

Creatine phosphokinase content in cerebrospinal fluid

PRELIMINARY REPORT OF FINDINGS IN MULTIPLE SCLEROSIS

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MOST of the many recent studies on enzymatic determinations of the cerebrospinal fluid (CSF) of patients with neurologic disease have been centered on the variations of creatine phosphokinase (CPK) values in regard to acute disorders of the central nervous system. The results often have been conflicting, contradictory, or negative.¹ There are some well-documented cases²⁻⁴ of significant increases of CPK content after extensive infarctions of the central nervous system. Little is known about such values in patients who have chronic neurologic diseases. Since CPK is an abundant enzyme in the central nervous system, and the indications are that the content increases when the central nervous system suffers injury,⁴⁻⁷ albeit the evidence has not yet been correlated with the various nosologic entities, we planned to determine the values of CPK in CSF specimens of randomly selected patients, and to compare the pathologic increases with the clinical evidence of disease for a possible correlation.

Materials and methods

One hundred patients, chosen at random, with various neurologic diseases were studied. The CPK values were determined in specimens of CSF of all the patients, and also for most of them, those in sera. The specimens were obtained by lumbar puncture, and the standard tests were applied—determination of cells, protein, globulins, Wassermann—and protein electrophoresis when indicated.

The CPK values were determined† by the automated fluorometric ninhydrin reaction.^{8, 9} In our laboratory, the normal range of CPK values in serum is 0 to 13.5 sigma units (1 sigma unit = $\mu\text{M}/\text{ml}$ creatine \times 20). The normal range in CSF was not known, therefore the values in 25 control subjects were determined to establish the normal range. The control subjects were patients who would undergo elective surgical procedures, and the spinal fluid specimens were obtained at the time of spinal anesthesia. No control subject was included who had neurologic manifestations or disease known to increase the serum CPK values.¹⁰⁻¹³ Blood specimens were obtained after the operations were performed, so the serum values were not applicable to our study.

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† Creatine phosphokinase determinations were made in the Department of Clinical Pathology under the direction of our colleague, Charles E. Willis, M.D.

The mean value of CPK in CSF was 1.6 U. (range, 0.0 to 5.0 U.). The S.D. = 1.6. We calculated the statistical normal range by adding 2.5 S.D. to the mean value. Thus, the normal range of CPK values in CSF was 0 to 5.6 U., and for clinical purposes 0 to 5.5 U.

Results and comment

Of the 100 patients studied (*Table 1*), eight showed values of 5.5 U. or higher (*Table 2*). Only one patient had a significant increase of CPK in serum, 61.5 U., with a CSF content of 7.0 U. We assume that there was CPK circulation between both compartments—blood and CSF—and excluded him as representative of a genuine increase of CPK in CSF. One patient was in the known category of recent brain infarction (60 hr before lumbar puncture), with a CPK value of 8.5 U. in CSF, in the absence of pleocytosis. A third patient was in the terminal

Table 1.—Diagnoses of all patients studied

Diagnosis		Patients, number
Multiple sclerosis		20
Cerebral infarction		19
Recent	13	
Old	6	
Convulsive disorder		10
Dementias without lateralizing signs		10
Anxiety reactions and depression		6
Polymyositis, myopathies, and fibrositis		4
Amyotrophic lateral sclerosis		3
Cerebellar ataxias		2
Cord tumor		2
Encephalopathy		2
Labyrinthitis		2
Metabolic coma		2
Meningitis		2
Neuropathy		2
Paraparesis (unknown cause)		2
Radiculopathy		2
Lymphocytic leukemia		2
Acute	1	
Chronic	1	
Brachial plexus neuritis		1
Collagen disease		1
Guillain-Barré syndrome		1
Headache		1
Hemifacial spasm		1
Myelopathy		1
Optic atrophy		1
Syphilis, stage 3		1
Total		100

Table 2.—*Data of eight patients with increased content of creatine phosphokinase in cerebrospinal fluid*

Patient	Diagnosis	Creatine phosphokinase content, U.	
		Cerebrospinal fluid	Serum
1	Multiple sclerosis	11.0	9.5
2	Multiple sclerosis	7.0	13.0
3	Multiple sclerosis	6.0	14.0
4	Multiple sclerosis	6.0	5.0
5	Multiple sclerosis	5.5	6.5
6	Recent infarction	8.5	Not known
7	Convulsive disorder	7.0	61.5
8	Terminal lymphocytic leukemia	6.0	3.0

stage of chronic lymphocytic leukemia with fever of long duration, recent onset of ptosis of the right eyelid, and a CSF protein content of 240 mg per 100 ml, probably representing meningeal and/or central nervous system infiltration; cultures of CSF had been repeatedly negative for bacteria and fungi.

The other five patients had been diagnosed as having multiple sclerosis (*Table 3*) that was clinically active at the time of lumbar puncture. None showed significant increases in the serum CPK values. For some of the patients, determinations of cell count, Wassermann test, protein content, and protein electrophoretic patterns were simultaneously made in CSF (*Table 3*).

Of the 100 patients studied, 20 had been diagnosed as having multiple sclerosis, eight of whom had shown recent signs of deterioration, and to this group belong the five patients with increased CPK values in CSF. Thus, we consider it significant that one fourth of the total number of patients with multiple sclerosis had increased CPK content in CSF, and all of them were showing signs of clinical activity. Repeated determinations were made in regard to two patients as follows.

Patient 2 had a value of 7.0 U. of CPK in CSF, during a period of extreme tiredness, slurred speech, and severe difficulty in walking. Twelve days later the patient returned for examination and stated that the general exhaustion had disappeared; the speech was slurred only occasionally, and the ability to walk was greatly improved. A lumbar puncture at that time disclosed a CPK value of 2.0 U. in CSF, with a serum CPK value of 9.0 U.

Patient 3 had a CPK value in CSF of 6.0 U. two weeks after the onset of acute exacerbation, with blurring of vision, diplopia, and difficulty in walking. Four weeks after the onset, the blurring of vision and diplopia had disappeared, and the ability to walk had much improved. At that time the CPK value in CSF had decreased to 0.5 U., with a normal serum CPK value of 5.5 U.

Table 3.—*Correlative data of five patients with multiple sclerosis and increased content of CPK in cerebrospinal fluid*

Patient	Clinical manifestations	Serum, CPK units	CPK units	Cerebrospinal fluid		
				Eryth- rocytes, no./mm ³	Protein elec- trophoresis	
					β- glob- ulin, %	γ- glob- ulin, %
1	Bitemporal pallor, quadriparesis, ataxia of limbs, nystagmus, decreased pallesthesia	9.5	11.9	—	—	—
2	Paraparesis, slurred speech, nystagmus	13.0	7.0	0	15	5
3	Retrobulbar neuritis, nystagmus, right hemiparesis	14.0	6.0	100	12	34
4	Paraparesis, hypesthesia right hand and leg	5.0	6.0	—	15	14
5	Bitemporal pallor, quadriparesis, slurred speech, nystagmus, hypesthesia left side of body, ataxia of limbs	6.5	5.5	—	17	6

Hypothesis

At this point we can hypothesize that the destruction of myelin or its consequences cause a small but significant increase of CPK content in CSF. As long as the demyelination continues, the CPK content would remain high. The destruction of myelin may stop, but the clinical manifestations would continue as long as the myelin is not restored. This would explain cases considered clinically active but with no CPK increase in CSF. Thus the CPK values could be a direct index of the state of the myelin, regardless of the clinical picture.

The above considerations are speculative, but prompted our interest in pursuing their validity. Accordingly we have planned to continue our study, restricting it to the demyelinating disorders, in an attempt to find the answer to multiple questions that have arisen, including the highly debated effects of adrenocorticotrophic hormone and steroids.

The CPK abnormalities encountered in the CSF are not specific of the demyelinating disorders. Our impression is that violent assaults—such as infarction, trauma, demyelination—to the central nervous system may cause such increases, and certainly multiple sclerosis can be regarded as an aggressive offender.

Summary

The creatine phosphokinase (CPK) content of cerebrospinal fluid (CSF) specimens of each of 100 patients with various neurologic disorders was determined. Eight of the patients had increased values, five of whom had been diagnosed as having active multiple sclerosis. A significant correlation has been established and acute demyelination is proposed to be incorporated into the list of causes of increased CPK values in CSF.

References

1. Lisak, R. P., and Graig, F. A.: Lack of diagnostic value of creatine phosphokinase assay in spinal fluid. *J.A.M.A.* **199**: 750-751, 1967.
2. Eisen, A. A., and Sherwin, A. L.: Serum creatine phosphokinase activity in cerebral infarction. *Neurology* **18**: 263-268, 1968.
3. Nathan, M. J.: Creatine phosphokinase in the cerebrospinal fluid. *J. Neurol. Neurosurg. Psychiat.* **30**: 52-55, 1967.
4. Schiavone, D. J., and Kaldor, J.: Creatine phosphokinase levels and cerebral disease. *Med. J. Aust.* **2**: 790-792, 1965.
5. Acheson, J., and others: Serum-creatine-kinase levels in cerebral vascular disease. *Lancet* **I**: 1306-1307, 1965.
6. Dubo, H., and others: Serum-creatine-kinase in cases of stroke, head injury, and meningitis. *Lancet* **2**: 743-748, 1967.
7. Herschkowitz, N., and Cummings, J. N.: Creatine kinase in cerebrospinal fluid. *J. Neurol. Neurosurg. Psychiat.* **27**: 247-250, 1964.
8. Conn, R. B., Jr., and Anido, V.: Creatine phosphokinase determination by the fluorescent ninhydrin reaction. *Amer. J. Clin. Path.* **46**: 177-184, 1966.
9. Willis, C. E.; Nosal, T., and King, J. W.: Automated-fluorometric determination of serum creatine phosphokinase by the ninhydrin reaction, p. 1-4, in *Automation in Analytical Chemistry*. Ardsley, N. Y.: Technicon Corporation, 1967.
10. De Castro, S.; Salazar, V., and Ojeda, J.: Modificaciones de la creatinfosfoquinasa (CFQ) sérica en las intervenciones quirúrgicas. *Med. Esp.* **51**: 110-115, 1964.
11. Fowler, W. M., Jr., and Pearson, C. M.: Diagnostic and prognostic significance of serum enzymes: II. Neurological diseases other than muscular dystrophy. *Arch. Phys. Med.* **45**: 125-130, 1964.
12. Okinaka, S., and others: Serum creatine phosphokinase; activity in progressive muscular dystrophy and neuromuscular diseases. *Arch. Neurol.* **4**: 520-525, 1961.
13. Salazar, V.; De Castro, S., and Ojeda, J.: Algunos aspectos clínicos de la creatinfosfoquinasa (CFQ) sérica. *Rev. Clin. Exp.* **93**: 243-252, 1964.