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Changes in CSF blood-brain barrier parameters in ischaemic cerebral infarction

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Summary. Total CSF protein and CSF/serum albumin and α2-macroglobulin ratios as indicators of a disturbed blood-brain barrier were determined in 39 cases of ischaemic cerebral infarction proved by computed tomography (CT). About 50% of the patients had a barrier disturbance, whereat the CSF serum albumin ratio was shown to be the most sensitive parameter. A disturbed blood-brain barrier was more often found in cases of large infarction, as shown by CT, and occurred most frequently in the first 2 weeks of illness. No correlation was seen between enhancement in CT and disturbance of the blood-brain barrier.

Key words: Brain infarction – Blood-brain barrier – CSF albumin – CSF α-2-macroglobulin – CT enhancement

Zusammenfassung. Gesamteiweiß, Liquor/Serum Albumin-Quotient und Liquor/Serum α2-Makroglobulin-Quotient als Parameter einer gestörten Blut-Hirn-Schrankenfunktion wurden bei 39 Patienten mit computertomographisch gesicherten ischämischen Hirninfarkten bestimmt. Mehr als die Hälfte hatten eine Schrankenstörung, wobei sich der Liquor/Serum Albumin-Quotient als empfindlichster Parameter erwies. Eine Schrankenstörung war bei ausgedehnten Infarkten häufiger. Sie trat hauptsächlich in den ersten beiden Krankheitswochen auf. Ein Zusammenhang mit dem Kontrastmittel-Enhancement im CT war nicht nachweisbar.

Disturbances of the blood-brain barrier (BBB) for proteins following ischaemic cerebral infarction have been studied in detail only in animals. Barrier disturbance could be demonstrated within a few hours after acute ischaemia, and was more frequent in cases of large infarctions [4]. There have only been a few studies on this disturbance in human cerebral infarction.

The questions dealt with in this report are:

1. How often is a disturbed BBB demonstrable in cases of human ischaemic infarction?

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Table 1. CSF parameters of a disturbed blood-brain barrier in patients with ischaemic cerebral infarction

Parameter of disturbed barrier function	Number of patients (CSF samples)[a]	%
Increased total CSF protein	18 (25)	46.2 (42.4)
0.45–0.5 g/l	(3)	
0.5 –0.6 g/l	(12)	
0.6 –0.7 g/l	(5)	
Above 0.7 g/l	(5)	
Increased CSF/serum albumin ratio	22 (31)	56.4 (52.5)
0.0073–0.009	(8)	
0.009 –0.012	(8)	
0.012 –0.015	(8)	
Above 0.015	(7)	
Increased CSF/serum α-2-macroglobulin ratio[b]	8 (15)	61.5 (48.4)

[a] $n = 39$ patients (59 CSF samples)
[b] CSF/serum α-2-macroglobulin ratio was only determined in 31 CSF samples of 13 patients

2. Which are the most sensitive parameters?
3. Is there a correlation with the size of the infarction area?
4. When does impairment of the barrier occur?
5. Is there a correlation between enhancement of contrast medium on computed tomography (CT) and the BBB dysfunction detectable by CSF investigation?

Subjects and methods

The following parameters were determined in 59 lumbar CSF samples of 39 patients suffering from ischaemic cerebral infarction:

1. Total CSF protein using the Biuret method (Testkombination Gesamteiweiß, Boehringer, Mannheim, FRG).

2. CSF albumin concentration by a radial immunodiffusion technique (LC-Partigenplatten, Behringwerke, Marburg, FRG). Serum albumin concentration was determined by the same method and CSF/serum albumin (R(alb)) was calculated.

3. CSF α-2-macroglobulin concentration by an immunoturbidimetric technique: 0.2 ml CSF sample was mixed with 0.36 ml 4% PEG buffer (1.38 g NaH_2PO_4, 8.5 g NaCl, 40 g polyethylenglycol, 0.4 mg methiolate and aqua bidest. ad 1000 ml) and 0.04 ml antiserum against human α-2-macroglobulin (Behringwerke, Marburg, FRG). Using buffer instead of antiserum as a blank value, the decrease in extinction was measured photometrically at 365 nm after 10 min (Eppendorf Photometer, Hamburg, FRG). Concentration was calculated using a dilution series of a standard serum (LN protein standard serum, Behringwerke, Marburg, FRG). Serum concentration was determined after predilution with 0.15 *M* sodium chloride solution. The CSF/serum α-2-macroglobulin ratio (R(α-2-macroglob)) was calculated.

A disturbed BBB was considered to be present, if total CSF protein exceeded 0.45 g/l, R(alb) was about 0.0073 or R(α-2-macroglob) was increased about 0.002, respectively.

Table 2. CSF parameters of a disturbed blood-brain barrier in patients with ischaemic cerebral infarction at different times after onset of illness

Barrier function[a]	Week of illness							
	1.		2.		3.		4.	
	Normal	Disturbed	Normal	Disturbed	Normal	Disturbed	Normal	Disturbed
Small infarcts[b]	10	5	5	3	3	1	5	1
Large infarcts[c]	0	10	1	5	2	3	2	3
All	10	15	6	8	5	4	7	4

[a] CSF/serum albumin ratio
[b] Maximum diameter of hypodense area in CT less than 1 cm ($n = 33$)
[c] Maximum diameter of hypodense area in CT about 1 cm ($n = 26$)

Maximum diameter of hypodense area in CT	Barrier function[a]	
	Normal	Disturbed
About 1 cm	2	15
Less than 1 cm	15	7

[a] CSF/serum albumin ratio

Table 3. CSF parameters of a disturbed blood-brain barrier in 39 patients with ischaemic cerebral infarction and relationship to size of infarction

Lumbar puncture (LP) was performed in 25 cases in the 1st week of illness, in 14 cases in the 2nd, in 9 cases in the 3rd and in 11 cases in the 4th week.

Within 24 h after each LP all patients were scanned by CT before and after i.v. injection of 60 ml contrast medium (Conray 60, Byk Gulden, Konstanz, FRG).

Results

Infarctions were supratentorial in 37 patients and infratentorial in 2. The maximum diameter of the hypodense area in CT was more than 1 cm in 17 cases and less in 22 cases; 56.4% had evidence of a disturbed BBB. Total CSF protein was increased in 46.2%, R(alb) in 56.4% and R(α-2-macroglob) in 61.5% of the patients (Table 1). Whereas all patients with an elevated total CSF protein also showed an increased R(alb), CSF total protein was normal in four cases with an increased R(alb). Whenever R(α-2-macroglob) was elevated, R(alb) showed increased values. In four cases increased R(alb) was found together with a normal R(α-2-macroglob). This suggests that R(alb) should be the most sensitive parameter for BBB disturbance.

Barrier disturbances were most frequently seen in the first 2 weeks after stroke, even on the 1st day. However, they were still detectable in some cases in the 4th week (Table 2).

A BBB disturbance was more often found in cases with large infarctions. Whereas in 15 of 17 patients with an infarction area larger than 1 cm maximum

Table 4. CSF parameters of a disturbed blood-brain barrier in patients with ischaemic cerebral infarction. Correlation with enhancement of contrast medium on CT scan

	Number of	
	Patients	CSF-samples/CT[a,b]
Contrast enhancement and normal CSF/serum albumin ratio	3	4
Contrast enhancement and increased CSF/serum albumin ratio	3	4
Contrast enhancement, all	6	8

[a] n = 39 patients (59 CSF samples, CT scans, resp.)
[b] Maximum interval between lumbar puncture and CT scan was 24 h

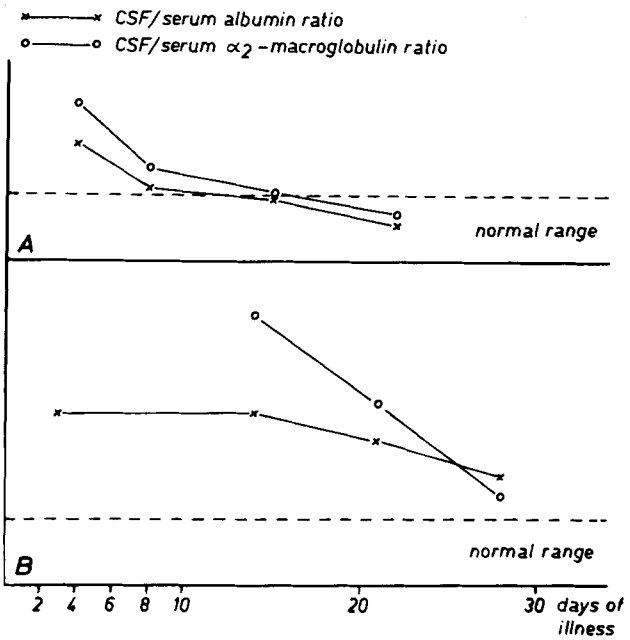

Fig. 1 A and B. Disturbances of blood-brain barrier in patients with ischaemic cerebral infarction. Time course. **A** Large infarction in the area of the left middle cerebral artery. Barrier impairment for albumin and α-2-macroglobulin, restitution in the second week of illness. **B** Large infarction in the area of the left middle cerebral artery. Barrier disturbance for albumin and α-2-macroglobulin. Disproportion in the beginning as an indicator of severeness. Barrier impairment still demonstrable in the fourth week of illness

diameter in CT showed increased R(alb), in 15 of 22 patients with smaller infarctions barrier function was normal (Table 3). The infarctions of six patients in this study were enhanced by contrast medium on CT. The enhancement was first detectable between the 12th and 22nd day of disease. Three of these patients had already been scanned on the 3rd day, a further patient on the 8th day. No enhancement was found on these occasions. Only three patients with an

enhancement on CT had an increased R(alb) as well. One of them had an elevated R(alb) on the 8th day, but no enhancement in CT at this time. On the 15th day, however, enhancement occurred on CT as R(alb) already had reached a normal level (Table 4).

The time course of the BBB disturbance of two patients suffering from severe ischaemic infarction in the area of the middle cerebral artery is shown in Fig. 1. The first patient had a moderate proportional increase in R(alb) and R(α-2-macroglob). Barrier disturbance was no longer detectable in the 2nd week. In the second patient the BBB disturbance was severe. R(alb) and R(α-2-macroglob) were not only more increased, but in addition the barrier was relatively more impaired for α-2-macroglobulin in the first 3 weeks. Barrier disturbance was still present after 4 weeks in this patient.

Discussion

More than 50% of the 39 patients in this study showed CSF changes suggesting a disturbed BBB. This percentage is slightly higher than that reported by Al-Kassab et al. [1], who examined a smaller number of patients. R(alb) was the most sensitive indicator of a barrier disturbance; sensitivity was lower for R(α-2-macroglob) and total CSF protein.

The frequency of BBB disturbances was higher in patients with a large infarction area on CT. Different results from other authors [1, 9] may be explained by the following: infarctions up to a diameter of 5 cm were considered as small by Al-Kassab et al. [1]; in the patients of Schliep and Felgenhauer [9] the severity of clinical symptoms was judged as an expression of the size of infarction. However, it should be remembered, that small infarctions in the internal capsule may result in a severe neurological deficit. Our results agree with those of studies carried out in rhesus monkeys, where a barrier disturbance was more often observed in animals with large infarctions [7].

Disturbances of the BBB were detected rather early in the course of infarction. They were mostly frequent in the first 2 weeks after stroke; in a few cases a damaged BBB was demonstrated on the 1st day after stroke. These results agree well with those of studies in animals, which suggest an increased permeability of the BBB for proteins a few hours after acute ischaemia [3].

The degree of BBB disturbance sometimes differed even when the extension of infarction in CT was rather similar. A disproportionate barrier disturbance shown by a relatively more increased R(α-2-macroglob) compared with R(alb), was also observed. These patients were considered to have a rather severe BBB disorder [9].

A disturbed BBB could sometimes be seen about 4 weeks after stroke, which is somewhat longer than reported in animal experiments [7].

Increased permeability of the BBB is considered to be a reason for the vasogenic form of brain edema [5]. The results of this study suggest that vasogenic edema sometimes occurs on the 1st day after stroke, as already reported in animals [3]. Extravascular leakage of proteins is caused by activated pinocytotic transport, since the capillary endothelium remains strikingly well preserved even after a few hours of ischaemia [4]. Pinocytosis might be activated by altered metabolic

conditions, as it coincides with an increased anaerobic glycolysis. CSF lactate concentration (an indicator of anaerobic glycolysis) correlates with the size of infarction and reaches its maximum level on the 3rd day after stroke [2]. BBB damage also occurs early in the course of illness and is more often found with large infarctions.

A correlation between increased permeability of the BBB for proteins and the occurrence of contrast enhancement in CT scan was not observed. The explanation may be that there is no single reason for enhancement. Sometimes enhancement can be observed on the 1st day after stroke and a disturbed BBB has been considered to be the cause [8]. We too have seen a few cases of early enhancement, but they are not considered in this study, because BBB parameters were not determined. On the other hand, reactive hypervascularization of the infarcted area has been assumed to be a cause of enhancement [6]. This would explain why enhancement is mostly seen in the 2nd and 3rd week after stroke and why certain patterns of enhancement occur, for example, in a predominantly peripheral one. Increased permeability of the BBB for proteins might not then show in the CSF.

References

1. Al-Kassab S, Olsen TS, Skriver EB (1981) Blood-brain barrier integrity in patients with cerebral infarction investigated by computed tomography and serum/CSF albumin. Acta Neurol Scand 64:438–445
2. Busse O (1982) Zur Prognose des ischämischen Hirninfarkts. Fortschr Med 100:1197–1200
3. Ito U, Ohno K, Tomita H, Inaba Y (1977) Cerebral changes during recirculation following temporary ischemia in mongolian gerbils, with special reference to blood-brain-barrier change. In: Schmiedek P (ed) Microsurgery for stroke: 3rd Symposium. Springer, Berlin Heidelberg New York, pp 29–38
4. Katzman R, Clasen R, Klatzo I, Meyer JS, Pappius HM, Waltz AG (1977) Brain edema in stroke. Stroke 8:510–540
5. Klatzo I (1967) Neuropathological aspects of brain edema: Presidential address. J Neuropathol Exp Neurol 26:1–14
6. Norton GA, Kishore PRS, Lin J (1978) CT contrast enhancement in cerebral infarction. Am J Roentgenol 131:881–885
7. Olsson Y, Crowell RM, Klatzo I (1971) The blood-brain barrier to protein tracers in focal cerebral ischaemia and infarction caused by occlusion of the middle cerebral artery. Acta Neuropathol 18:89–102
8. Pullicino P, Kendall BE (1980) Contrast enhancement in ischaemic lesions. Neuroradiology 19:235–239
9. Schliep G, Felgenhauer K (1978) Serum-CSF protein gradients, the blood-CSF barrier and the local immune response. J Neurol 218:77–96

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