (29), CNS manifestations include thrombosis of basilar artery, ischemia and aneu-

rysm, seizures, hemiplegia, or frank cerebral hemorrhage. Severe neurological signs that are present without evidence of major thrombosis may be presumed to be caused by multifocal small vessel occlusive disease. The patient would usually have angiokeratoma corporis diffusum. All the features are due to infiltrations by glycosphingolipids.

A number of studies reveal details of great interest. Inatomi described the interesting case of a woman with cerebellar infarction and a family history of recurrent similar trichoepitheliomas and death due to subarachnoidal hemorrhage (30). Araki, et al. reported a 63-year-old man who had experienced cerebral infarction and myocardial infarction at an early age. A fundoscopic examination to evaluate hypertensive and diabetic changes revealed angioid streaks. Therefore, a skin biopsy was performed despite the absence of characteristic skin lesions and validated a diagnosis of pseudoxanthoma elasticum years after the onset of cardiovascular disease (31). The case of a woman with clinical manifestations of giant–cell arteritis, positive temporal artery biopsy and an excellent response to prednisone, who developed massive cerebral infarcts after 5 days of treatment has also been described (32, 33). Three children with pronounced livedo reticularis that had been present since birth (cutis marmorata telangiectatica congenitalis) were followed to the age of 8, 17, and 21 years. During childhood they developed frequent recurrent transient stroke–like hemipareses, affecting either side of the body, associated with ipsilateral pain, headache, visual symptoms, dysphasia, fits and confusion. Intellectual failure and, in one, a progressive spasticity followed. Attacks were more frequent in winter. Other problems included abnormal peripheral vascular responses to temperature change, gastro-intestinal tract bleeding, glaucoma, local tissue hypertrophy and, renal involvement with hypertension. Their condition represented a form of congenital vasculopathy (34). Anticonvulsants, anti-migraine agents, antiplatelet drugs and flunarizine proved ineffective. Nifedipine prevented further attacks in one patient and reduced attacks in another, but has not helped the third child. An 8-month-old boy presented with a right hemiplegia of sudden onset after 20 days of Kawasaki disease, which was not being treated initially with gamma globulin (35). The case of a patient diagnosed with scleroderma who presented with right hemiparesis, focal seizures, optic atrophy and gangrene of digits has been described (36). There was no evidence of peripheral nerve or muscle involvement. MRI showed multifocal infarcts in both cerebral hemispheres and MR angiography revealed poor flow in bilateral carotid arteries with collateralization from posterior circulation. Improvement was achieved with phenytoin, nifedipine, antibiotics and immunosuppressants. Occlusion of the middle cerebral artery in a 16-year old girl revealed a left atrial myxoma associated with mucocutaneous lentiginosis (37). As this cardiocutaneous syndrome is a familial disorder with autosomal dominant inheritance, cardiac ultrasound examination of all family members was recommended.

The effect of stroke on existing skin diseases

Stroke may be said to have a sparing effect on scleroderma (38): The paretic limb is spared in patients who develop rheumatic diseases after a hemiplegic stroke. This has been described previously in rheumatoid arthritis, gout, and osteoarthritis. Sclerodermic skin changes are absent in the completely paretic limb and markedly reduced in the weak leg. Inflammation may be modified either by neuropeptides or by an anatomical neurological lesion, and this may explain the phenomenon.

The clearing of psoriasis after stroke (39, 40) has been described.

The side effects of medications that are used to treat cerebrovascular diseases may affect the skin diseases. One example of this is the administration of aspirin, a cyclo-oxygenase inhibitor, which does not ameliorate pruritus (41) except in polycythemia vera. In this case, the action may affect platelet adhesiveness rather than prostaglandin formation.

Reflex sympathetic dystrophy (42) is a poorly defined syndrome in which an individual, following an injury, develops pain out of proportion to the initial injury. Many dermatological manifestations accompany this syndrome, such as edema, erythema, pallor, cyanosis, hypo and hypertrichosis, hypo and hyperhidrosis, onychodystrophy, blistering, white nails, ridging and ulcers.

Unilateral pruritus (43, 44) has been reported as a complication of pure unilateral pontine infarct. Trigeminal trophic syndrome (45), a rare cause of facial ulceration, has also been reported after an ischemic infarct.

Excessive sweating from cerebral infarction has been reported rarely in the available literature (46) on stroke, and its pathophysiological mechanisms and clinical significance have remained obscure. Hyperhidrosis typically involves the face and arm and is transient, lasting from 2 days to 2 months. No association with Horner's syndrome, hypothalamic dysfunction, or any other autonomic dysfunction has been observed. The phenomenon of hyperhidrosis, however, is attributed to a lesion of the putative sympathoinhibitory pathway that controls sweating. This pathway might originate in the cortex, possibly in the operculum, and make terminal connections with the contralateral thoracic spinal cord. Contralateral hyperhidrosis can be observed in the late phase after lateral medullary infarct and is likely to be due to lesion of the sympathetic pathway passing

through the lateral medulla, which inhibits sudomotor neurons. Evaluation of sympathetic skin response may help to explain such clinical disorders (47). Assessment of sweating may provide a new, important aspect in the evaluation of stroke patients.

Nail pathology in patients with hemiplegia (48) is presented in three main patterns: longitudinal reddish striation, neapolitan nails and unilateral clubbing. Hemiplegia precedes the nail damage by approximately 40 months. Unilateral pterygium inversum unguis (49) is a nail abnormality in which the distal aspect of the nail bed/hyponychium adheres to the ventral surface of the nail plate, resulting in obliteration of the distal groove.

Prognosis

About 75% of patients survive the acute stage of focal stroke. The immediate mortality of those with aneurismal subarachnoidal hemorrhage is 30%, with a recurrence rate of 50% in the first 6 months and 3% annually thereafter. 1/2 to 3/4 of those surviving an acute stroke achieve functional independence, mostly within 1 to 3 months. After a completed episode of stroke there is an annual recurrence rate of 8-11% (50).

Conclusion

The large incidence of cerebrovascular diseases emphasizes the need to understand the economic implications of its consequences and complications. The interpretation of these economic implications at an international level calls for a highly professional attitude in the treatment of all aspects of these diseases. This review highlights the importance of studying the dermatological predictive signs of stroke and of interpreting certain skin changes. The results of dermatological observations and studies provide insight into the problems of stroke pathogenesis and distribution, and these have a considerable impact on well-qualified health care (17).

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