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Clinical Significance of Oxidizable Substances in the Cerebrospinal Fluid

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Determination of the sugar level in the CSF is the main diagnostic procedure in meningitis. A decrease in the sugar level is accompanied by an increase in the lactic acid level, as has been shown by Geldrich [5] in tuberculous, and by De Sanctis et al. [3] in purulent, meningitis. Determination of lactic acid is so laborious as to make it unsuitable for diagnostic purposes. Apart from the concentration of lactic acid, those of pyruvic acid, uric acid, citric acid and other substances are also increased in the CSF, but a quantitative estimation of all these would entail too much work. Oxidimetry offers a suitable method for gaining information about the total amount of all organic substances. Some of them (e. g. pyruvic acid and uric acid) are easily oxidized at room temperature, while lactic acid is generally oxidized at 100°C. The oxidimetric method yields useful data concerning CSF values under physiological and pathological conditions.

Method

Cold oxidation is carried out at 21°C in acid medium with cerium sulphate, hot oxidation at 100°C in alkaline medium with potassium permanganate. Details of these procedures have been published [1, 2]. The oxidizable residuum obtained at 100°C means the number of milli-equivalents (normal ml) of potassium permanganate consumed for the oxidation of 1 litre of protein- and sugar-free spinal fluid. The normal value is 30 to 60 meq. Cold oxidation value means the number of 1/10 meq (n/10 ml) of cerium sulphate consumed for the oxidation of 1 litre of protein-free spinal fluid at 21°C during the indicated time. At 21°C practically no sugar is oxidized. Normal values of cold oxidation are, in 10 minutes 10 to 20; in 4 hours 30 to 60; in 24 hours 60 to 80 tenths meq (n/10 ml).

Results

Data regarding patients suffering from purulent meningitis are assembled in Table I. Cold oxidation was neglected in the first five cases. It can be seen that no close correlation exists between cell count, protein and sugar contents. The amount of oxidizable substances (cold and hot alike) rose considerably in all cases. Oxidation values became normal along with the decrease in cell count. Disintegration

TABLE I

Purulent meningitis

No.	Name	Age, years	Protein, mg per 100ml	Cell count	Sugar, mg per 100 ml	Oxidizable residue	Cold oxidation	
							10'	4 hrs
1.	K. K.	1	162	8 500	61	149	—	—
2.	U. Sz.	2	300	11 200	56	132	—	—
3.	I. R.	5	150	10 000	3	206	—	—
4.	K. T.	1	144	2 000	2	129	—	—
5.	I. Sz.	32	60	700	27	132	—	—
6.	G. H.	8	140	2 000	45	126	—	130
7.	I. B.	6	80	2 800	45	116	39	118
8.	I. P.	3	150	4 000	39	110	55	140
9.	Sz. E.	32	225	6 500	10	227	80	240
10.	I. C.	42	228	5 200	29	112	35	185
11.	G. L.	30	170	2 500	12	146	15	128
12.	I. N.	1½	128	6 500	39	136	—	128
13.	I. K.	5	70	1 200	28	—	26	100
14.	F. P.	36	225	550	8	—	40	258
15.	T. M.	4 ms	215	4 800	9	160	33	182

of white blood cells does not explain the high value of oxidizable residuum at the onset of the disease, since that residuum decreased in proportion with the decrease in cell count. The sugar level is usually low, but may also be normal.

In acute tuberculous meningitis (Table II), both the hot and the 4-hour cold oxidation values rose, but less than in purulent meningitis. In some cases the 10-minute cold oxidation values, too, exceeded the normal level. All pathologic values returned gradually to normal along with the subsidence of the disease. For details, see our earlier papers [1, 2].

In cases of serous meningitis (Table III), the sugar level tended to decrease, while hot and 4-hour cold oxidation values showed an upward tendency. The decrease in sugar and increase in oxidation values were less marked than in most cases of purulent or tuberculous meningitis.

Disturbances of the sensorium were the predominant clinical manifestation of meningoencephalitis (Table IV). Owing to the meningitic involvement, both the protein contents and the cell count increased. In contradistinction to cases of pure serous meningitis, the sugar values were increased.

In cases of encephalitis (Table V) accompanied by grave disturbances of the sensorium but no meningeal reaction, the CSF protein level and cell count remained normal, while the

TABLE II

Tuberculous meningitis

No.	Protein mg per 100 ml	Cell count	Sugar mg per 100 ml	Oxidizable residue	Cold oxidation	
					10'	4 hrs
1.	150	60	13	95	35	120
2.	102	180	18	106	25	115
3.	120	230	34	108	35	163
4.	80	140	36	94	20	98
5.	133	100	23	112	20	105
6.	300	40	30	126	25	114
7.	170	80	36	118	45	175
8.	112	60	17	120	45	120
9.	100	100	40	100	20	90
10.	270	765	40	107	30	90
11.	330	450	11	110	40	120
12.	124	375	7	107	20	125
13.	245	160	17	94	40	105
14.	108	100	51	91	25	135
15.	133	135	17	82	15	90
16.	300	125	3	144	40	170
17.	130	350	2	120	20	110
18.	135	80	7	141	40	180

TABLE III

Serous meningitis

No.	Name	Protein, mg per 100 ml	Cell count	Sugar, mg per 100 ml	Oxidizable residue	Cold oxidation	
						10'	4 hrs
1.	S. M.	45	650	55	85	30	86
2.	I. M.	90	750	59	64	15	80
3.	J. A.	52	85	46	73	25	67
4.	F. B.	72	950	40	81	30	105
5.	É. U.	120	1600	62	102	30	95
6.	Á. K.	42	605	45	74	20	80
7.	Á. Sz.	76	1060	42	72	20	90
8.	E. T.	150	3000	33	92	40	95
9.	Zs. K.	40	180	52	74	15	85

TABLE IV

Meningoencephalitis

No.	Name	Protein, mg per 100 ml	Cell count	Sugar, mg per 100 ml	Oxidizable residue	Cold oxidation	
						10'	4 hrs
1.	E. P.	45	220	74	77	20	80
2.	T. H.	80	750	60	73	10	85
3.	M. P.	70	450	77	82	25	95
4.	P. F.	45	95	94	75	30	100
5.	M. R.	112	450	83	86	25	90

TABLE V

Encephalitis

No.	Name	Protein, mg per 100 ml	Cell count	Sugar, mg per 100 ml	Oxidizable residue	Cold oxidation	
						10'	4 hrs
1.	G. P.	18	3	116	46	10	55
2.	F. M.	36	4	62	52	15	55
3.	A. G.	18	3	94	43	15	60
4.	R. R.	32	5	86	48	10	60
5.	E. S.	15	3	77	60	20	55

TABLE VI

Polyradiculitis

No.	Name	Protein mg per 100 ml	Cell count	Sugar mg per 100 ml	Oxidizable residue	Cold oxidation	
						10'	4 hrs
1.	J. Z.	102	4	55	47	15	55
2.	Á. B.	157	3	58	56	10	50
3.	R. H.	136	3	57	46	15	45
4.	F. C.	128	5	56	52	20	50

sugar level was elevated. The amount of oxidizable substances did not exceed normal values.

In polyradiculitis (Table VI) the CSF protein level was high, while cell count and sugar content were normal, as also the oxidation values.

DISCUSSION

The above partial results are summarized in Table VII. It can be seen that exceptionally quite high cell counts were registered in serous meningitis. Since in purulent meningitis

TABLE VII

Diagnosis	Protein, mg per 100 ml	Cell count	Sugar, mg per 100 ml	Oxid. res. meq/litre	Cold oxidation n/10 meq/litre
Healthy controls			46—68	40—60	32—60
Mean	15—40	0—5	59	50	46
Purulent meningitis	60—300	550—11,000	2—61	110—227	100—258
Mean			28	145	160
Tuberculous meningitis	80—300	100—765	2—51	82—144	90—180
Mean			23	110	123
Serous meningitis	40—150	85—3000	33—62	64—102	67—105
Mean			48	80	87
Meningoencephalitis	45—112	95—750	60—94	73—86	80—100
Mean			78	79	90
Encephalitis	15—36	3—5	62—116	43—60	55—60
Mean			87	50	57
Polyradiculitis	102—157	3—5	55—58	46—56	45—55
Mean			57	50	50

beside an exceedingly high cell count the sugar contents may remain normal or show a slight decrease, the sugar level is not a reliable indicator of the intensity of the inflammatory process. In some cases of serous meningitis the amount of sugar was below normal, nearly similar to the levels observed in the initial phase of tuberculous meningitis; thus its value in differential diagnosis is questionable. In cases of encephalitis with disturbed sensorium where the cell count is elevated owing to the meningeal reaction, the CSF sugar level mostly tended to exceed normal values, the sugar-decreasing action of meningitis having been overcompensated by the sugar-increasing effect of encephalitis. The CSF sugar level was markedly elevated in cases of encephalitis characterized by a disturbed sensorium for several days and a lack of meningeal reaction in the CSF. Except that for protein, all values were normal in polyradiculitis.

It is clear from the Tables that the value for oxidizable residue invariably rose when the meninges revealed signs of inflammation and that no rise occurred if the meninges were not affected. The increase in oxidizable residue depends, thus, on the presence of meningitis. It follows that this value is a more reliable indicator of meningeal involvement than the sugar content, and not merely in purulent but also in other conditions. The oxidizable residue was found to increase in even those cases of meningitis in which this disease would have seemed improbable on the evidence of the normal or supernormal level of sugar. This does not mean that de-

termination of the CSF sugar level is superfluous: the two tests are supplementing each other well.

In some cases of subacute tuberculous meningitis, protein contents and cell count were elevated, and neither the sugar level nor that of the oxidizable residuum provided diagnostic orientation.

Let us now examine the questions (i) which substances are bringing about a rise in the amount of oxidizable residuum; (ii) where are they produced; (iii) how far do they contribute to the reduction of the sugar level?

ad (i). Geldrich [5] and De Sanctis et al. [3] observed an elevated lactic acid level in cases of purulent and tuberculous meningitis. In the same conditions, Ferencz and Boda [4] demonstrated in the CSF an increased level of uric acid, while Ricci et al. [7] high pyruvic and citric acid levels. It is due to a combination of all these substances that the total amount of oxidizable residue is increased.

The rise in the 10-minute oxidation value is chiefly due to uric acid, pyruvic acid and citric acid, since these substances oxidize readily. The rise beyond 10 minutes is chiefly due to lactic acid and presumably some other substances.

ad (ii). In purulent and tuberculous meningitis the concentration of lactic acid rises both in the blood and in the CSF, but the elevation is considerably more pronounced in the latter. An insignificant part of the above-said product gains access to the CSF by way of diffusion, the major part is produced by the inflamed meninges themselves.

ad (iii). The amount of sugar contained in the CSF depends on the blood sugar, the permeability of the meninges, and the degree of sugar splitting. Meningeal permeability is known to be increased in meningitis, while the level of blood sugar depends on dietary factors and fluctuates around the normal value. Except in cases of pronounced hypoglycaemia, increased permeability ought to cause a rise in the CSF sugar level. Varga and Kun [9] found that neither leucocytes nor bacteria were responsible for the diminution of sugar. This is due either to an interaction of leucocytes and bacteria (phagocytosis) [6] or to increased glycolysis in the inflamed meninges [8]. Williams [10], while accepting the theory of phagocytosis, points to the increased metabolism of the cells lining the arachnoid.

The role of phagocytosis is disproved by the facts that phagocytosis is insignificant in tuberculous meningitis and the decrease in the CSF sugar level is pronounced nevertheless; besides, a decrease of the sugar level occurs in viral meningitis, too. It is not only in the subarachnoid space that lactic acid is produced. Owing to increased but imperfect combustion it is mainly in the inflamed meninges that sugar breaks down to lactic acid and other acid products, and this process counteracts the effect of increased permeability. These two factors influence the sugar con-

tents of the CSF, although other pathophysiological factors may also have their role in the effect.

Summary

The amount of oxidizable residue has been studied in the cerebrospinal fluid. After establishing the normal values, the changes observed in different inflammatory conditions of the central nervous system and its membranes have been studied. The value for oxidizable residue was highest in purulent meningitis, markedly elevated in tuberculous meningitis, moderately so in serous meningitis and encephalomeningitis, and normal in cases of encephalitis and polyneuritis. The pathophysiological backgrounds and the diagnostic value of the observed phenomena have been discussed.

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