CSF Enzymes in Lacunar and Cortical Stroke

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SUMMARY Cerebrospinal fluid enzyme levels of creatine kinase (CK), lactate dehydrogenase (LDH), glutamate oxaloacetate transaminase (GOT) and angiotensin converting enzyme (ACE) were studied in 40 acute stroke patients comprising 20 lacunar strokes and 20 cortical strokes. A marked elevation of at least one of the enzymes CK, GOT or LDH was seen in 80% of cases of cortical stroke. No elevation was seen in lacunar stroke with CK, GOT or ACE and only a slight elevation with LDH. Within the cortical group, there was a correlation between the site, size of infarction seen on CT scan and enzyme level.

These findings may help to explain the previously noted unpredictability of rises in CSF enzymes in stroke patients. In certain instances, a study of CSF enzymes may be of use to distinguish cortical from lacunar stroke. A precise diagnosis of lacunar infarction is important for management purposes, entry into stroke treatment trials or description of new syndrome types.

SINCE FISHER AND OTHERS established the five lacunar syndromes1-5 by careful clinicopathological correlation, it has become obvious that other conditions may mimic these syndromes.5-9 Cortical infarction is the most important of these conditions, since the pathophysiology of its development is considered to be embolic and a search for a proximal site of embolization with carotid angiography may be warranted. This in contrast to lacunar infarction, which is usually due to small vessel hypertensive disease and angiography is avoided. With the introduction of CT scanning, it has become obvious that partial lacunar syndromes frequently exist,9 and it is in this group that the distinction between lacunar and cortical infarction may be even more difficult.

This study examines the possibility that the appearance of enzymes in the cerebrospinal fluid (CSF) may be a useful and simple adjunct to other tests in detecting cortical involvement, thereby assisting in the distinction between cortical and lacunar syndromes. A review of the current methods of diagnosis of lacunar infarction is also given and inference about the nature of release of enzymes into the CSF in stroke is made.

Patients, Materials and Methods

A total of 40 stroke patients were studied in two groups. The first group comprised 20 consecutive patients with lacunar syndromes in whom the site of infarction was documented on CT Scan. Further precision of diagnosis was established by the finding of a normal EEG11 and no abnormality on a standard battery of neuropsychological tests.1 The second group consisted of 20 consecutive patients with 'cortical' stroke; hemiplegia was accompanied by cortical signs such as dyspraxia, dysphasia and agnosia, focal abnormality on EEG contralateral to the physical deficit, abnormalities on neuropsychological testing and confirmation of the site of infarction on CT Scan.

A neurological score was devised for each patient based on motor and sensory deficit; a score of 0-6 was given for each of face, arm and leg (motor and sensory) ranging from no deficit (score, 0) to maximal deficit (score, 6). Thus maximal deficit involving face, arm and leg gave a total score of 36.

Lumbar puncture was performed within 48 hours of admission and estimates of creatine kinase (CK), Glutamic oxaloacetic transaminase (GOT), Lactic dehydrogenase (LDH) and angiotensin converting enzyme (ACE) were made. ACE was chosen because of its known concentration in the region of the basal ganglia.12 Total CSF CK has been shown to be almost entirely brain isoenzyme (CK BB).13 Serum for en-
zyme levels was taken at the time of lumbar puncture. Assay for CK, GOT and LDH were performed within 24 hours, while those for ACE were stored at −4°C prior to assay but not for longer than 12 weeks. Control samples of serum and CSF were taken and treated in the same way from patients with no neurological symptoms. Assay for CK was performed using Boheringer ultraviolet N-acetyl cysteine activated kit, that for GOT using the Boheringer ultraviolet single test kit and for LDH the Calbiochem Statapaks kit. ACE was assayed using the fluorimetric method of Friedland and Silverstein. Statistical analyses used were the Wilcoxon Rank Sum test, Spearman Rank test, and students t test. An estimate of volume of infarction in the cortical group was obtained by taking half the product of the horizontal dimensions of infarction by the number of CT cuts in which the infarction appeared.

Results

Of the 20 patients with lacunar stroke, 18 were identified as having the syndrome of pure motor hemiplegia, one sensorimotor stroke and one ataxic hemiparesis. Median age of patients with lacunar stroke was 63 years, cortical stroke 60 years and controls 61 years. Neurological deficit scores at presentation were similar in the lacunar and cortical groups (t = 0.62, p < .5). Lumbar puncture was performed at times ranging from 16 hours to 13 days post stroke.

A marked elevation of CSF CK was seen in patients with 'cortical' stroke compared to that of lacunar stroke (T = 284, p < 0.01) while lacunar stroke CSF CK levels did not differ from controls (T = 362.5, N.S.) (fig. 1(a)). GOT was also elevated in cortical compared to lacunar stroke (T = 318.5, p < 0.02), but the difference was not as dramatic. Again, the lacunar and cortical groups were similar (T = 349, N.S.) (fig. 1b). The greatest difference between lacunar and cortical group was seen with CSF LDH (fig. 1(c)) (T = 251.5, p < 0.01). A small but significant elevation in LDH was seen in the lacunar group compared to the controls (T = 303.5, p < 0.01). No elevation of CSF ACE occurred in either stroke group (fig. 1d).

None of the four enzymes studied showed elevation in the serum and no correlation between CSF and serum levels existed. In two patients with lacunar stroke, repeated lumbar punctures were performed up to 11 days after stroke but no elevation of the CSF enzymes above the established control range (mean ± 2 s.d.) occurred.

Within the cortical group, infarctions seen on CT Scan in 15 cases communicated with subarachnoid CSF. In 2 instances, infarctions were restricted to the deep subcortex by an adequate cortical collateral blood supply. Several were more peripherally placed but no definite communication with CSF could be seen. By individual inspection, elevation of enzyme level was more likely to have occurred with more peripheral infarctions. A correlation between size of infarction and a function of combined enzyme level existed (r = 0.5977, p < 0.005).

Discussion

The lack of precision of diagnosis of lacunar infarctions is illustrated by the varying frequencies of this form of stroke in the few series published. Wolf found that 13% of ischaemic strokes could be identified as lacunar, 15 Mohr et al. 18% in the Harvard Stroke Registry and 20% in another recent study. Indeed, one of the faults of many stroke treatment trials has been the failure to recognize lacunar strokes as a separate group. In clear examples of the classical syndromes of pure motor hemiplegia, ataxic hemiparesis, the dysarthria clumsy hand syndrome, sensorimotor stroke and pure sensory stroke, diagnosis may not be difficult, particularly if care is exercised to exclude other mimickers of these syndromes. The diagnosis of partial lacunar syndromes may occur in up to 22% of all lacunar syndromes, the most common example being that of pure motor paresis of arm and leg with sparing of the face. Less frequent examples include pure motor brachiofacial paresis, pure motor monoparesis of arm, leg or face alone and dysarthria alone. The presence of these partial syndromes has been established by careful clinical-CT correlation and in the case of brachial monoplegia, clinicopathological correlation. It is with this group of partial lacunar syndromes that the most diagnostic difficulty may be experienced, partly because of the motor deficits produced (particularly brachiofacial) are more commonly due to cortical rather than lacunar infarction. Even the full syndrome of pure motor hemiplegia may occasionally be imitated by cortical infarction. Unfortunately, the CT scan, on occasions, may not register the presence of infarction, particularly when peripheral and small, where artifact or gyral convolutions may confuse the picture. Similarly, the EEG may not invariably register the presence of cortical infarction. Currently it is the authors' practice to use the following diagnostic criteria to establish the diagnosis of hemispheric lacunar infarction in cases where precision of diagnosis is important for management purposes, or research interest:

1. Localization of the site of acute pathological change to the region of the internal capsule by careful clinical examination, taking care to exclude cortical involvement by using a series of bedside higher cortical function tests.

2. The finding of a normal EEG in the presence of the neurological deficit.

3. No abnormality found on neuropsychological testing after the administration of a standard battery of tests.

4. Recognition of the five lacunar syndromes, which are likely to form approximately 80% of the group isolated thus far: the remaining 20% comprising partial syndromes and represent an important but less well recognized group.

5. Confirmation of the site of infarction on CT scan.

Apart from the recognition of five classical lacunar syndromes, a study of the frequency of clinical events
CORTICAL INFARCTION  LACUNAR INFARCTION  CONTROLS

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may also be helpful. While many lacunar strokes have a leisurely onset, a proportion may have rapid, dramatic bursts of hemiplegia or other neurological deficits, a phenomenon to which has been attached the epynom ‘The Capsular Warning Syndrome’. The other circumstance in which a flurry of neurological events may occur is that of incipient carotid occlusion but may easily be distinguished by the presence of cortical signs or focal abnormality on EEG.

A standard battery of neuropsychological testing was found to be normal when administered to many of Fisher’s cases of pure hemiplegia and the experience of the authors has been similar, although subtle abnormalities such as poor retrieval of verbal information with left capsular infarction, defects in visual memory and abnormalities of frontal lobe function with both left and right capsular infarction were found in a recent study when more sophisticated tests were used.

The results of the current study suggest that enzyme appearance in CSF is related to the size and site of infarction. In certain instances a study of CSF enzymes may clarify further the diagnosis of lacunar infarction syndromes by identifying occult cortical infarction. The most useful enzyme would appear to be CK, since no elevation of this enzyme was found in the lacunar group, although as seen in figure 1(c), LDH may be also useful since elevation in the lacunar group was very small and a level above which LDH never rises in lacunar disease could be established. In the longitudinal study with repeated lumbar punctures up to 11 days post stroke, a giant lacune of volume 15 ml was shown on CT and no elevation of LDH occurred. If CK and LDH were taken together, 80% of ‘cortical’ infarctions showed elevation above the normal range.

Previous studies of CSF enzymes in stroke have shown unpredictable rises in enzyme level leading one author to despair of its diagnostic usefulness, although recent interest has focused on the use of CSF CK as an index of cerebral damage in a variety of conditions. The previously observed unpredictability of appearance of enzymes in CSF may have been in part due to the presence of unrecognized lacunar syndromes and the degree to which infarction has been confined to the deep subcortex by brisk collateral blood flow.
The finding of lack of elevation of CSF CK in patients with lacunar syndromes while a very slight elevation with LDH was seen is an intriguing one. CK BB is most likely of neuronal and astrocytic origin and quickly denatures at 37°C. 

Presumably, in cases of lacunar infarction, all enzymes are released into the extracellular space but during the diffusion process, denaturation of CK has occurred before CSF spaces are reached. Alternatively, the lack of elevation of CSF CK could reflect a paucity of CK BB in the capsular region compared to cortical grey matter, a concept supported to some extent by recent studies. Differing vulnerabilities of astrocytic and neuronal elements to ischemia, or at least differing propensities to release contained CK BB may also be responsible for differing CSF enzyme levels in lacunar compared to cortical infarction.

The application of CSF enzyme study to further establishing certainty of diagnosis of lacunar infarction should be a restricted one, but may be useful in establishing index cases of interest, particularly those of new lacunar syndromes.

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