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METABOLISM OF FAT IN SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

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The white matter of brain contains 60 per cent of fat, half of them being myelin lipids (Autilio et al.[2]). In the lipid layers of the lamellae of the myelin sheat the molecules of cholesterol, galactolipids (cerebrosides) and phospholipids (sphingomyelin) are arranged in a definite architectonic pattern (Hills and Spector[13]).

The demyelinating diseases could be ascribed to some abnormality in the processes of repair and reposition of myelin (Sperry and Waelsch[24]). At the eighth day of wallerian degeneration an accumulation of cholesterol esters is already found (Adams[1]); the synthesis of phospholipids is also increased (Smith[23]), owing probably to the proliferation of the Schwann cells. In allergic experimental encephalomyelitis the metabolism of cholesterol is little changed, but the synthesis of galactolipids and phospholipids is increased[23]; yet in old lesions, similar to those of multiple sclerosis, a decrease of phospholipid and the presence of cholesterol esters were found (Cumings[10]).

Laboratory studies on the lipid metabolism in the demyelinating diseases are almost limited to the researches in multiple sclerosis. The results of the numerous investigations on the lipid metabolism in this disease[22] are not always agreeing. Lafontaine[14, 15] found an increase of the phospholipid and cholesterol levels both in the blood and cerebrospinal fluid. Bernsohn and Namajuska[4] found lower concentrations of the blood phospholipids in their patients than in normal subjects. Gerstl et al.[11], studying the dienoic fatty acids of the blood serum, found lower concentrations in the patients with active disease than in those in the inactive state. Plum and Fog[20], however, failed to demonstrate any definite variation of the blood contents of total lipids, total cholesterol and phospholipids in patients with multiple sclerosis and in their normal material. Green et al.[12] found an increase of the cerebrospinal fluid concentration of cholesterol (mostly in the esterified

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fraction), which was correlated with the degree of functional deficit of the patients. Sercl et al.[22] found a decrease of the phospholipids and esterified cholesterol in the blood of patients, while no variation in the concentration of total or free cholesterol was evidenced. Baker et al.[3] found a significant reduction of the percentage of linoleic acid, particularly when the neurologic conditions were worse.

In *subacute combined degeneration of the spinal cord* (SCDSC) the investigations on the fat metabolism are scarce. Cárrega et al.[9] found high levels of phospholipids and cholesterol in the cerebrospinal fluid. Canelas [5] found an increase of the phospholipid content in the blood serum, while the blood cholesterol levels were normal. In a case studied by Green et al.[12] the cholesterol in the cerebrospinal fluid was increased, mostly in the free fraction.

Muller [17], Miettinen [16], and Palva [19] found low concentrations of blood cholesterol in cases of vitamin B_{12} deficiency; the fact was correlated by Palva to the decrease of coenzyme A activity in liver [13], which could hinder the synthesis of the lipidic coats of axons and red blood cells. Some investigations actually demonstrate that the antianemic treatment yields an increase of the cholesterol and phospholipid contents of the blood serum [5, 9].

Besides these disorders of the lipid metabolism, in SCDSC an impairment of the intestinal absorption occurs. These alterations are sometimes not restricted to deficient absorption of vitamin B_{12} and affect other metabolic fields, giving rise to malabsorption syndromes, frequently without evident abdominal manifestations, in a form name "cryptic" by Spillane and Wells [25].

With the purpose of investigating this matter, in 10 cases of SCDSC the absorption, clearance and utilization of labeled fat was studied. The relationship between the pattern of the neurologic manifestations and the disorder of fat metabolism was also analysed.

MATERIAL AND METHODS

Material — Ten cases of SCDSC have been studied. The diagnosis was based on the following criteria: (a) Characteristic neurologic picture, always represented, though in varied degree, by signs of peripheral nerve involvement (dysesthesias, muscle tenderness, hypoactive or absent deep reflexes, hypotonus, peripheral cutaneous hypesthesia) and a dorsal funiculi syndrome (impairment of deep sensation, Romberg's sign, ataxia of the extremities), and in 8 cases by a pyramidal syndrome (Babinski's sign and, eventually, when the peripheral involvement was very mild, hyperactive deep reflexes, clonus and automatisms). The cerebrospinal fluid examination disclosed no alteration in the cell count; regarding the total protein content, only in case 3 a slight increase was found. (b) Gastric achlorhydria in all cases, histamine-fast in 9; in all cases but one (case 4, submitted to partial gastric resection) the anacidity was constitutional. (c) Changes of the peripheral blood in the sense either of a macrocytic (2 cases) or an iron-deficient anemia (3 cases). (d) Signs of inhibited maturation at the bone marrow examination of 3 cases.

Methods — The *neurologic* involvement was evaluated in a semiquantitative way [6]. Each patient received a score for the peripheral, dorsal funiculi and pyramidal syndromes, as well as for the whole neurological picture (Table 1).

Case No.	File No.	UET of B_{12}-Co^{57} (%)		Neurologic manifestations			
		Single	B_{12}+IF	Peripheral	Dorsal funiculi	Pyramidal	Total
1	5600	15.7	—	62	76	0	138
2	4932	5.7	7.0	34	35	40	109
3	5466	0.8	3.8	54	74	39	167
4	5322	8.6	4.5	75	86	67	228
5	5181	0.5	8.1	86	133	45	264
6	5210	6.9	3.0	20	10	45	75
7	5108	5.4	14.0	147	101	0	248
8	5635	0.8	13.3	30	81	108	219
9	5875	3.1	14.5	10	10	79	99
10	5757	9.2	—	80	100	4	184

Table 1 — Results of the urinary excretion test of vitamin B_{12} and evaluation of the neurologic manifestations. IF = intrinsic factor. UET = urinary excretion test.

The *absorption of radioactive* (Co^{57}) *vitamin* B_{12} was studied through the Schilling's urinary excretion test [21]; levels lower than 10 per cent were considered as abnormal and in all cases but one, a second test with the association of intrinsic factor * was performed.

Triolein or *oleic acid* labeled with 20 μC of I^{131} was diluted to a volume of 10 ml with carrier triolein or oleic acid. The fat or fatty acid was then added to whole milk to make a volume of 200 ml. This mixture was homogenized in a blender for 5 minutes, at which time it was uniformly suspended. Milk was used as a carrier for the labeled fat in order to more closely approximate a physiologically stabilized fat emulsion. After a 12-hour fast each patient was given a test meal and venous blood samples were taken in a heparin wetted syringe 2, 4, 6 and 24 hours later. A 5 ml aliquot of unclotted blood was counted in a scintillatioon well counter (whole blood radioactivity). Another aliquot, treated with potassium iodide and trichloroacetic acid to separate the lipoprotein-bound iodine, was also assayed for radioactivity. The total blood volume was assumed to be 7.2 per cent of the body weight. With the given activity in the 5 ml portions and the calculated total blood volume, the total whole blood and lipid blood radioactivity were determined and expressed as a percentage of the ingested fat (%D). The total urine output was collected for 72 hours and the stools were also collected over the same period.

After ingestion of a triolein or oleic acid test meal, the mean whole blood radioactivity usually increases by the 4th or 6th hour to a peak value of 12 per cent (lipid blood value, 4 per cent), and then gradually wanes so that after 24 hours nearly 2 per cent (lipid blood value 0.2 per cent) remains. The organic fraction represents less than 50 per cent of the total. Urine collections of 72 hours contain between 20 and 40 per cent of the administered radioactivity, and the average fecal radioactivity over this period is usually less than 2 per cent.

RESULTS

Four cases (No. 2, 4, 5 and 7) showed disorders of fat metabolism: in 2 of them a deficient absorption through the intestinal wall was demonstrated, 3 cases showed an impaired clearance of fat, and 2 had a decreased utilization of fat (Table 2); 3 cases had steatorrhea. In 3 of these 4 cases a previous diagnosis of malabsorption syndrome was made through the Schilling's test. The more severe

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disorder of fat metabolism was found in a patient who had been submitted to partial gastric resection. In case 7 a deficiency of intrinsic factor such as is seen in pernicious anemia had been evidenced.

Case	Blood						Lipid/W. blood (%)	Urine 72 h (%D)	Feces (%D)
	Whole blood			Lipoprotein fraction					
	Peak		Radioact. 24 h (%D)	Peak		Radioact. 24 h (%D)			
	Hour	%D		Hour	%D				
1	6th	10.83	3.42	6th	3.64	0.50	33	49.15	1.91
2	4th	11.82	4.03	4th	5.84	1.18	49	66.11	9.97
3	4th	13.63	3.52	4th	6.14	0.73	51	73.18	1.59
4	6th	4.23	—	6th	2.31	—	50	16.07	31.39
5	4th	12.34	4.10	4th	4.49	0.71	36	74.17	0.00
6	—	—	—	—	—	—	—	91.31	2.36
7	6th	5.99	2.16	6th	2.63	0.63	44	44.42	7.78
8	4th	11.44	4.09	4th	2.83	0.45	40	77.18	0.00
9	6th	11.67	2.52	6th	4.25	0.43	36	54.55	2.10
10	4th	16.48	2.29	4th	6.75	0.41	41	58.58	2.39

Table 2 — Absorption, clearance, and utilization of labeled fat. %D = percentage of the ingested fat. Lipid/W. bl. = lipid/whole blood ratio.

Nerologic syndromes	Fat metabolism		Significance (t) of the difference
	Normal	Impaired	
Peripheral	42.7 ± 27.0	85.5 ± 46.7	1.858
Dorsal funiculi	58.5 ± 36.7	88.7 ± 40.8	1.184
Pyramidal	45.8 ± 42.1	38.0 ± 27.9	0.323
Total	147.0 ± 53.9	212.2 ± 70.4	1.666

Table 3 — Average score of neurological manifestations in patients with normal and impaired fat metabolism.

The mean urinary excretion of labeled vitamin B_{12} in the 4 cases showing disorders of lipid metabolism was 5.05 per cent ±3.36. In the remaining 6 cases with normal fat metabolism the mean was 6.09 per cent ±5.81. The difference between these means was not significant ($t = 0.32$).

The statistical analysis of the differences between the averages of the peripheral, dorsal funiculi and pyramidal syndromes in the groups with impaired and normal lipid metabolism disclosed no significant values (Table 3). In spite of this result, which is mostly derived from the little size of the sample, it can be seen that the peripheral and dorsal funiculi syndromes were more severe in the 4 cases with disorders of fat metabolism than in the normal cases, while the pyramidal syndrome was almost the same in the two groups. The whole neurological picture was also more severe in the 4 cases with impairment of fat metabolism.

DISCUSSION

The correlation between the impairment of fat metabolism and the pattern of the neurological manifestations in SCDSC was opposite to what hap-

pens with the absorption of vitamin B_{12}. We have actually found that the deficiency of cyanocobalamine absorption in SCDSC is mostly correlated to the degree of involvement of the corticospinal tracts, while the signs of damage of the peripheral nerves and/or the dorsal funiculi keep no relationship with it [7, 8].

These results seem to indicate that the impairment of lipid metabolism evidenced in this study of SCDSC bears no direct relationship with the demyelinating process in general, and would rather attend the deficiency of metabolites (probably the vitamins of the B-complex) other than vitamin B_{12}, which play a more significant role in the preservation of the peripheral nerves. This is in full agreement with the well known fact that the B-complex avitaminoses usually produce a peripheral neuropathy only, the involvement of the central nervous system being exceptional.

SUMMARY

In 10 cases of subacute combined degeneration of the spinal cord the absorption, clearance and utilization of labeled fat was studied. In 4 cases disorders of the lipid metabolism were found.

Although not significantly, the peripheral and dorsal funiculi syndromes were more severe in the 4 cases with impaired fat metabolism than in the normal cases, while the pyramidal syndrome was almost the same in the two groups. The whole neurological picture was also more severe in the 4 cases with disorders of fat metabolism.

These results seem to indicate that the impairment of lipid metabolism evidenced in such cases bears no direct relationship with the demyelinating process in general, and would rather attend a deficiency of metabolites (probably B-complex vitamins) other than vitamin B_{12}, which play a more significant role in the preservation of the peripheral nerves.

RESUMO

Metabolismo dos lípides na mielose funicular

Em 10 casos de mielose funicular foram estudadas a absorção, a depuração e a utilização de lípides radioativos. Em 4 dêsses casos foram verificadas alterações do metabolismo lipídico.

Embora não significantemente, as síndromes periférica e funicular dorsal mostraram-se mais intensas nos 4 casos com distúrbios do metabolismo lipídico que nos demais, enquanto a síndrome piramidal foi aproximadamente semelhante nos dois grupos de pacientes. A sintomatologia neurológica global também se apresentou mais intensa nos 4 casos com alterações do metabolismo lipídico.

Êstes resultados parecem indicar que as alterações do metabolismo das gorduras demonstradas nesses casos não se vinculam diretamente ao processo desmielinizante em geral, parecendo antes refletir uma carência de metabólitos (provàvelmente vitaminas do complexo B) diversos da vitamina B_{12},

que desempenhariam papel mais importante na preservação dos nervos periféricos.

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