

EFFECT OF CORTICOTROPIN ON THE ABSORPTION OF VITAMIN B₁₂ IN THE SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

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The treatment of subacute combined degeneration of the spinal cord (SCDSC) is based on a pretended etiological unity between the hematologic and neurologic manifestations, according to the old concept of the neuro-anemic syndrome. The first attempt of treatment of that disease was the liver therapy, introduced in 1926 by Minot and Murphy²³, but the neurologic results did not correspond to the success observed in the anemic condition. In 1947, the discovery of the folic acid strengthened the doubts on the etiological unity of the hematologic and neurologic syndromes; actually, the initial findings of Spies et al.³¹, later confirmed by several investigators, showed that the folic acid, although improving the blood conditions, had no effect on the neural involvement or even made it worse. The advent of the vitamin B₁₂ was received as the solution of the therapeutic problem, for it influenced both the hematologic and neurologic manifestations.

Unfortunately the initial enthusiasm did not last very long and it was found that the neurologic improvement, though generally greater than that yielded by the liver extract alone — and opposite results were reported by Murphy and Howard²⁵ — was not comparable to the brilliant hematologic effect. In spite of the fact that some authors stress that the deficiency of vitamin B₁₂ is a fundamental stone in the building up of SCDSC^{24, 27}, and although Spillane and Wells³² have adopted the term "B₁₂ neuropathy" suggested by Richmond and Davidson²⁷, it has been demonstrated that the deficiency of vitamin B₁₂^{1, 3, 6, 9, 12, 22, 25, 34, 35} and even achlorhydria^{2, 11, 27, 30, 34, 37} are not constant in SCDSC. According to Boudin et al.³, in SCDSC there is a more complex deficiency than an isolated avitaminosis B₁₂. And even Richmond and Davidson²⁷, owing to some significant exceptions to the rule of vitamin B₁₂ deficiency, were constrained to formulate the hypothesis that another substance, neuropoetin, besides vitamin B₁₂ but closely related to it, is necessary for the integrity of the nervous system.

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On the other hand, the long-term study of the experimental demyelinating encephalomyelitides (Wolf et al., apud Kolb²⁰) showed histopathologic features in many ways comparable with those of the so-called primary demyelinations, the poverty of the inflammatory process, the reaction of the astroglia, and in the oldest lesions the relative preservation of the axons and the marked gliosis, deserving particular mention.

Taking into account that such experimental demyelinations have an allergic mechanism, and owing to the good results afforded by ACTH in some demyelinating diseases, we started in 1953 to use it in the treatment of SCDSC⁵. The results were fully analyzed in 1960⁴ and it was evidenced that ACTH alone had an effect similar to liver extract, though inferior to vitamin B₁₂.

Therefore, corticotropin was used on the assumption that the demyelination of SCDSC was due to an auto-immune process, a viewpoint defended by Roger²⁸ in 1954. Now, however, we ought to accept an additional justification for the use of ACTH in the treatment of SCDSC, owing to the increase of vitamin B₁₂ absorption promoted by this hormone, according to the pioneer report of Glass (1955) in a case of sprue¹³. Since then, many other authors^{7, 8, 9, 10, 14, 16, 17, 21, 33} have confirmed that finding, regarding both the ACTH and corticosteroids, and either in the malabsorption syndrome or in pernicious anemia. It was demonstrated also that the hypophysectomy and the adrenalectomy cause a deficiency of vitamin B₁₂ absorption which can be counteracted, respectively, by ACTH and corticosteroids³⁶.

The hypothesis that corticotropin would enhance the secretion of intrinsic factor¹⁶ is hardly admissible, because it would not be in agreement with the results in cases of pernicious anemia with atrophic gastritis¹⁵. It is more probable that the hormone interferes at the intestinal level, enhancing the absorption of the vitamin regardless of a binding with intrinsic factor to make up the B₁₂-IF complex. Besides this way of action, ACTH mobilizes the organic stores of vitamin B₁₂ (Meites et al., apud Glass¹⁵).

Another mechanism of the ACTH action would be through the increment of the pyridoxine synthesis^{18, 26}, since the deficiency of vitamin B₆, leading to cortico-adrenal atrophy³⁶, gives rise to a vicious circle hindering the absorption of vitamin B₁₂. On the other hand, in swines, a B₆-deficient diet can produce demyelination of the peripheral nerves and dorsal funiculi³⁵.

In this paper the effect of ACTH on vitamin B₁₂ absorption in 9 cases of SCDSC is analyzed.

MATERIAL AND METHODS

Material — Nine cases of SCDSC were studied. The diagnosis was based on the following criteria: (a) Characteristic neurologic picture, always represented, in varied degree, by peripheral nerves and dorsal funiculi involvement, and in most cases by a pyramidal syndrome. (b) Gastric anacidity in every case, histamine-fast in all cases but one (case 5); achlorhydria was constitutional in 7 cases and due to partial gastric resection in cases 5 and 8. (c) Changes of the peripheral blood in 6 cases, either in the sense of macrocytic hyperchromic or iron-deficient anemia. (d) Inhibition of maturation at bone-marrow examination in 4 cases.

According to the results of the urinary excretion test of labeled vitamin B₁₂, the diagnosis were: malabsorption syndrome (4 cases), deficiency of intrinsic factor, pernicious-anemia type (2), and undetermined deficient absorption (3).

Methods — Corticotropin was administered by intravenous perfusion in an average dosis of 12.5 to 25.0 mgm./day, diluted in 500 ml. of a 10 percent glucose solution, at a rate of 20 drops/minute. The therapeutic scheme lasted from 19 to 43 days, and the total dosis of ACTH varied from 237 to 505 mgm. (Table 1). The usual care with this kind of treatment was taken.

The absorption of labeled vitamin B₁₂ (formerly Co⁶⁰ and later Co⁵⁷) was studied through the Schilling's urinary excretion test². Excretion levels lower than 10 percent 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 three cases.

The Schilling's test was repeated either immediately after completion of treatment (6 cases) or 28 days (2 cases) and 45 days later (1 case). In cases 3 and 4 the test with vitamin B₁₂ plus intrinsic factor was done, respectively, 10 and 5 days after the treatment with ACTH had been started (table 1), thus introducing an error of interpretation concerning the effect of intrinsic factor on the absorption of the vitamin, at least in case 3, where an increased absorption was evidenced.

RESULTS

The results are summarized in tables 1 and 2. Except in cases 6 and 9 an increase in the absorption of vitamin B₁₂ was found. The mean difference of the whole group of cases is in the limit of significance.

Case N.º	File Nº	ACTH		Excretion of B ₁₂ (percent)			Number of days after completion of treat- ment	Interval between last UET and test after completion of treat- ment
		Days	Total dosis (mgm)	Before ACTH		After ACTH		
				Single	Plus IF			
1	5108	32	265	5.41	14.03	7.23	45	62
2	5875	20	250	1.61	14.51	3.09	1	26
3	5181	19	237	0.50	8.15	11.53	1	9
4	5210	20	250	6.93	3.00	11.01	1	15
5	5322	19	227	8.65	4.55	15.89	1	37
6	5466	22	275	0.97	3.78	0.63	1	56
7	3385	23	287	8.14	—	11.36	28	59
8	4846	43	505	2.39	—	4.50	28	28
9	5757	20	500	9.18	—	4.70	1	15

Table 1 — Effect of ACTH on vitamin B₁₂ absorption in cases of subacute combined degeneration of the spinal cord.

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Case	Diagnosis	Difference of B ₁₂ excretion after ACTH
1	Deficiency of intrinsic factor	+ 1.82
2	Deficiency of intrinsic factor	+ 1.48
3	Malabsorption	+ 11.03
4	Malabsorption	+ 5.08
5	Malabsorption	+ 7.24
6	Malabsorption	- 0.34
7	Undetermined deficient absorption	+ 3.22
8	Undetermined deficient absorption	+ 2.11
9	Undetermined deficient absorption	- 4.48
Mean difference		+ 3.02 ± 4.45
Significance of the mean		t = 2.041
Probability		0.1 < P < 0.05

Table 2 — Statistical analysis of the effect of ACTH on radioactive vitamin B₁₂ absorption in cases of subacute combined degeneration of the spinal cord.

DISCUSSION

The increase of vitamin B₁₂ absorption was observed either in cases of malabsorption syndrome or in cases of lack of intrinsic factor probably due to gastric atrophy. In case 1, with a pernicious anemia pattern of deficient B₁₂ absorption, a test of absorption of labeled triolein showed steatorrhea, suggesting that there was also impairment of the intestinal absorption, besides the lack of intrinsic factor. The effect of ACTH was evidenced also in two patients submitted to partial gastric resection (we have no experience in cases of total gastrectomy, a condition in which Gordin¹⁶ found no effect of prednisone on the vitamin B₁₂ absorption). In one of these cases (n.º 5) the test with labeled triolein showed a fecal excretion of 31.4 percent, pointing to a marked degree of steatorrhea; so, in this case, the ineffectiveness of the association of intrinsic factor and the deficient fat absorption pointed to an impairment of the absorption of vitamin B₁₂ through the intestinal wall.

The failure of ACTH to increase vitamin B₁₂ absorption occurred in a case with undetermined deficient absorption (the test B₁₂ + IF was not done) and in a case of malabsorption syndrome.

Though the rate of increment in B₁₂ absorption after the ACTH series was small in most of cases, the results in cases 3 and 5 must be emphasized, since the degree of urinary excretion raised, respectively, more than 11 and 7 percent. It deserves to be stressed that in these two cases there was a malabsorption syndrome, namely an impairment of the vitamin B₁₂ absorption through the ileal mucosa.

In order to study a possible mobilizing effect of ACTH on the radioactive vitamin B₁₂ stores, the intervals between the last urinary excretion test and the test after completion of treatment were analyzed (Table 1). It is easily noticed that in the 7 cases with increase of vitamin B₁₂ absorption these periods were the most varied, lasting from 9 to 62 days. And also in the 2 cases with decrease of absorption the intervals were very dissimilar, namely 15 and 56 days. So, it seems that this effect of ACTH did not play a significant role in the results.

Likewise, the time elapsed between the completion of treatment and the repetition of the Schilling's test had no apparent relationship with the results.

SUMMARY

The absorption of vitamin B₁₂ was studied in 9 cases of subacute combined degeneration of the spinal cord before and after the administration of intravenous ACTH in a therapeutic scheme lasting from 19 to 43 days. In 7 cases an increase of absorption was evidenced. The mean difference of change in the urinary excretion test of radioactive vitamin B₁₂ was near the limit of significance.

This finding reinforces the indication of the use of corticotropin in subacute combined degeneration of the spinal cord, since the hormone will act both on the allergic component of the demyelinating process and on the deficiency of vitamin B₁₂ absorption. Though the material here analyzed is too small to warrant a definite conclusion, our results suggest that ACTH influences the vitamin B₁₂ absorption through the intestinal wall, and not by means of an increase of intrinsic factor secretion or a mobilization of vitamin B₁₂ stores.

RESUMO

Efeito da corticotropina sobre a absorção de vitamina B₁₂ na mielose funicular

Foi estudada a absorção de vitamina B₁₂ em 9 casos de mielose funicular antes e após a administração de ACTH por via intravenosa em um esquema terapêutico com duração variável entre 19 e 43 dias. Em 7 casos foi verificado aumento da absorção. A diferença média de modificação no teste de excreção urinária de vitamina B₁₂ radioativa situou-se próximo do nível de significância estatística.

Este resultado reforça a indicação do emprego de corticotropina na mielose funicular, pois o hormônio irá atuar tanto sobre o componente alérgico do processo desmielinizante, quanto sobre a carência de vitamina B₁₂ resultante do déficit de absorção. Embora o material aqui analisado seja muito pequeno para garantir uma conclusão definitiva, nossos resultados demonstram que, provavelmente, o ACTH age sobre a absorção da vitamina B₁₂ através da mucosa intestinal, e não mediante o aumento de secreção do fator intrínseco ou a mobilização dos depósitos dessa vitamina.

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