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The Prognostic Value of the Non-Protein Nitrogen (NPN) Content in the Serum and the Cerebrospinal Fluid

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SUMMARY. The amounts of total protein and nonprotein nitrogen (NPN), together with the pH were determined in serum and lumbar cerebrospinal fluid (CSF) of controls and comatose patients before and after death. The serum/CSF ratio of NPN was calculated. Under normal conditions the value of this ratio is 1.65. The decrease of this value is a sign of worsening of barrier functions. If the NPN content of the serum and CSF becomes identical, i.e., when the serum/CSF ratio approaches or even equals 1.0, and at the same time the pH decreases in the CSF, then the prognosis is hopeless.

KEY WORDS: Serum and CSF Nonprotein Nitrogen - Barrier Functions - Serum/CSF Ratio - Prognostic Value.

ZUSAMMENFASSUNG. Der Gesamteiweiß- und der Rest-N-Gehalt, sowie der pH-Wert des Blutes und des lumbalen Liquors wurden bei Kontrollen und bei komatösen Patienten vor und nach dem Tode bestimmt. Der Blut-RN/Liquor-RN Quotient wurde errechnet. Normalerweise ist der Wert dieses Quotienten 1,65, seine Abnahme weist auf eine Störung der "Schranken"-Funktionen hin. Die Prognose kann als hoffnungslos beurteilt werden, wenn sich der Wert des Blut/Liquor Quotienten 1,0 nähert, oder sogar der Rest-N-Gehalt des Blutes und des Liquors gleichwertig werden, und gleichzeitig der pH im Liquor pathologisch abnimmt.

SCHLÜSSELWÖRTER: Rest-N im Blut und Liquor - Schranken-Funktionen - Blut/Liquor Quotient - Prognostische Bedeutung.

In agreement with several authors (among others Siesjö et al., 1968; Zupping, 1972) the investigation of about 1300 patients' blood and CSF led us to the conclusion that the composition of the CSF gives more reliable information about the normal and pathologic metabolic processes of the CNS than that of the blood (Molnár, 1972, 1973, 1974, 1975). The literature concerning the electrolyte and carbohydrate content, and acid-base charac-

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teristics of the CSF is extremely vast (see Davson, 1972; Leusen, 1972; Fenstermacher & Rall, 1972; Molnár, 1974; Molnár & Kovács, 1974, and many others).

Of the substances containing NPN, numerous investigators have studied in the CSF of animals and humans the quantity of urea and its changes (Bradbury & Davson, 1953; Bering & Avman, 1960; Kleeman et al., 1961; Davson et al., 1962; Bradbury et al., 1963, Javid & Settlage, 1965; Davson, 1967). In humans Bradbury et al. (1963) found both in ventricular and lumbar CSF less urea than in the blood. Lumbar CSF contains less urea (28.1 ± 9.2 mEq/l) than serum (34 ± 10.9 mEq/l) according to Sambrook et al. (1973).

Few data (Lickint, 1951; Pruckner & Manuelidis, 1951; Bammer & Schaltenbrand, 1968) can be found regarding the NPN content of the CSF and its changes. This and an accidental observation led us to perform systematic examinations.

CASE REPORT

Mrs. A. G., age 37, was admitted to our clinic because of unconsciousness gradually deepening to coma. Signs of focal organic lesion of the nervous system could not be found. Among laboratory findings the NPN content of the serum (134.2 mg/100ml) was unambigously pathologic. According to the consulting internist it did not explain the unconsciousness. At that time a lumbar puncture was made. We found the same amount of NPN (134.4 mg/100 ml) in the water-clear CSF as in the serum, that is, the serum/CSF ratio was practically 1.0. The patient died. (Findings at autopsy: chronic nephritis, cerebral edema.) We began on the basis of this experience a series of investigations, which gave us useful data for general practice too.

MATERIALS AND METHODS

The quantity of NPN was measured in the serum and lumbar CSF of controls and in comatose patients. At the same time the total protein and pH values of the CSF were determined, the latter because other authors (Zupping, 1972; Sambrook et al.,1973) and ourselves as well have found a strict correlation between the severity of the damage in the nervous system and the pH of the CSF.

NPN was measured by the titrimetric method of Rappaport & Eichhorn (1947) and pH by the aid of a "Radelkis" microanalyzer (Type OP-210/1). The total protein content of CSF was determined according to Exton (see Gernand & Hajek, 1966; Krüger et al., 1970).

We chose as controls 186 individuals who had no symptoms referable to organic damage of the nervous system. The values found in the controls were compared with those of the total protein in CSF, and the NPN and pH values in the serum and CSF of 23 comatose patients who were treated because of serious, mainly cerebrovascular disease causing death. We divided the patients into two groups according to whether their CSF was bloody (11 cases) or water-clear (12 cases). The quantity of NPN and the pH were determined repeatedly in every patient and also within 10 or 20 min after death. As far as possible

the amount of total protein in the CSF was also measured repeatedly. In the statistical analysis of the serum/CSF ratios the method of Kolmogorow and Smirnow was used; in that of all the other data Student' s paired T-test was used.

RESULTS

NPN was 28. 00 mg/100 ml in the serum, and 17. 42 mg/100 ml in the CSF of controls. We found significantly more NPN in the serum and CSF of comatose patients than in the controls. The difference was more pronounced between the values obtained in the controls and in the dead (Table 1).

According to our measurements the serum/CSF NPN ratio is normally 1. 65. The difference between the serum/CSF NPN ratio of the controls and of the patients having water-clear CSF was markedly significant. The differences between control serum/CSF NPN values and those found in bloody CSF or after death were not statistically significant, because of the great variance in the number of cases compared (Table 1).

The quantity of total protein was nearly the same in the water-clear CSF of the controls and in the dead. In the bloody CSF the total protein content was evidently very high and great differences could be found from patient to patient as well (see Table 1, mean value, and S. D.).

The pH values in CSF of comatose patients were acid, whereas the pH of blood was normal or even augmented, and decreased only after death. Postmortem the pH was about 7. 00 in blood and even less in the CSF.

We wish to expound in detail our findings in two patients and a control because they demonstrate different kinds of changes better than do average values.

From one of our patients (K. N. , age 74) who was treated because of occlusion of the left internal carotid artery, blood and CSF were taken for measurement of NPN and pH 6 days before his death, 5 times during the 30 h preceding death, and 5 min after his death. We found normal values at the time of the first examination. Later, however, simultaneously with the worsening of his state, the quantity of NPN in serum and CSF gradually became equal and the value of the serum/CSF ratio approached 1 (Table 2).

In Table 3 the NPN and pH values in serum and CSF of a patient (Mrs S. P. , age 55) operated on for relapsing malign brain tumour can be seen. She was stuporous at the time of the first measurement. Later her state definitely improved. Simultaneously with this improvement of the absolute quantity of NPN both in the serum and CSF, and the serum/CSF ratio approached normal. The change of the value of pH was not characteristic, either in serum or in CSF.

The values of one of our controls (S. G. , age 36) are presented in Table 4. Samples were taken from his blood and CSF 5 times during which his somatic state did not change.

DISCUSSION

Few data can be found in the literature concerning the blood-CSF change of NPN. According to Lickint (1951) the urea and NPN content of CSF behave practically in the same way. It was our starting point in trying to explain our results.

Table 1. Parameters - NPN, pH, total protein content - measured in serum and CSF of controls and patients (mean values and S. D. N: number of measurements)

			Serum NPN mg/100 ml	CSF NPN mg/100 ml	Serum/ CSF NPN	CSF Total Protein mg/100 ml	Serum pH	CSF pH	Serum/ CSF pH
Controls			28.00 ± 4.90 N: 186	17.42 ± 4.27 N: 186	1.65 ±0.28 N: 186	27.83 ± 6.46 N: 132	7.378 ± 0.044 N: 142	7.332 ± 0.060 N: 116	1.006 ± 0.006 N: 116
Patients	Water-clear CSF	before death	80.64* ± 31.05 N: 30	66.50* ± 30.97 N: 31	1.28** ± 0.20 N: 30	28.76 ± 12.88 N: 24 N. S.	7.412*** ± 0.071 N: 31	7.302**** ± 0.064 N: 31	1.015 ± 0.008 N: 31 A. S.
		after death	85.76* ± 26.11 N: 10	72.70* ± 30.72 N: 11	1.36 ± 0.18 N: 9 N. S.	28.02 ± 17.56 N: 8 N. S.	7.048* ± 0.098 N: 12	6.951* ± 0.146 N: 13	1.011 ± 0.026 N: 12 N. S.
	Bloody CSF	before death	63.24* ± 30.66 N: 15	54.33* ± 27.46 N: 16	1.25 ± 0.18 N: 15 A. S.	354.26*** ± 330.71 N: 10	7.414** ± 0.070 N: 16	7.249* ± 0.051 N: 17	1.022**** ± 0.009 N: 16
		after death	86.50** ± 34.65 N: 7	76.80** ± 37.37 N: 7	1.16 ± 0.13 N: 7 A. S.	207.53 ± 146.71 N: 3 N. S.	6.993* ± 0.097 N: 7	6.841* ± 0.139 N: 7	1.022 ± 0.024 N: 7 N. S.

Statistical significance of change from control value * = P = 0, ** = P < 0.005, *** = P < 0.01, **** = P < 0.05
A. S. = almost significant (P < 0.07), N. S. = not significant (P > 0.1)

Table 2. Changes of parameters studied in the case of patient K. N., aged 74

	6 days before death	30	26	16 hours	9	2.5	5 min after death
				before death			
Serum NPN mg/100 ml	36.2	113.0	114.0	114.0	114.0	114.0	113.0
CSF NPN mg/100 ml	19.8	97.7	107.0	113.0	112.0	114.0	114.0
Serum/CSF NPN	1.83	1.16	1.06	1.01	1.01	1.00	0.99
Serum pH	7.466	7.503	7.570	7.440	7.360	7.303	6.970
CSF pH	7.375	7.405	7.345	7.293	7.263	7.265	6.974
Serum/CSF pH	1.012	1.013	1.030	1.020	1.013	1.005	0.999

Table 3. Changes in the same parameters shown in Table 2 in another patient, Mrs S. P., aged 55

	10/3/73	10/9/73	10/22/73
Serum NPN mg/100 ml	49.0	32.2	34.2
CSF NPN mg/100 ml	41.2	24.2	19.2
Serum/CSF NPN	1.19	1.33	1.77
Serum pH	7.540	7.490	7.472
CSF pH	7.325	7.370	7.295
Serum/CSF pH	1.029	1.016	1.023

Table 4. Same parameters as in Tables 2 and 3 in a control case

	4/20/73	4/27/73	5/4/73	5/11/73	5/29/73
Serum NPN mg/100 ml	26.5	26.5	23.0	26.5	23.2
CSF NPN mg/100 ml	16.7	13.8	14.2	16.5	11.7
Serum/CSF NPN	1.58	1.92	1.61	1.60	1.98
Serum pH	7.303	7.405	7.440	7.290	7.328
CSF pH	7.375	7.378	7.378	7.309	7.355
Serum/CSF pH	0.990	1.004	1.008	0.997	0.996

Urea is a water-soluble product of metabolism. It gets on the way of diffusion from blood to nervous tissue and CSF (Davson, 1972). Its concentration is higher in blood than in CSF, according to Fenstermacher & Johnson (1966) because for the water-soluble molecules the blood-brain-CSF barrier is a mosaic-like membrane, the water-filled pores of which are of 0.8 nm in diameter, forming a mechanic obstacle among others for the molecules of urea too. Ventricular CSF contains less urea than subarachnoidal, obviously because urea can diffuse to CSF on its way from the ventriculus to the subarachnoidal space.

It is possible that in our patients longlasting unconsciousness led to insufficiency of the systemic blood circulation and as a consequence to the decrease of blood supply to the kidneys. For this reason, and because of the intermittent accompanying exsiccation the NPN level of blood increased and azotemia developed.

In the controls the CSF contains less NPN than the blood. It proves the intact functioning of barriers. The fact, that in the state of deep coma the values of NPN in CSF and serum become gradually equal confirms the damage to the barriers, that is, at least, that the permeability of the blood-CSF barrier increases for NPN.

The functional or morphologic lesion of the blood-brain-CSF barrier and the pathologic increase of different - occasionally toxic - metabolic products in the CSF (and in the nervous tissue?) according to our results justifies a grave prognosis. We drew the conclusion on the basis of our previous observations that the increase in carbohydrate metabolism products in the CSF - "the luxury glucose supply of the brain" (Molnár, 1973, 1975) - may early call attention to the poor prognosis. Data collected in the present investigation completing and agreeing with the earlier ones might serve in clinical practice as a fundamental basis for judging the severity and prognosis of the disease.

We consider it well-established that the pathologic increase of nitrogen-containing substances in the CSF (if the NPN ratio of serum/CSF is about 1) proves unambigously the severe disorder in the barriers' functions. If at the same time the value of pH in CSF decreases as well, we may consider the prognosis to be hopeless.

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