Latent tetany, magnesium and HLA tissue antigens

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Zusammenfassung

Bei 50 weiblichen ambulanten Patienten mit latenter Tetanie wurden HLA-Gewebeantigene, Erythrozyten-Mg und Plasma-Mg ermittelt. Es konnte in diesem Kollektiv ein Überwiegen von HLA-B 35 (34 %) beobachtet werden im Vergleich zur Häufigkeit des Vorliegens des B 35-Antigens in einer Kontrollpopulation (18 %), bestehend aus gesunden Blutspendern ($p < 0{,}006$). Das HLA-B 35-Antigen ist, wie früher gezeigt wurde, mit niedrigen Blut-Mg-Spiegeln assoziiert; auch Patienten mit latenter Tetanie weisen charakteristischerweise erniedrigte Mg-Konzentrationen auf. Die vorliegenden Daten lassen folglich vermuten, daß mit B 35 assoziierte genetische Faktoren durch Senkung des Blut-Mg bei prädisponierten Personen das Auftreten eines latenten tetanischen Syndroms begünstigen.

Summary

HLA tissue antigens, red blood cell and plasma magnesium concentrations have been determined in a group of 50 female latent tetany outside patients. An excess of HLA-B 35 subjects (34 %) is observed in this group, by reference to the phenotypic frequency (18 %) of the B 35 antigen in a control population of healthy blood donors ($P < 0.006$). The HLA-B 35 antigen has previously been shown to be associated with low blood Mg levels; latent tetany patients are also characterized by low blood Mg values. The present data suggest, therefore, that B 35 associated genetic factors may favor the appearance of a latent tetany syndrome by lowering blood Mg values in predisposed subjects.

Résumé

Le groupage HLA et les concentrations en Mg du plasma et des érythrocytes ont été déterminés chez 50 spasmophiles de sexe féminin. Les sujets porteurs de l'antigène HLA-B 35 sont significativement plus fréquents 34 %; $P < 0{,}006$) dans ce groupe que dans la population témoin de donneurs de sang en bonne santé (18 %). Des recherches antérieures ont montré l'existence de magnésémies basses chez les sujets porteurs du groupe HLA-B 35; les spasmophiles sont également caractérisés par des magnésémies basses. Les présentes données suggèrent, donc, que des facteurs génétiques associés au groupe tissulaire B 35 puissent favoriser l'apparition de la spasmophilie en contribuant à l'abaissement de la magnésémie chez des sujets prédisposés.

Introduction

Normocalcemic latent tetany is a clinical syndrome involving subjective, objective, biological and electrophysiological disorders. Its diagnosis raises several difficulties (variety and functional aspect of complaints) which can be overcome by the use of precise criteria, mainly electrophysiological, described in the methodology.

Latent tetany symptoms generally develop on a neuro-muscular hyperexcitability constitutional basis, named **spasmorhythmia** by *Engelbeen* et al. [7]. This constitutional state is revealed, in asymptomatic subjects, by the appearence of spontaneous activity in muscles submitted to a ten minute ischemia. Several factors, still poorly defined, can break down the apparent state of equilibrium evidenced by **spasmorhythmic** subjects, and trigger latent tetany characterized by electromyographic, *Chvostek* and *Trousseau* signs, functional disorders and complaints, decreased levels of plasma and red blood cell (RBC) magnesium (Mg) [4, 19] and a tendency to idiopathic hypercalciuria [16]. The triggering of latent tetany can be ascribed to primary disturbances of calcium and Mg metabolisms, to secondary iatrogenic effects on these metabolism (diuretics, oral contraceptives, laxatives), to sleep troubles, emotional and psychological factors and/or changes in dietary habits [5, 8, 20]. Moreover, latent tetany is often a familial disease which suggest the involvement of genetic traits in its etiology.

On the other hand, RBC Mg concentrations and to a lesser extent plasma Mg concentrations, are controlled by genetic factors in men [1, 2, 11, 12] and in mice [13]. Some of these factors are associated directly or indirectly with the major histocompatibility complex since human subjects carrying the HLA tissue group B 35 exhibit significantly lower RBC and plasma Mg levels than individuals carrying other HLA antigens [10, 11, 12]. A similar association has also been demonstrated in the mouse [13].

Thus, latent tetany has a constitutional and a familial character; Mg metabolism is genetically regulated and appears to be in-

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volved in latent tetany. The occurrence of relationships between latent tetany and Mg controlling genetic factors can, therefore, be rightfully suspected. More precisely, we can hypothetize that latent tetany may be associated with HLA-B 35 since the carriers of this tissue antigen have lower blood Mg values. In order to test this hypothesis, we have studied the distribution of HLA-A and B groups in latent tetany patients currently consulting our clinic at the University of Liège. Preliminary results on 50 patients are presented here.

Populations and methods

Our populations of latent tetany subjects is defined according to rigorous criteria: positive *Chvostek* sign after hyperpnea and positive electromyographic test in all cases. This test is performed by inserting a detection needle in the first dorsal interosseous muscle of the hand and by recording the electromyogram (EMG) during a ten minute ischemia of the upper limb, the following ten minutes of recovery and a three minute hyperpnea. The EMG is considered to be positive when an intense Trousseau electric sign is observed under ischemia or when a spontaneous repetitive activity (doublets or multiplets) is recorded for more than three minutes after ischemia or during the hyperpnea. The clinical symptoms are the following: asthenia (100 %), vertigo (80 %), palpitations (75 %), dysesthesia (70 %) myalgia and muscular cramps (66 %), tachycardia, respiratory oppression and colon irritability [8, 17]. The 50 subjects chosen for HLA grouping were adult females under fifty, randomly taken among the latent tetany outside patients consulting our department. The severity of the symptoms were not taken into account and the possible occurence of other affections was excluded by a thourought clinical and paraclinical examination. The phenotypic distribution of HLA-A and B antigens of these patients was compared to that of healthy blood donors of the Liège area.

Plasma and RBC Mg concentrations were determined by atomic absorption spectrophotometry according to the usual standardized sampling and analytical procedure [21].

Tab. 1: Phenotypic frequency in % of the total number (n) of subjects, of HLA-B antigens in a group of latent tetany outside patients and in a control group of healthy blood dono-rs living in the same geographical area. P = threshold of significance of X^2 calculated from the distribution of each antigen (carriers and non-carriers) in the two compared groups. N.S. = non significant (P > 0,05)

HLA-B antigens	Latent tetany (n = 50)	Controls (n = 1814)	P
	%	%	
B 5	20	13,9	N.S.
B 7	18	21,4	N.S.
B 8	12	17,4	N.S.
B 12 (44, 45)	38	28,6	N.S.
B 13	4	3,9	N.S.
B 14 (64, 65)	4	7,8	N.S.
B 15 (62, 63)	14	13,3	N.S.
B 16 (38, 39)	6	7,9	N.S.
B 17 (57, 58)	2	7,8	N.S.
B 18	10	10,3	N.S.
B 21 (49, 50)	6	3,7	N.S.
Bw22 (54, 55, 56)	0	4,7	N.S.
B 27	10	8,1	N.S.
B 35	34	18,5	< 0,006
B 37	0	0,6	N.S.
B 40 (60, 61)	14	11,7	N.S.
Bw47	0	1,5	N.S.

Results

The phenotypic frequency of HLA-B antigens is given comparatively for 50 latent tetany patients and 1814 healthy blood donors, in Tab. 1. An increased frequency of B 35 subjects in the patient group (34 %) in comparison to the controls (18 %) is the only significant result (χ^2 = 7,6; P < 0,006). No significant variation is observed for the HLA-A groups (data not shown).

In 47 of our patients, RBC and P Mg concentrations were also determined (Tab. 2). As expected, their mean values are at the lower limit of the normal span of variation observed in healthy people [17]. Furthermore, among these patients, the HLA-B 35 subjects have still lower values than the other individuals; the difference is, however, small and non-significant.

Tab. 2: Plasma and RBC Mg concentrations (Means and standard-deviations) determined in 47 latent tetany outside patients classified according to the presence or absence of the HLA-B 35 antigen. (normal values: Plasma Mg: 0,75 – 1,00 mmol/l; RBC Mg: 2,00 – 2,85 mmol/l.)

Latent tetany patients		Plasma Mg mmol/l	RBC Mg mmol/l
B 35	(n = 16)	0,78 ± 0,057	1,91 ± 0,21
non B 35	(n = 31)	0,81 ± 0,062	2,01 ± 0,23
Total	(n = 47)	0,80 ± 0,061	1,98 ± 0,23

Discussion

The increased frequency of the B 35 antigen in our latent tetany group of patients is quite significant ($P < 0{,}006$). This result should, nevertheless, be confirmed on a larger number of subjects since it bears a discrepancy with those previously published by *Hatem* et al. [9] on 40 latent tetany subjects. These authors observe only slightly significant decreases of frequency for the HLA-B 35 ($P < 0{,}02$), B 12, B 17 and B 40 ($P < 0{,}05$) antigens. However, the HLA typing of these series involve some inaccuracies: B 15 grouped with B 16 and an arbitrary distinction between B 12 subjects (7,5 % in the latent tetany and 23,3 % in the control group) and some subjects carrying Bw 44, which is in fact a subdivision of B 12 (15 % among latent tetany and 3,3 % in the controls). Moreover, the criteria used for the patient selection are not described in details. The population tested by Hatem et al. could, therefore, be different from ours.

The main interest of the results summarized in this paper resides in their agreement with our starting hypothesis: in our group of patients the only significant increase in frequency is exhibited by the HLA-B 35 antigen which was previously shown to be associated with low blood Mg levels [10, 11, 12]. This finding agrees equally well with the possible role of Mg metabolism in certain associations between HLA and diseases as previously proposed by *Dausset* and *Henrotte* [3]. In the present investigations HLA-B 35 patients also show lower blood Mg values than non-B 35, although the difference is not significant, probably for want of data.

The mechanisms involved in the genetic regulation of blood Mg and the relationships with HLA antigens are not known; they have been discussed with more details in previous papers [11, 12]. Let us simply recall that HLA-B 35 individuals seem to be more frequent ($P < 0{,}04$) among stress sensitive subjects (type A behavior as defined by *Jenkins* [18]) than among type B controls [14]. Under a well standardized stress, the RBC Mg content of stress sensitive type A subjects decreases more ($P < 0{,}01$) than that of type B [15]. Thus, the lower RBC Mg level observed in HLA-B 35 subjects could be the result of larger Mg losses due to the cumulative effects of repeated stresses. The possible occurence of a greater stress sensitivity in B 35 subjects is in good keeping with the association between B 35 and latent tetany described here, since latent tetany patients themselves appear to be particularly stress-sensitive [6]. Genetic defects in Mg transport systems (decreased intestinal absorption, increased renal loss) could also be associated with the HLA-B 35 antigen.

Whatever the mechanisms involved, our findings suggest that B 35 associated genetic factors may favor the appearance of a latent tetany syndrome by inducing a down regulation of blood Mg concentrations. These genetic factors would, then, only trigger the development of latent tetany in spasmorhythmic subjects, whose constitutional and perhaps familial susceptibility to hyperexcitability would depend upon other genetic factors than those at stake in the HLA-Mg relationship.

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