DISTRIBUTION OF IODINE IN BLOOD SERUM AND IN CEREBROSPINAL FLUID

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Conflicting reports in the literature on the amount and distribution of iodine in the blood and in the cerebrospinal fluid suggested the reinvestigation of these problems with reliable methods. The iodine contents of the serum and spinal fluid were determined for 6 patients who were free from meningeal disorders and had normal spinal fluid proteins. To a second group of 8 similar patients approximately 0.1 Gm. of inorganic iodine in the form of compound solution of iodine U. S. P. was administered daily for three to seven days before the samples of spinal fluid were obtained. Organic iodine in the form of thyroid was given instead of inorganic iodine to an additional patient. Finally, 1 patient with meningovascular syphilis and high spinal fluid proteins was studied. The recently developed permanganate acid ashing method of Riggs and Man[1] avoids the positive errors of previous methods. In addition, in serum by precipitation with zinc sulfate and sodium hydroxide the diffusible inorganic iodine was differentiated from the precipitable (protein-bound), nondiffusible iodine.[2] Furthermore, the determinations were made in duplicate on large aliquots of cerebrospinal fluid obtained in the preparation of patients for pneumoencephalography.

The older literature on cerebrospinal fluid iodine has been reviewed by Katzenelbogen.[3] With the exception of the recent work of Klassen,

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1. Riggs, D. S., and Man, E. B.: A Permanganate Acid Ashing Micromethod for Iodine Determinations: I. Values in Blood of Normal Subjects, J. Biol. Chem. **134**:193, 1940.

2. Man, E. B.; Smirnow, A. E.; Gildea, E. F., and Peters, J. P.: Serum Iodine Fractions in Hyperthyroidism, J. Clin. Investigation **21**:773, 1942.

3. Katzenelbogen, S.: The Cerebrospinal Fluid and Its Relation to the Blood, Baltimore, Johns Hopkins Press, 1935.

Bierbaum and Curtis,[4] spinal fiuid iodine has been estimated by older methods which either were not sufficiently sensitive or were subject to positive errors. Consequently, some authors [5] have found considerable amounts, 10 to 20 micrograms per hundred cubic centimeters, while others [6] have obtained the barest traces, even in patients who had been ingesting large amounts of iodine for several months. It is obvious that with this uncertainty as to methods the older data on the relation of serum iodine and cerebrospinal fluid iodine must be interpreted with caution.

METHODS

The spinal fluid used in these studies was collected from each patient when the cerebrospinal system was drained for pneumoencephalographic examination. The puncture was made in the third or fourth lumbar space, and as each 10 cc. of fluid was removed the same amount of air was injected. The first 10 cc. of fluid was taken in a separate tube for cytologic and serologic examination, and the rest was collected in a chemically clean flask for the chemical studies. No iodine was used in the preparation of the patient, and special precautions were taken to see that no iodine was free in the room air.

Iodine was determined on duplicate aliquots of spinal fluid by the permanganate acid ashing method of Riggs and Man.[1] Most aliquots were large, 20 to 80 cc., a factor which increased the accuracy of the determinations. In 4 instances smaller amounts were used, and this fact has been indicated in the table.

Proteins were measured by the Denis-Ayer [7] method for cerebrospinal fluid proteins. The samples of blood were taken shortly before the lumbar puncture. The serum was analyzed for total iodine and protein-bound iodine by methods previously described.[8]

DATA

A variety of patients were studied, as indicated in the table. Six patients presenting various symptoms of early intellectual deterioration or unexplained convulsions, but free from meningitis, tumor of the brain or syphilis, who had not received any iodine except minute amounts in the hospital diet, constituted the

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6. Cruchet, R.: Valeur de la perméabilité méningée en neurologie infantile, Compt. rend. Soc. de biol. **2**:591, 1904. Catton, J. H.: Studies of the Spinal Fluid During Iodid Medication by Mouth, J. A. M. A. **67**:1369 (Nov. 4) 1916. Cohen, H.: The Passage of Iodine into the Cerebro-Spinal Fluid, Lancet **1**:127, 1924. Sicard, J. A., and Brecy, M.: Méningite cérébrospinale ambulatoire curable. Cytologie du liquide céphalo-rachidien, Bull. et mém. Soc. méd. d. hôp. de Paris **18**:369, 1901.

7. Ayer, J. B.; Dailey, M. E., and Fremont-Smith, F.: Denis-Ayer Method for the Quantitative Estimation of Protein in the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **26**:1038 (Nov.) 1931.

8. Riggs and Man.[1] Man and others.[2]

first group. A second group of 8 similar patients were given by mouth 30 minims (2 cc.) of compound solution of iodine U. S. P. daily for two to seven days before withdrawal of their spinal fluid. One patient, case 15, with meningovascular

Comparison of Iodine in the Blood Serum and in the Cerebrospinal Fluid

		Serum Iodine		Spinal Fluid			
Case	Age, Yr.	Total, Micrograms per 100 Cc.	Precipitable, Micrograms per 100 Cc.	Iodine, Micrograms per 100 Cc.	Aliquots, Cc.	Protein, Mg. per 100 Cc.	Comment and Results of Pneumoencephalographic Examination
				No Iodine Administered			
1	44	5.0	...	0.2	50	16.7	Progressive degenerative cerebral disorder; cortical atrophy and dilatation of ventricles
2	26	5.6	...	0.2	50	27	Injury to left frontal region of head, followed by convulsions; dilatation of left lateral ventricle
3	28	4.9	...	0.1	60	30	Psychopathic personality; low intelligence; cortical atrophy; dilatation of ventricles
4	44	8.8	...	0.4	80	11	Intellectual deterioration; cortical atrophy
5	31	5.0	...	<0.1	35	18	Chronic headaches; multiple complaints; bilateral cortical atrophy; dilatation of ventricles
6	26	6.1	5.4	0.1	25	32	Rare convulsions; queer compulsive behavior
				After Oral Administration of Compound Solution of Iodine 2 to 7 Days			
7	26	342.0	7.7	3.0	12	39	Ventricles not visualized
8	33	94.0	7.3	1.0	30	25	Repeated convulsions; bilateral cortical atrophy and dilatation of ventricles
9	55	29.0	5.9	1.6	7	48	Depressed and agitated mood with generalized tremor
10	36	121.0	5.9	2.7	9	32	Paranoid schizophrenia
11	38	303.0	5.7	11.8	30	85	Depression and failing memory; bilateral cortical atrophy; dilatation of ventricles
12	58	522.0	5.8	6.1	15	11	Cerebral arteriosclerosis; slight cortical atrophy; hydrocephalus ex vacuo
13	46	.....	6.3	3.3	35	40	Cortical scarring after head injury, with distortion of temporal horn of left ventricle; queer apathetic behavior; diabetes mellitus
14	27	.....	...	5.0*	25	42	Apathy and confusion; schizophrenia (?); ventricles not visualized
15	44	873.0	...	22 *	35	160	Meningovascular syphilis, positive Wassermann reaction
				After Administration of Desiccated Thyroid, 10 grains (0.65 Gm.) Daily for Two weeks and 15 grains (0.975 Gm.) for Third Week			
16	50	13.9	9.6	0.5	27	23	Depression; semistupor; basal metabolic rate —15 per cent; moderate cortical atrophy

* Blood was present in the spinal fluid.

syphilis was also given compound solution of iodine. Finally, 1 patient, case 16, with stupor of unknown origin, was given desiccated thyroid, 10 grains (0.65 Gm.) daily for two weeks and then 15 grains (0.975 Gm.) for one week previous to withdrawal of cerebrospinal fluid.

RESULTS

As can be seen in the table, in the spinal fluid of patients to whom no iodine was given only traces, less than 0.1 to 0.4 microgram per hundred cubic centimeters, of iodine were found in contrast to relatively large amounts, 4.9 to 8.8 micrograms per hundred cubic centimeters, in the blood serum. When sufficient inorganic iodine had been given to increase the serum iodine to as much as 522 micrograms per hundred cubic centimeters, only a very slight increase in iodine occurred in the cerebrospinal fluid. It is noteworthy that in the patient with meningitis, with a total iodine content of the serum of 873 micrograms per hundred cubic centimeters, considerable iodine entered the spinal fluid. Although there were red blood cells in the spinal fluid of this patient, the elevation in iodine was greater than would have been expected from the number of erythrocytes. Furthermore, in 2 patients high spinal fluid proteins tended to be associated with a high iodine content. Administration of desiccated thyroid to the patient in case 16 increased greatly the iodine in the serum but did not appreciably affect the iodine in the cerebrospinal fluid.

COMMENT

It can be concluded that only traces of iodine normally occur in the cerebrospinal fluid. The large aliquots of fluid used and the extreme sensitiveness of the method employed establish this point conclusively. These results confirm the observations of Klassen, Bierbaum and Curtis,[4] who used a dichromate ashing method but had less fluid for analysis.

It is noteworthy that the readily diffusible inorganic iodine did not pass in any quantity from the serum into the spinal fluid. The diffusibility of serum inorganic iodine has been previously demonstrated by Riggs, Lavietes and Man [9] in the case of red blood cell and cellophane membranes. It is clear therefore that serum inorganic iodine is prevented by some barrier from passing into the spinal fluid. The experiments of Wallace and Brodie [10] on dogs suggested such a barrier. They, however, used enormous amounts of iodine and employed one of the older macrochemical methods for iodine, thereby rendering uncertain the interpretation of their results in the case of human beings.

The protein-bound iodine, probably hormonal iodine, of serum showed no tendency to enter the spinal fluid, as might have been expected from the fact that it is not readily diffusible.

These results constitute further evidence of the unique nature of the cerebrospinal fluid. Chlorides resemble iodides so far as ionization

9. Riggs, D. S.; Lavietes, P. H., and Man, E. B.: Investigations on the Nature of Blood Iodine, J. Biol. Chem. **143**:363, 1942.

10. Wallace, G. B., and Brodie, B. B.: On the Source of the Cerebrospinal Fluid: The Distribution of Bromide and Iodide Throughout the Central Nervous System, J. Pharmacol. & Exper. Therap. **70**:418, 1940.

and diffusion are concerned; yet they are present in larger amounts in spinal fluid than in blood serum. Iodides, on the other hand, are found only in traces in the spinal fluid and, unlike the chlorides, appear to be selectively prevented from entering the spinal fluid. In contrast to the chlorides, calcium compounds behave in a manner similar to the iodides. While present in the spinal fluid in considerable quantities, calcium seems to be selectively prevented from diffusing from serum to spinal fluid in many conditions associated with hypercalcemia, in which much of the calcium is known to be in the diffusible form.[11] These observations lend support to the conception of the existence of a special blood–spinal fluid barrier.

CONCLUSIONS

Only minute amounts of iodine, less than 0.1 to 0.4 microgram per hundred cubic centimeters, are present in the spinal fluid, in contrast to relatively large amounts, 4.9 to 8.8 micrograms per hundred cubic centimeters, in the blood serum.

When the inorganic iodine of serum is increased to more than 100 micrograms per hundred cubic centimeters for days or a week, only a slight rise of 1 to 6 micrograms per hundred cubic centimeters occurs in the spinal fluid unless the protein content of the cerebrospinal fluid is also elevated.

There is, therefore, a definite barrier for iodine between the serum and the cerebrospinal fluid.

These observations add further evidence indicating the unique nature of cerebrospinal fluid as compared with other body fluids. They illustrate the peculiarly selective properties of the blood–cerebrospinal fluid barrier.

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11. Merritt, H. H., and Bauer, W.: The Equilibrium Between Cerebrospinal Fluid and Blood Plasma: IV. The Calcium Content of Serum, Cerebrospinal Fluid, and Aqueous Humor at Different Levels of Parathyroid Activity, J. Biol. Chem. **90**:233, 1931.