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Cerebral Blood Flow and Metabolism in the Wernicke–Korsakoff Syndrome *

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Summary. Cerebral blood flow and metabolism were measured by the iodoantipyrine-4-^{131}I method in nine patients and by the nitrous oxide method in three patients with the Wernicke–Korsakoff syndrome.

Cerebral blood flow and cerebral oxygen and glucose consumption were strikingly reduced from the normal, whereas cerebral vascular resistance was increased.

Total cerebral metabolism and blood flow may be greatly reduced even though the cerebral metabolic defect is confined to circumscribed anatomical areas. Profound reduction in brain metabolism is not necessarily reflected in alterations of consciousness or awareness as has been previously suggested, or in electroencephalographic abnormalities. This appears to provide cogent support for the neurophysiological principle that disturbance of consciousness is a function of the location of the lesion, not the over–all degree of metabolic defect.

The absence of improvement of cerebral metabolic functions in two patients who were restudied after an additional 2 to 3 weeks of treatment confirms the clinical impression of incomplete recovery in many such patients.

Introduction

The syndrome first described in 1881 by Carl Wernicke (1) and presently considered to be characterized by disturbances in ocular motility, dementia, severe dysfunction of retentive memory, ataxia, and peripheral neuritis has been the object of many clinical and neuropathological studies (2–7). It is most frequently observed in severe chronic alcoholics and is thought to be the consequence of nutritional deficiency. The mental abnormalities may be permanent despite improvement of the other clinical manifestations after adequate dietary therapy (8–10). This study was undertaken to measure the cerebral circulatory and metabolic defects that occur in this syndrome as a means of further identifying its basic pathophysiology.

Methods

Cerebral blood flow (CBF) was measured by the iodoantipyrine-4-^{131}I method (IAP) (11) ten times in nine patients and by the nitrous oxide method of Kety and Schmidt (12) four times in three patients. The diagnosis was a clinical one and depended upon the criteria now accepted as characteristic of Wernicke–Korsakoff syndrome (13). All the patients were known alcoholics in the age range from 35 to 64. They were initially studied from 5 to 28 days after admission to the hospital and initiation of appropriate dietary therapy. Two patients were restudied after an additional 2 to 3 weeks of treatment.

A complete neurological examination including a detailed mental status evaluation was done at the time of the blood flow studies. A scoring system yielding a minimum of four points and a maximum of sixteen points was established by classifying the signs in four major categories: disturbances in ocular motility, mental abnormality, peripheral neuropathy, and cerebellar ataxia in order to compare the degree of the clinical and cerebral circulatory and metabolic abnormalities. In no instance

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was there evidence of accompanying uremia, hepatic encephalopathy, dehydration, or electrolyte imbalance.

In the nitrous oxide studies patients inhaled the gas for 14 minutes to avoid error that might be introduced by low blood flow values. Each recorded value for IAP CBF represents the mean of several minute-to-minute determinations (11). There were no anthropological differences in head size or shape between the control and experimental groups and no mechanical variations in the procedure as conducted on the two groups. In the N_2O procedures arterial and venous samples for gas analyses were drawn immediately before, at the midpoint of, and immediately after the procedure. The final arteriovenous difference used in calculation of CMR_{O_2} was the mean of these. The final arterial–venous oxygen difference used in the IAP CMR_{O_2} calculations was the mean of at least three such determinations made simultaneously with the blood flow procedure. Blood oxygen content was measured by the manometric method of Van Slyke and Neill (14). Blood pH, P_{CO_2}, and P_{O_2} were determined with an Instrumentation Laboratories electrode system maintained at 37° C. The electrodes were calibrated before and after each determination with previously analyzed gases for P_{O_2}, P_{CO_2}, and for pH on National Bureau of Standards buffers. Appropriate corrections of P_{O_2}, P_{CO_2}, and pH were made for effects of temperature, the metabolic changes occurring in blood with the passage of time, and the measured difference between the response of the oxygen electrode to gases and to blood (15–17).

Blood glucose was determined by the enzymatic method described by Washko and Rice (18). Each arterial–cerebral venous difference is the mean of at least four separate arterial and venous samples drawn during the course of each blood flow determination. All analyses were made in duplicate. Accuracy of P_{O_2} and P_{CO_2} determinations was checked by the calculated result from oxygen content with Severinghaus' nomogram and the Henderson–Hasselbalch equation; mean arterial pressure was monitored on a Sanborn recorder for direct arterial puncture. An electroencephalogram was made in all but two instances within 48 hours of the time of the blood flow study. Cerebral metabolic rate of oxygen consumption (CMR_{O_2}), cerebral glucose consumption (CMR_{gl}), and cerebral vascular resistance (CVR) were calculated in the conventional manner (11).

Results

The cerebral circulatory and metabolic functions are summarized in Table I. The controls for the antipyrine-^{131}I studies were in a comparable age range (11), and the controls from the nitrous oxide studies were obtained from five hospitalized patients in a similar age group without demonstrable cerebral disease. The IAP cerebral blood flows varied from 554 to 829 ml per minute, with a mean of 652 ml per minute. This represents a reduction of 34% from the

TABLE I

*Cerebral circulatory functions in the Wernicke-Korsakoff syndrome**

No.	Subject	Age	Sex	CBF		CMR_{O_2}		CMR_{gl}		CVR		MAP
				IAP	N_2O	IAP	N_2O	IAP	N_2O	IAP	N_2O	
		years		*ml/min*	*ml/min/100 g brain*	*ml/min*	*ml/min/100 g brain*	*mg/min*	*mg/100 g brain*	*U*		*mm Hg*
1.	F. E.	54	F		30		2.2		2.4		3.5	104
2.	S. E.	35	F		46		2.0				2.4	110
3.	A. M.	55	M		38		1.4		3.0		2.7	104
				561†	28	31	1.5	58	2.9	23.7	4.7	133
4.	H. C.	44	M	554		27				25.6		142
5.	J. R.	51	F	564		34				18.3		103
6.	B. M.	63	F	599		39				17.7		106
7.	M. W.	50	M	655		48		65		18.5		121
8.	K. C.	38	F	683		38		53		16.5		113
				604‡		33		60				
9.	W. M.	52	M	723		42		88		10.9		82
10.	T. J.	64	M	752		42		48		12.2		92
11.	C. W.	35	M	829		58		90		13.9		115
Mean		51		652	36	39.2	1.8	66.2	2.8	16.9	3.3	110
± SE				28		3.1		6.3		1.5		4.7
Control mean				996	65	62.8	4.0	94.0	5.9	9.0	1.5	88
± SE				38		3.2		6.2		0.4		1.8
p				<0.01		<0.01		<0.02		<0.01		<0.01

* CBF = cerebral blood flow; CMR_{O_2} and CMR_{gl} = cerebral metabolic rate of oxygen and glucose consumption; CVR = cerebral vascular resistance; MAP = mean arterial pressure; IAP = the iodoantipyrine-4-^{131}I method; N_2O = the nitrous oxide method.

† Repeat study 29 days later.

‡ Repeat study 15 days later.

TABLE II

*Cerebral metabolic functions in the Wernicke-Korsakoff syndrome**

No.	Subject	$(a-v)_{O_2}$	$(a-v)_{gl}$	$\frac{(a-v)_{gl}}{(a-v)_{O_2}}$	CRQ	Sa_{O_2}	Pa_{CO_2}	apH	aCO_2	Pv_{O_2}	Pv_{CO_2}	Hgb
		vol/ 100 ml	*mg/ 100 ml*			%	*mm Hg*		*vol/ 100 ml*	*mm Hg*	*mm Hg*	*g/100 ml*
1.	F. E.	7.4	8.0	1.09	0.87	95.0	32.9	7.450	42.4	41.1	41.5	11.7
2.	S. E.	4.2			1.04	91.1	38.3	7.463	42.7	36.0	45.0	12.2
3.	A. M.	3.8	7.9	2.10	0.91	93.3	32.5	7.476	49.6	25.5	38.7	7.4
		5.4†	10.3	1.89	1.10	94.5	39.6	7.435	50.4	33.1	48.6	10.1
4.	H. C.	4.8			0.97	88.9	37.5	7.435	45.6	38.5	46.2	10.4
5.	J. R.	6.0			0.94	89.0	38.8	7.445	49.7	39.5	48.5	14.6
6.	B. M.	6.6			0.88	90.3	46.9	7.388	54.4	29.0	57.3	11.1
7.	M. W.	7.3	10.0	1.37	1.01	90.0			44.1	30.6		12.7
8.	K. C.	5.6	7.8	1.39	0.90	95.5	37.3	7.400	44.9	33.2	47.5	9.9
		5.4‡	10.0	1.81	0.98	95.7	37.7	7.406	42.3	30.1	46.9	10.8
9.	W. M.	5.8	12.2	2.10	1.05	91.2	42.5	7.370	46.0	29.3	50.1	13.9
10.	T. J.	5.6	6.4	1.14	0.75	92.8	38.4	7.436	48.9	28.6	47.3	9.1
11.	C. W.	7.1	10.9	1.54	0.94	88.7	39.6	7.386	43.2	30.4	51.5	13.1
Mean		5.8	9.3	1.60	0.95	92.0	38.5	7.425	46.5	32.7	47.4	11.3
± SE		0.3	0.6	0.13	0.03	0.7	1.2	0.008	1.1	1.3	1.4	0.6
Control mean		6.4	9.2	1.37	0.96	94.1	41.0	7.385	46.0	32.0	49.0	13.2
± SE		0.3	0.7	0.14	0.10	1.2	1.6	0.020	0.7	1.2	1.9	0.3
p		>0.1	>0.7	>0.6	>0.8	>0.2	>0.5	>0.2	>0.6	>0.8	>0.4	<0.01

* $a-v_{O_2}$ and $a-v_{gl}$ = arterial–cerebral venous oxygen and glucose differences; CRQ = cerebral respiratory quotient; Sa_{O_2} = arterial oxygen saturation; Pa_{CO_2} = arterial carbon dioxide tension; apH and aCO_2 = arterial pH and CO_2; Pv_{O_2} and Pv_{CO_2} = venous O_2 and CO_2 tension; Hgb = hemoglobin.
† Repeat study 29 days later.
‡ Repeat study 15 days later.

control value of 996, a statistically significant difference with a p value less than 0.01. The nitrous oxide values varied from 28 to 46 ml per minute per 100 g brain, as compared to the mean normal control of 65. CMR_{O_2} as calculated for the IAP method varied from 27 to 58 ml O_2 per minute with a mean of 39. This is significantly different from the normal mean of 63 ml O_2 per minute, with p value less than 0.01. A reduction of similar magnitude was noted in CMR_{O_2} measured by the N_2O method (1.8 ml O_2 per minute per 100 g brain as compared to a normal value of 4.0).

Mean CMR_{gl} by IAP measurement was 66 mg glucose per minute. This is a statistically significant reduction from the normal value of 94 (p value < 0.02). Mean CMR_{gl} in three measurements by the N_2O method was 2.8 mg glucose

TABLE III

Clinical summary of the Wernicke–Korsakoff syndrome

No.	Subject	EEG	Pertinent clinical findings*						Days of treatment	Liver function
			EOM	Nys	Psy	Ment	PN	Ataxia		
1.	F. E.	Abnormal	—	+	+	+	+	+	5	Cirrhosis
2.	S. E.	Normal	—	+	—	+	—	—	28	Impaired
3.	A. M.	Abnormal	+	+	+	+	+	+	6	Cirrhosis
		Abnormal	—	+	—	+	—	—	35	Cirrhosis
4.	H. C.	Normal	—	+	+	+	+	+	6	Cirrhosis
5.	J. R.	Normal	—	+	+	+	+	+	7	
6.	B. M.	Normal	—	+	+	+	—	—	8	Normal
7.	M. W.	Normal	+	+	+	+	+	—	9	Impaired
8.	K. C.	Normal	—	+	—	+	+	+	20	Normal
		Normal	—	+	—	+	+	+	35	Normal
9.	W. M.	Abnormal	—	+	+	+	—	—	20	Normal
10.	T. J.		—	—	+	+	—	—	14	Normal
11.	C. W.		—	+	—	+	—	—	8	Impaired

* Abbreviations: EOM = abnormality of extraocular movement; nys = nystagmus; psy = Korsakoff's psychosis; ment = mental confusion and disorientation; PN = peripheral neuropathy.

per 100 g brain as compared to the control value of 6.0. Mean CVR by IAP measurement was 17 as compared to a control value of 9.0, a highly significant increase that was reflected in a proportional increase in the N_2O studies.

Table II summarizes the values of the measured blood constituents. Arterial–cerebral venous oxygen and glucose differences, the ratio of the differences of arterial–cerebral venous glucose to oxygen, cerebral respiratory quotient, arterial O_2 saturation, arterial CO_2 tension, venous O_2 tension, arterial pH, and arterial and jugular CO_2 contents were all within normal limits, showing no significant variation from the controls. There was a mild anemia in the patient group as compared to the controls.

Table III summarizes the pertinent clinical data. There was no correlation between CBF and clinical severity or between CMR_{O_2} and clinical severity. The electroencephalogram was abnormal in three of the patients with the most severe clinical signs. The abnormalities consisted of diffuse irregular theta rhythms. None of these patients showed any disturbance of consciousness at the time the EEG was made.

Discussion

The reduction in total CBF as well as CBF per unit weight of brain tissue, decreased CMR_{O_2} and CMR_{gl}, and increased CVR are the major cerebral circulatory and metabolic abnormalities in patients with the Wernicke–Korsakoff syndrome. The increased CVR can be partially accounted for mathematically by the elevated mean arterial pressure in this group of patients, but a clue to the physiological explanation for the increased CVR may be found in the observation that the mean arterial–cerebral venous oxygen and glucose differences were normal. A reduction of CBF in the presence of normal brain metabolism is accompanied by widened arterial–cerebral venous oxygen and glucose differences (19–22), and those instances in which cerebral metabolic rate is reduced as a consequence of primary reduction in blood flow manifest increased oxygen and glucose extraction (20, 23, 24). Although the normal values for oxygen and glucose extraction in these patients in the face of profoundly reduced CMR_{O_2} and CMR_{gl} do not prove that the reduction of brain metabolism is the primary event, the reasoning from the analogy of the above cited examples would suggest that this is so. In this event the elevated vascular resistance is another example of the well-known and remarkable property of the cerebral vasculature to regulate itself to meet the lessened demand of the tissues for blood.

This is consistent with what is known to occur in other metabolic and toxic encephalopathies such as myxedema, methyl alcohol poisoning, general anesthesia, pernicious anemia, and insulin hypoglycemia (25–30). Although mean jugular venous P_{O_2} was normal in this study, in four instances a striking reduction from normal of CBF and CMR_{O_2} was associated with jugular P_{O_2} values well above the usual normal range, further suggesting the inability of the cerebral cells to extract oxygen normally.

An alternative explanation for the reduced brain metabolism in these patients is that CBF is reduced as a consequence of occlusive cerebral vascular disease or a "vasculitis" in the Wernicke–Korsakoff syndrome. Although this hypothesis cannot be excluded absolutely on the basis of these data, it seems unlikely. There is no pathological confirmation of such a phenomenon. In addition, as has been cited above, cerebral hemodynamic studies in occlusive cerebral vascular disease due to hypertension or atherosclerosis or both demonstrate that there is increased oxygen extraction as CBF decreases.

The pattern of relationship of normal arterial–cerebral venous oxygen differences with depressed CMR_{O_2} is consonant with the clinical evidence suggesting the Wernicke–Korsakoff syndrome to be a cerebral metabolic disorder sometimes of striking reversibility. The results do not differentiate between a toxic and a nutritional cause for the metabolic disorder, but clinical and pathological evidence clearly shows that it is the latter. The striking pathological lesions in these patients attest to the morphological disturbance that can occur as a consequence of a nutritional defect. A similar relationship exists in pernicious anemia (vitamin B_{12} deficiency), although the cerebral pathologic lesion in this disorder is not so distinctive as the spinal lesion. If the site of the pathology is a clue to the anatomical localization of the metabolic defect in the Wernicke–Korsakoff

syndome, one must conclude that thiamine deficiency has a specific effect on the metabolism of cells in the periaqueductal and periventricular gray matter, the mammillary bodies, the dorsomedial nuclei of the thalamus, the hypothalamus, the cerebellum, the hippocampi, and the fornices (3, 7), sparing large areas of the brain, specifically the cerebral cortex, which lacks characteristic lesions. These data further clearly demonstrate that fairly localized metabolic defects may result in striking reduction of total cerebral blood flow and metabolism. This degree of reduction in brain metabolism is usually thought to be accompanied by altered states of awareness of significant degree (general anesthesia, hypoglycemic coma, hepatic encephalopathy, elevated blood alcohol, and so forth), but our evidence shows convincingly that this relationship is not constant, and that disturbance of consciousness is a function of the location of the lesion, not the degree of metabolic defect, for drowsiness was not a characteristic of the clinical state of these patients. The data on the two patients who were restudied after an additional 2 to 3 weeks of treatment (A. M. and K. C.) confirm the clinical observation that recovery in this illness is usually incomplete. It is well known that the mental disorders, particularly the disturbance of retentive memory, may persist for months and even indefinitely. As a matter of fact, some degree of residual abnormality is the rule. In these two patients there was no improvement in brain blood flow or metabolism.

The normal cerebral respiratory quotient in these patients was somewhat surprising, since it might be theorized that the co-carboxylase defect of thiamine deficiency with its resultant alteration of aerobic glucose metabolism might significantly reduce RQ, perhaps by resultant metabolism of cerebral lipids. If this occurs, it was not reflected in our study, perhaps because of the thiamine treatment that all these patients had received in the interval between the time of hospital admission and the study.

We cannot explain the lack of correlation between CBF or CMR_{O_2} and clinical severity according to the arbitrary system described above; probably this is a reflection of the inadequacy of such a clinical grading scheme.

The occurrence of diffuse electroencephalographic abnormalities of a nonspecific nature in only three of these patients, none of whom had altered consciousness, strongly indicates that EEG abnormalities do not necessarily occur in altered cerebral metabolic states.

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