Autoantibodies in untreated and treated essential hypertension: relationship to histocompatibility leucocyte antigen-B15 and vascular complications

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Summary
1. The presence of autoantibodies and the histocompatibility leucocyte antigen (HLA) antigen B15 was studied in relation to vascular complications (WHO III) in 148 patients with essential hypertension.
2. Nine of 36 patients with WHO stage III hypertension had autoantibodies, compared with seven out of 78 normotensive controls.
3. The frequency of B15 was 36.1% in hypertensive patients with stage III hypertension and 14.8% in controls. Nine of 18 patients with cerebral complications had B15 and four out of 18 with cardiac complications had B15.
4. The relative risk of vascular complications was 3.4 times higher in B15-positive patients with essential hypertension compared with B15-negative patients.
5. This study suggests that B15-positive patients with essential hypertension represent a subgroup with a higher risk of vascular complications. Long-term studies are needed to determine whether B15 might serve as predictor for vascular complications.
6. The study adds further support to suggestions of a genetic and possibly HLA-linked connection between essential hypertension, diabetes and autoimmunity.

Key words: antigen B15, autoantibodies, autoimmunity, essential hypertension (WHO stage III), HLA-antigen B15.

Abbreviation: HLA, histocompatibility leucocyte antigen.

Introduction
The prevalence of antinuclear factor or antinuclear antibodies (ANF or ANA) has been found to be significantly higher in both untreated and treated hypertensive patients than in normotensive controls (Kristensen & Andersen, 1978; Wilson, Bullock & Booth, 1978). IgG-ANF was related to blood pressure in untreated patients and fundal changes in both untreated and treated hypertensive patients; in the treated patients the prevalence of at least one autoantibody was associated with ischaemic ECG changes.

As the HLA-B15 in a subsequent study was found to be elevated in hypertensive patients with a family history of hypertension or with autoantibodies (Kristensen, Andersen, Lamm & Kissmeyer-Nielsen, 1977), the inter-relationships between autoantibodies, B15 and vascular complications have been studied.

Material and methods
It was possible to tissue-type 149 of the originally 164 hypertensive patients and 61 of the 80 normotensive controls (Kristensen, 1978). One HLA-B15-negative male was subsequently excluded, as he was found to have renovascular hypertension. Detailed reasons for exclusions will be published elsewhere.

The hypertensive series comprised 85 males and 63 females (age range 17–69 years) and the normotensive control group consisted of 32 males and 29 females (age range 21–61 years).

Cerebro-cardiovascular complications were diagnosed according to standard medical procedures and had been recorded by medical staff before tissue-typing was performed. Such patients
are classified as stage III patients (WHO, 1962). The data used refer to status at admission. Autoantibodies of IgG and IgM class were demonstrated by means of the indirect immunofluorescence method (Andersen & Beutner, 1972). Antibodies against the following tissue components were considered: nucleus, smooth muscle, glomerulus, parietal cell and mitochondria. The sera were tested in doubling dilutions. A titre $\geq 20$ was considered positive.

HLA-ABC tissue-typing was performed as previously described (Kissmeyer-Nielsen & Kjerbye, 1967). Tissue-typing of our control series has recently been completed.

**Results**

Thirty-six patients (29 males and seven females) were found to be in WHO stage III: 18 had cerebral (strokes, transient ischaemic attacks, encephalopathy and retinal thrombosis) and 18 had cardiac complications (myocardial infarction, congestive heart insufficiency and angina pectoris).

The incidence of at least one autoantibody was 25% (nine of 36) in these patients and 9% (seven of 78) in the normotensive controls ($P < 0.05$). Titres of autoantibodies ranged from 20 to 640 in patients and the titre was 20 in six, and 40 in only one, of the controls.

The frequency of B15 was 36.1% (13 of 36) in patients with WHO stage III hypertension and 14.8% (nine of 61) in the controls, which was somewhat lower than previously reported in blood donors (19%). Patients with cerebral complications had B15 in 50% of the cases (nine of 18, $P < 0.005$); patients with cardiac complications had a frequency of B15 of 22.2% (four of 18, N.S.).

Three of the 13 B15-positive patients in the WHO stage III group had autoantibodies and autoantibodies were found in six of the 23 B15-negative patients with hypertension in this stage.

A comparison of clinical data in B15-positive and B15-negative patients was then carried out (Table 1). The male/female ratio in the B15-positive group was twice that in the negative group, whereas no difference with respect to age, blood pressure, body weight and serum creatinine were found. The known duration of the hypertension varied greatly and ranged from 1 to 192 months in each group.

There was a 3-4-fold higher relative risk of vascular complications among B15-positive patients ($P < 0.01$, Table 1). The prevalence of at least one AB in the B15-positive group was about twice that in the B15-negative group. Familial predisposition to hypertension was found in 21 of 27 B15-positive patients and in 43 out of 114 B15-negative patients ($P < 0.001$). Information about the family could not be obtained from one B15-positive and six B15-negative patients. Thirty-nine of the males had familial disposition. Of these, 16 were B15-positive. These two groups were also comparable with respect to the above clinical parameters. Nine of the 16 B15-positive males with familial disposition to hypertension were in WHO III, as opposed to seven out of 23 B15-negative

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<td>Mean values $\pm$ SD are shown. $^*P &lt; 0.01$; $^{**}P &lt; 0.05$.</td>
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<td>Prevalence of at least one autoantibody</td>
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males. Twenty-five of the females had the disposition and five of these were B15-positive. These two groups were, however, not comparable. Mean age in the B15-positive females was 59 years and 44 years in the B15-negative females.

Discussion

The results from the present investigation showed that patients with WHO stage III hypertension had AB almost twice as often as normotensive healthy subjects. This is in good agreement with the results from population studies, which demonstrated an association between cardiovascular morbidity and mortality (Mathews, Whittingham, Hooper & Mackay, 1973).

Moreover, the study showed that, despite equal age, known duration of the hypertension, blood pressure, body weight and serum creatinine concentrations, HLA-B15-positive patients had AB about twice as often as the B15-negative patients, and that the risk for vascular complications was 3.4-fold higher among B15-positive patients than B15-negative patients.

Similar studies have not yet been published. It is, however, noteworthy that B15 (and B8) and AB are associated with insulin-dependent diabetes (Nerup, Platz, Andersen, Christy, Egebjerg, Lyngsøe, Poulsen, Ryder, Thomsen & Svejgaard, 1976; Farid, Barnard, Pepper, Noel, Kelly, Davis, Hobeika & Marshall, 1978; Lendrum, Walker, Cudworth, Woodrow & Gamble, 1976), and with systemic lupus erythematous (Grumet, Conkell, Bodmer, Bodmer & McDevitt, 1971; Waters, Konrad & Walford, 1971; Celand, Bell, Williams, & Saurino, 1978), especially as in these diseases vascular damage is also rather frequent.

In the whole series of patients in the present material, the frequency of B15 or B8 was not increased, whereas both Löw, Schersten, Santor, Thulin & Mittelmann (1975) and Gaulde, Michel & Safar (1978) found an increase in B8 in patients with essential hypertension. In the latter study B15 was also increased, but in none of the studies were patients evaluated with respect to vascular damage or presence of AB.

The observation that hypertensive patients with cerebral complications had B15 in 50% of the cases, as compared with a frequency of B15 in only 22-29% of patients with cardiac complications, deserves comment. In a previous communication (Kristensen & Petersen, 1978) an association between the atherosclerotic C3-F gene and hypertensive coronary heart disease was demonstrated, whereas no association between this gene and cerebral complications could be found.

The present findings of a possible inter-relationship between AB, B15 and vascular complications seems to support suggestions of a genetic and possible HLA-linked connection between essential hypertension, diabetes and autoimmunity (Mathews, Whittingham & Mackay, 1974), and suggest that B15-positive hypertensive patients represent a new subgroup at higher risk for vascular complications.

References


