VITAMIN B_{12} IN THE PATHOGENESIS OF SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

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The etiopathogenesis of subacute combined degeneration of the spinal cord (SCDSC) is still a matter of controversy. In spite of the numerous investigations made in the last years, concerning particularly the metabolism of vitamin B_{12}, some fundamental aspects of the disease process are still unknown. It is granted that the finding of deficient absorption of vitamin B_{12} and/or the absence of chlorhydropeptic secretion lead to the diagnosis of SCDSC in the face of a characteristic clinical picture. Nevertheless, recent researches on this subject evidence that it can not be stated, as some authors pretend [18, 24], that the funicular myelosis results exclusively from vitamin B_{12} deficiency. Typical clinical pictures of the disease have been reported in patients with normal absorption of cyanocobalamin [6, 31]. Even achlorhydria is not a constant feature of the affection [2, 8, 18, 26, 31, 34].

In order to study the relationship between the absorption of vitamin B_{12} and SCDSC, 29 cases of this disease were studied. The absorption of labeled vitamin B_{12} was compared with the severity of the symptomatology as a whole, and particularly with the signs of involvement of the peripheral or central nervous system.

MATERIAL AND METHODS

Material — Twenty-nine cases of SCDSC were studied. The diagnosis was based on the following criteria: (a) Characteristic neurological picture, always represented, though in varied degree, by peripheral nerve (dysesthesias, muscle tenderness, hypoactive or absent deep reflexes, hypotonia, superficial hypoesthesia with a peripheral distribution in the limbs) and dorsal funiculi syndrome (impairment of deep sensation, Romberg's sign, ataxia of the extremities), and in most cases (23 patients) by a pyramidal syndrome (Babinski sign, spasticity, hyperactive deep reflexes, clonus, automatisms). The cerebrospinal fluid examination disclosed no alteration in the cell count or in the total protein content; in 14 cases the electrophoresis or CSF proteins was made, showing in 6 a rise of the concentration of β-globulin; the level of this globulin was significantly correlated to the severity of the nervous involve-

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ment, and a trend to a negative correlation between β-globulin and excretion of vitamin B_{12} in urine was also found [28]. (b) Gastric achlorhydria in all cases, histamine-fast in 26; in 23 cases the anacidity was constitutional, in 5 (cases 3, 10, 16, 26, 29) it resulted from partial gastric resection, and in one (case 28) from total gastrectomy. (c) Changes of the peripheral blood, either of the macrocytic anemia type (9 cases) or iron-deficient anemia (11 cases). (d) Signs of inhibited maturation of the bone marrow examination in 8 cases (Table 1).

Case — File nº	*Blood*	*Bone marrow*	*Gastric acidity*	*Excretion of labelled B_{12} (%)*	
				Single	*Plus IF*
1 — 2975E	Normal	Inhib. mat.	Absent	21.56	—
2 — 3533E	h.A.	—	Absent	11.20	—
3 — 3575E	h.A.	Normal	Absent*	16.90	—
4 — 3710E	Normal	Normal	Absent	21.37	—
5 — 3736E	Normal	Normal	Absent	13.72	—
6 — 3854E	M.H.A.	Inhib. mat.	Absent	10.67	—
7 — 4459E	Normal	Normal	Absent	11.55	—
8 — 5600E	M.A.	—	Absent	15.75	—
9 — 42325A	—	—	Absent	12.10	—
10 — 437479	h.A.	—	Absent*	11.86	—
11 — 1881E	M.H.A.	Inhib. mat.	Absent	0.00	5.56
12 — 2016E	M.H.A.	Normal	Absent	6.02	0.00
13 — 4932E	Normal	—	Absent	5.70	7.00
14 — 5181E	h.A.	Inhib. mat.	Absent	0.50	8.10
15 — 5210E	Megalo	Inhib. mat.	Absent	6.90	3.00
16 — 5322E	h.A.	Normal	Absent*	8.60	4.50
17 — 5466E	Normal	Inhib. mat.	Absent	0.80	3.80
18 — 2443E	h.A.	Normal	Absent	0.80	10.32
19 — 2623E	M.H.A.	Normal	Absent	3.52	18.30
20 — 4396A	M.H.A.	Normal	Absent	0.37	21.07
21 — 4480A	M.H.A.	Inhib. mat.	Absent	1.05	10.88
22 — 5108E	Normal	Normal	Absent	5.40	14.00
23 — 5635E	h.A.	—	Absent	0.80	13.30
24 — 5875E	h.A.	Normal	Absent	3.10	14.50
25 — 3385E	h.A.	Normal	Absent	8.14	—
26 — 4846E	M.H.A.	Inhib. mat.	Absent	2.40	—
27 — 5757E	Normal	Normal	Absent	9.20	—
28 — 465108	h.A.	—	Absent	0.71	—
29 — 523732	h.A.	—	Absent	0.32	—

Table 1 — Subacute combined degeneration of the spinal cord: identification and diagnosis. M.H.A. = *macrocytic hyperchromic anemia;* h.A. = *hypochromic anemia;* Inhib. mat. = *inhibition of maturation;* IF = *intrinsic factor;* * = *slight response to histamine.*

According to the result of the urinary excretion test of vitamin B_{12}, the patients were divided into four groups: (1) patients with normal absorption (cases 1-10); (2) patients with deficiency of vitamin B_{12} absorption, not corrected by intrinsic factor, i.e. malabsorption syndrome (cases 11-17); (3) patients with deficiency of intrinsic factor of the pernicious anemia type (cases 18-24); (4) patients with deficient absorption in which the test of B_{12} + IF was not performed; 3 patients in this last group had been submitted to gastrectomy and an intrinsic factor deficiency could be presumed [11,17], but the finding of a malabsorption syndrome (with steatorrhea disclosed by the labeled triolein test) in other patient who suffered gastric resection (case 16) prevented the inclusion of them in group 3.

Methods — The neurological involvement was evaluated in a semiquantitative way[5]. Each patient received a score for the peripheral, dorsal funiculi and pyramidal syndromes (Table 2).

The absorption of labeled vitamin B_{12} (in the first cases Co^{60} and lately Co^{57}) was studied through the Schilling's urinary excretion test[25]. Levels of excretion lower than 10 per cent were considered as indicative of deficient absorption. When abnormal results were found, the test was repeated with the association of intrinsic factor *, except in the last 5 cases.

The results were submitted to conventional statistical analysis.

Group	*Case*	*Peripheral syndrome*	*Dorsal funiculi syndrome*	*Pyramidal syndrome*	*Total*
Normal absorption	1	36	103	23	162
	2	30	76	60	166
	3	10	18	34	62
	4	32	10	0	42
	5	62	125	20	207
	6	76	19	0	95
	7	44	19	15	78
	8	62	76	0	138
	9	86	92	16	194
	10	20	9	0	29
		458	547	168	1,173
Malabsorption	11	24	71	78	173
	12	50	116	110	276
	13	34	35	40	109
	14	86	133	45	264
	15	20	10	45	75
	16	75	86	67	228
	17	54	74	39	167
		343	525	424	1,292
Intrinsic factor deficiency	18	14	24	54	92
	19	20	36	5	61
	20	17	38	50	105
	21	28	5	34	67
	22	147	101	0	248
	23	30	81	108	219
	24	10	10	79	99
		266	295	330	891
Undetermined deficient absorption	25	102	136	69	307
	26	125	139	122	386
	27	80	100	4	184
	28	8	9	0	17
	29	18	10	30	58
		333	394	225	952

Table 2 — Subacute combined degeneration of the spinal cord: neurological symptomatology (quantitative evaluation).

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RESULTS

Our results (Tables 3 and 4) show that the normality of vitamin B_{12} absorption can not refute the diagnosis of SCDSC, made on the grounds of achylia, hematologic alterations and the classical neurological picture. The whole neurological picture showed no significant correlation with the absorption of vitamin B_{12} (Table 5).

Group	*Peripheral syndrome*		*Dorsal funiculi syndrome*		*Pyramidal syndrome*		*Total*	
Cases 1-11 Normal absorption	45.8±24.8		54.7±44.2		16.8±19.3		117.3± 64.4	
Cases 12-18 Malabsorption	49.0±25.0	49.6±41.5	75.0±42.8	63.9±47.7	60.6±24.5	51.5±36.9	184.6± 76.1	165.0±101.0
Cases 19-25 Intrinsic factor deficiency	38.0±48.6		42.1±36.0		47.1±38.6		127.3± 74.8	
Cases 26-29 Undetermined deficient absorption	66.6±51.6		78.8±65.1		45.0±51.0		190.4±157.7	

Table 3 — Subacute combined degeneration of the spinal cord: averages of the neurological symptomatology according to the absorption of B_{12}.

Group	*Peripheral syndrome*	*Dorsal funiculi syndrome*	*Pyramidal syndrome*	*Total symptomatology*
Cases 12-18 Malabsorption	0.261	0.944	3.974*	1.971
Cases 19-25 Intrinsic factor deficiency	0.437	0.622	2.148*	0.295
Cases 26-29 Undetermined deficient absorption	1.076	0.854	1.583	1.222
Cases 12-29 Deficient absorption	0.265	0.506	2.768*	1.350

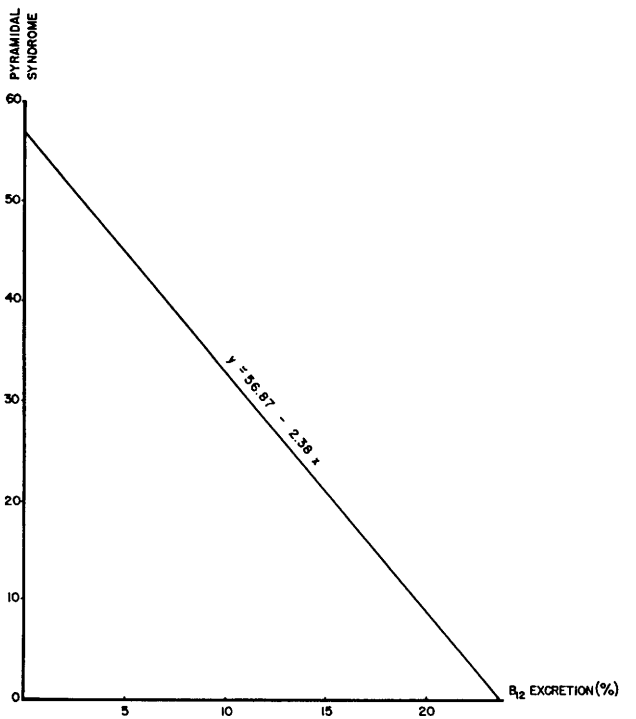
Table 4 — Subacute combined degeneration of the spinal cord: significance of the difference (t) of neurological symptomatology in the groups with deficient B_{12} absorption, as compared to the averages in the group with normal absorption.
** Significant value.*

Actually, in spite of the views of Mollin and Ross [18], and Richmond and Davidson [24], several investigations [1,4,9,13,14,15,19,27,31,33] demonstrate that deficiency of Vitamin B_{12} is not, necessarily, a constant in SCDSC.

Our results evidence, however, that the pattern of the neurological picture varies with the degree of vitamin B_{12} absorption. While the peripheral and the so-called dorsal funiculi syndromes showed no difference in the groups with normal (cases 1-10) or deficient absorption (cases 11-29), the pyramidal syndrome — which unquestionably reflects the involvement of the spinal cord — is significantly more severe in the patients with deficient absorption (Table 4). Studying the correlation between vitamin B_{12} absorption and the degree of corticospinal tract lesion, a negative correlation was found (Table 5 and graph 1). Regarding the impairment of the deep sensation (generally restricted to disturbances of the vibration sense) and the consequent ataxia, it is not possible, on clinical grounds, to separate them from the other signs of peripheral involvement and to ascribe them sharply to a lesion of the fasciculi gracilis and/or cunneatus.

Pyramidal syndrome	$r = -0.431$	$t_r = 2.482$	$0.02 > P > 0.01$
	$b = -2.38$	$t_b = 2.482$	$0.02 > P > 0.01$
Total symptomatology	$r = -0.129$	$t_r = 0.676$	$0.6 > P > 0.5$

Table 5 — Correlation between the excretion of B_{12}-Co^{57} and the neurological picture in 29 cases of subacute combined degeneration of the spinal cord.



Graph 1 — Regression line between the pyramidal syndrome and the absorption of radioactive vitamin B_{12}.

DISCUSSION

Trying to explain our results, we must remind that the study of the concentrations of vitamin B_{12} few days after repeated injections showed that in the brain they were one of the lowest [7]. But, in a long-term study, Whipple (apud Wangensteen [32]) found that the brain stores one of the greatest amounts of vitamin B_{12}, which is only surpassed by the heart.

Vitamin B_{12} deficiency may decrease the coenzyme-A activity in the liver, thus hindering the systems of the lipid axon sheaths synthesis [22]; actually, the maintenance of the myelin sheath is difficult in the presence of vitamin B_{12} deficiency (Alexander, apud Palva [22]).

On the other hand, studies of the intracellular partition of folic acid and vitamin B_{12} concentrations [16, 20, 29, 30] showed that the vitamin is mainly stored in the mitochondria. Folic acid functions in several enzymic systems, while vitamin B_{12} is confined to certain enzymes of the mitochondria [30]. Vitamin B_{12} and folic acid take part in the synthesis of ribonucleic (RNA) and deoxyribonucleic acids (DNA) [12, 21, 23] but only vitamin B_{12} is essential for the reactions related to RNA synthesis [21], while it is dispensable for the synthesis of DNA [3].

The significance of the role of vitamin B_{12} in RNA synthesis is inferred from the fact that the RNA is metabolized mainly in the cytoplasm and nucleolus, being essential for the life of perennial cells, as the nerve cells; its deficiency would affect the long spinal axons [33]. According to our results, the vitamin B_{12} would be more significant for the integrity of the long corticospinal axons than for the peripheral nerves.

SUMMARY

The absorption of labeled vitamin B_{12} in 29 cases of subacute combined degeneration of the spinal cord was studied. The diagnosis was based on the classical neurologic picture and on the presence of gastric achlorhydria and eventual blood or bone marrow changes. The neurologic manifestations were evaluated in a semiquantitative way and were correlated to the results of the urinary excretion test of vitamin B_{12}.

The absorption of vitamin B_{12} was not significantly correlated to the neurologic picture as a whole, or to the peripheral and dorsal funiculi syndromes. However, a significant negative correlation was found between the pyramidal syndrome and the absorption of vitamin B_{12}.

The results are confronted with the significance of vitamin B_{12} in the synthesis of myelin sheaths and ribonucleic acid, the essential role of RNA for the life of the nerve cells and the long axons being emphasized.

RESUMO

Papel da vitamina B_{12} na patogenia da mielose funicular.

Foi estudada a absorção da vitamina B_{12} radioativa em 29 casos de mielose funicular. O diagnóstico baseou-se na clássica sintomatologia neu-

rológica e na presença de acloridria gástrica e eventuais alterações hematológicas. As manifestações neurológicas foram avaliadas de modo semiquantitativo e correlacionadas com os resultados do teste de excreção urinária da vitamina B_{12}.

Não foi verificada correlação significante da absorção da vitamina B_{12}, quer com a sintomatologia nuerológica total, quer com as síndromes periférica e funicular dorsal. Contudo, foi encontrada significante correlação negativa entre a síndrome piramidal e a absorção da vitamina B_{12}.

Os resultados são confrontados com o papel desempenhado pela vitamina B_{12} na síntese das bainhas de mielina e do ácido ribonuclêico, sendo salientada a importância dêste último para a vida das células nervosas e dos longos axônios.

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