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Adenylate Kinase Activity in Cerebrospinal Fluid in Connection with Transitory Ischaemic Attacks

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ABSTRACT

Adenylate kinase activity was measured in cerebrospinal fluid of healthy normal individuals and those having suffered from transitory ischaemic attacks (TIA). Normally, no adenylate kinase was present in cerebrospinal fluid. A slight but distinct activity was always registered in the 11 cases studied in connection with TIA. Cerebrospinal fluid of 2 patients was also analysed in a symptom-free interval (at least 2 weeks after the stroke) and no adenylate kinase activity was found.

INTRODUCTION

In transitoric ischaemic attack (TIA) the clinical manifestations may be pronounced while at the same time the underlying cerebral disorder is subtle in its changes. It has consequently proved difficult to substantiate the pathologic conditions with ordinary laboratory methods. Thus, cerebral angiography and scintigraphy generally do not give any further information about the localized area involved (2). Nevertheless, there are reasons to believe that cell damage—reversible and possibly irreversible to some extent—occurs. Consequently, a leakage takes place of intracellular compounds into the extracellular medium. Among these, enzymes are of special interest as indicators of cell damage and could be expected to appear primarily in the cerebrospinal fluid (CSF). The normal blood–CSF barrier results in CSF-enzyme concentrations that are relatively independent of their serum levels (1, 7).

Enzyme determinations, especially ASAT and LD, have been performed to a limited extent in the CSF in various pathological conditions, such as cerebral infarction, tumour, and multiple sclerosis (4, 8, 9, 19). It was recently shown (3) that adenylate kinase is a more sensitive indicator of slight cell damage, at least for the myocardium, than is ASAT and LD.

To our knowledge, no studies have so far been published concerning adenylate kinase activity in cerebrospinal fluid, neither under normal conditions nor in connection with TIA. Nor have any other enzymes been determined in CSF in connection with TIA. The aim of the present study was to investigate whether the adenylate kinase in CSF could be used as a sensitive marker of impaired cells of the brain tissue in connection with TIA.

PATIENTS AND METHODS

According to WHO criteria (16) transitory ischaemic attack (TIA) is defined as a focal neurological deficit on a vascular basis and commonly lasts some minutes (though never exceeding 24 h), leaving no residual deficit.

Patients

No. 1. Female, aged 64. Known mitral stenosis. Aphasia and weakness of right arm twice during 4 h. Duration of each spell, 15–30 min.

No. 2. Male, aged 60. Sudden vertigo, dysarthria and numbness in the face for 2 h. Three months later admitted comatose and died within a few hours. Autopsy revealed complete thrombosis of the left carotis interna artery and a large cerebral infarction.

No. 3. Male, aged 56. Hypertension and hyperlipoproteinemia for at least 3 years. Sudden dysarthria and right hemiparesis; was unable to walk.

No. 4. Male, aged 60. Weakness and paresthesia in the left arm and to a slight degree in left leg. Unsteadiness on attempt to walk. Transitory Babinski sign on left side. Attack lasting for about 3 h.

Table I. *Adenylate kinase activity in CSF from 11 patients with TIA*

Patient no.	Adenylate kinase activity (mU/ml)
1	0.95
2	1.15
3	0.85
4	0.70
5	1.20
6	0.65
7	0.80
8	0.50
9	0.60
10	1.05
11	0.75

No. 5. Female, aged 70. Woke up with a left-sided hemiparesis, which disappeared within 2 h.

No. 6. Male, aged 61. Hypertension for at least 10 years. Diabetes mellitus for one year. Paresis of the right arm and a short attack of blurred vision.

No. 7. Male, aged 65. Headache, rightsided hemiparesis and aphasia. Turned out to have a polycytemia vera.

No. 8. Male, aged 47. Hypertension known for 3 years. Short attack of dysarthria and weakness of the right arm for 3 h.

No. 9. Male, aged 59. Headache, dysarthria and right-sided facial palsy for 4 h.

No. 10. Male, aged 80. Aphasia and right-sided hemiparesis for one h.

No. 11. Female, aged 73. Hypertension and diabetes mellitus for 5 years. Left-sided hemiparesis and Babinski's sign for 12 h. Was re-admitted 2 months later with complete left-sided hemiplegia.

Lumbar puncture was performed well within 24 h after onset of symptoms. In cases 3 and 7 another spinal fluid examination was made after at least 2 weeks, in a symptom-free interval. Simultaneously a blood sample was drawn for analysis of serum adenylate kinase activity.

Normals: Cerebrospinal fluid from 18 patients without any sign of neurological disorder was obtained in connection with lumbar tap for spinal anesthesia.

To rule out any presence of blood in the spinal fluid, sample controls were routinely run for hemoglobin analysis as has been described for serum in an earlier paper (3).

0.5 ml of spinal fluid was routinely used for analysis. The samples were immediately chilled with ice and brought to the laboratory for analysis. The method described by Frithz et al. (3) was followed exactly, with the exception that the spectro-photometric analysis was performed in a Zeiss spectro-photometer connected to an Oltronic stabilizer to eliminate background fluctuations. Duplicate controls containing all compounds except the sample, were always run concomitantly, thereby correcting for the small background activity due to slow physicochemical decay of ATP and possible ADP contamination of the ATP batch. Serum was concomitantly analysed for adenylate kinase activity. Enzyme activity was expressed in milliunits (mU) per ml as has been described previously (3).

RESULTS

No adenylate kinase activity was detected in any of the control spinal fluid samples, provided that the samples were not contaminated with blood. Therefore, we have reason to believe that normally no adenylate kinase is present in spinal fluid.

The 11 patients with TIA all displayed a clear adenylate kinase activity (Table I). The highest activity observed was 12.0 and the lowest 5.0 mU/ml. No one of the patients had any elevation of the adenylate kinase in serum according to the standard levels determined earlier (3). In the two cases, numbered 3 and 7, with activities around 8 mU/ml during the TIA, new analyses were performed after recovery (at least 14 days after the TIA). No adenylate kinase activities were detected in the CSF on these symptom-free occasions.

DISCUSSION

Although the clinical picture of TIA is alarming, the underlying conditions are not easily demonstrated by laboratory methods. Also, the pathophysiological process in the brain parenchyma is subtle, and the changes are probably reversible. Therefore, ordinary angiograms and brain scintigrams are of no specific aid in visualizing the pathologic condition (2). However, studies on regional blood flow in patients with TIA have revealed an impaired circulation (6, 10, 11, 12). Thus, there is experimental evidence of reduced blood supply to distinct areas of the brain during and some time after TIA. Since brain tissue and especially the neuron are highly dependent on the oxygen supply for its metabolism and normal function, there is good reason to assume changes on a cellular level in any case of reduced oxygen supply. The aerobic metabolism including the tricarboxylic acid cycle plays a central role in brain tissue for the maintenance of normal levels of ATP (13).

Furthermore, it has been claimed recently that the integrity of the plasma membrane, as assessed by its ability to prevent leakage of intracellular enzymes, is dependent upon the energy content of the cell (5, 15, 17). Since it was demonstrated in an earlier paper (3) that adenylate kinase was more sensitive as a marker of ischemic injury of the

myocardium than are the transferases (ASAT, ALAT) and lactate dehydrogenase (LD) it was tempting to study the possible presence of adenylate kinase in spinal fluid in connection with TIA.

The question then arises whether adenylate kinase is normally present in spinal fluid, e.g. in enlarged quantities with increased age as reported by Spolter & Thomson (14) who found such an increase for ASAT and LD. The normals in the present study ranged in age from 24 to 80 years and it was not possible to detect adenylate kinase activity in their spinal fluids in any single case. Therefore the normals studied were comparable on an age basis to the persons suffering from TIA. Furthermore, the enzyme seems to disappear completely after a certain time after the TIA. The disappearance of the enzyme most probably indicates a restitution of the intracellular metabolism also comprising the integrity of the plasma membrane. The disappearance of the enzyme may also be due to a total loss of the functions of some cells concerned.

The levels of adenylate kinase activity in CSF were not high compared with the activities found in serum in connection with myocardial infarction (3) though clearly demonstrable, especially since normally no adenylate kinase is present in CSF. This finding is however not surprising considering the subtle changes of the brain parenchyma that probably take place. The patients differed from each other as regards the level of adenylate kinase activity in spinal fluid. All patients with TIA so far examined displayed a clear-cut adenylate kinase activity in their CSF. Due to the limited number of patients investigated, it is not possible to state whether the occurrence of adenylate kinase in spinal fluid in connection with TIA is obligatory or not. The variability of the level of enzyme activity may reflect variation of the amount of brain tissue involved, although the topographic location of the amount of the TIA also might influence the amount of enzyme released into the spinal fluid.

A method has been described in which the extent of myocardial infarction in man is assessed by mathematical analysis of the rise in plasma enzyme levels, mainly involving ASAT, ALAT and LD (18). Furthermore the amount of adenylate kinase in serum after infarction parallels that of the transferases and LD (3). Therefore, a higher level of adenylate kinase activity in spinal fluid during and after TIA might indicate a more extensive involvement of also the brain parenchyma.

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