Association between the C3F-gene and essential hypertension

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Summary

1. The complement 3 (C3) phenotype distribution in 112 patients with essential hypertension was compared with the distribution in 316 normotensive control subjects.

2. A significant increased frequency of the C3F-gene was found among the patients (0.2637 vs 0.1721, \( P = 0.0031 \)), indicating an association between the C3F-gene and essential hypertension.

3. The relative risk of essential hypertension was calculated to be 1.90 for C3F-positive individuals.

4. The association between the C3F-gene and essential hypertension was stronger among the untreated patients, where a relative risk of 3.89 was found for C3F-positive subjects.

5. A significant negative correlation was found between the C3F-positivity and the severity of the hypertensive disease estimated by eye ground changes. This might be in accordance with a negative natural selection of C3F-positive hypertensive patients.

6. The study supports the hypothesis that immunogenetic factors may be of pathogenetic importance in essential hypertension.

Key words: complement C3 polymorphism, essential hypertension.

Abbreviations: C3, third component of the complement system; BP, arterial blood pressure; FH, fundus hypertonicus.

Introduction

In recent years there has been increasing evidence for immunological changes in essential hypertension [1]. Ebringer & Doyle [2] and Kristensen [3] demonstrated raised levels of serum immunoglobulins. Gudbrandsson, Hansson, Herlitz, Lindholm & Nilsson [4] and Kristensen & Andersen [5] reported increased frequency of autoantibodies, Olsen [6] showed delayed hypersensitivity and Gudbrandsson et al. [4] found increased lymphocyte reactivity against arterial wall antigens in patients with essential hypertension compared with healthy control subjects. However, it is still uncertain whether these changes are primary or secondary to the pressure-induced vascular lesions of essential hypertension. In many immunological processes the complement system is involved and in this system the third component (C3) has a key position [7]. In the present study C3 polymorphism in respect of the two common alleles C3F and C3S has been evaluated in patients with essential hypertension and in normotensive control subjects.

Material and methods

The hypertensive group consisted of consecutive patients aged below 70 years, who were treated for essential hypertension during the period of the study in a department of internal medicine. The patients had a systolic blood pressure (BP) above 160 mmHg and/or a diastolic BP (phase V) above 105 mmHg after 10 min rest in supine position on at least three occasions. All patients had been extensively examined to rule out secondary forms of hypertension. None of the patients included had severe renal insufficiency. The 112 patients with essential hypertension comprised 45 females aged 23–69 years (mean 51.9) and 67 males aged 18–67 years (mean 49.3). Twenty-eight of the patients (25%) were receiving no medication at the time of C3 typing. The rest (75%) were being treated with diuretics, methyldopa, hydralazine or β-adrenoceptor...
blocking agents. The severity of the hypertensive vascular disease was graded according to the Keith, Wagener and Barker classification of hypertensive retinal changes.

The normotensive control population comprised 316 unrelated healthy subjects selected consecutively from a population study. The controls were without previous hypertension and had a systolic BP lower than 140 mmHg and a diastolic BP lower than 95 mmHg at the time of C3 typing. Blood pressure was measured in the same way as in the patients but in the sitting position after 5 min at rest. The control group consisted of 141 females and 175 males. The mean age in the controls was 43.4 years (range 29–61).

Both the hypertensive patients and the controls consented to participate in the study after being informed of the investigation.

The C3 phenotyping was performed on plasma samples by means of horizontal high voltage agarose gel electrophoresis by the method described by Teisberg [8]. The materials and apparatus used were: agarose (Litex type HSA, Denmark); electrophoresis apparatus (Dansk Laboratorieudstyr, Copenhagen) cooled to 10°C by a thermostatted water bath (Hetofrig, Birkerød). The gels were stained after fixation and drying with Coomassie Brilliant Blue R (Sigma B-0630) dissolved in ethanol/acetic acid/water (45:10:45, by vol.) for 10 min and destained in 4% (w/v) acetic acid for 10 min.

Only the common C3 phenotypes S, FS and F [9] were included in the calculations.

Three hypertensive patients and two normotensive controls had rare C3 variants and were therefore excluded from the material.

The C3F and FS classes were pooled in the statistical calculations. P = 0.0031 for unity of hypertensive patients vs controls (Fisher's exact test). The C3F-gene frequencies of the two alleles C3F and C3S were: in the hypertensive group, C3F = 0.2637 and C3S = 0.7363; in the normotensive controls, C3F = 0.1725 and C3S = 0.8275. Assuming a Hardy-Weinberg equilibrium in the normotensive group good agreement was found between observed and expected values (P > 0.95). The relative risk of essential hypertension determined by the method of Woolf [10] was calculated to be 1.90 for the C3F-positive individuals.

There was significantly higher frequency of C3F-positivity among the untreated hypertensive patients compared with the patients treated with the antihypertensive drugs (18 of 28 patients vs 34 of 84 patients, P = 0.024, Fisher's exact test). The relative risk of the disease for C3F-positive untreated hypertensive patients and normotensive controls was 3.89.

When the hypertensive patients were classified according to the degree of eye changes (fundus hypertonicus, FH, 0–IV) logistic regression analysis showed a significant decrease in the frequency of C3F-positive individuals (FH: 17/28; FH-I: 14/21; FH-II: 18/52; FH-III: 3/9; FH-IV: 0/2; P = 0.0035). Positive family history of hypertension (parent or sibling) did not influence the C3-type distribution significantly in the hypertensive group, nor did a classification according to age, although seven out of ten patients below 30 years were found to be C3F-positive.

Discussion

The results indicate an association between the C3F-gene and essential hypertension with a relative risk for the disease of 1.90 for C3F-positive individuals. This association was stronger among the untreated hypertensive patients, with a relative risk of 3.89. The frequency of the
C3F-gene in the normotensive controls was a little lower than that earlier reported in a Danish population study [9]: 0.172 vs 0.183 (N.S.), but this might be expected as some of the individuals in the population study might have hypertension.

The association between the C3F-gene and essential hypertension could be due to a genetic linkage between the C3-gene and the trait for essential hypertension. However, the heterogeneity with regard to the C3 phenotype distribution according to antihypertensive treatment, and the negative correlation between C3F-positivity and hypertensive retinal changes, suggest that the C3 polymorphism plays a role in the pathogenesis of essential hypertension. Previously it has been shown that the C3F component has an enhanced effect compared with the C3F in the immune adherence reaction in experiments in vitro [11]. Thus an increased efficiency of the C3F component during the complement activation causing cell membrane damage and enhanced permeability of the endothelium might explain the association between the C3F-gene and essential hypertension.

The negative correlation between the severity of the hypertensive disease estimated by fundoscopy and C3F-positivity is consistent with natural negative selection of C3F-positive patients. This could be due to an increased mortality of patients with essential hypertension who had the C3F-gene compared with patients who did not have the C3F-gene.

A positive association between the C3F-gene and atherosclerosis has earlier been reported by Sørensen & Dissing [12] and confirmed by Kristensen & Petersen [13]. In the latter study [13], a significantly increased frequency of C3F-gene in a group of 68 untreated patients with essential hypertension with a mean age of 38–39 years (range 16–61), compared with age-matched normotensive healthy subjects, was found; however, these authors did not conclude that the C3F-gene played an aetiological role in essential hypertension, but stated that the presence of the C3F-gene might accelerate vascular disease. In our opinion the results of the present study together with the findings of Kristensen & Petersen [13] support the existence of a genetically determined immunological abnormality predisposing to essential hypertension, and suggest that immunological changes could be primary to vascular damage in essential hypertension.

Acknowledgments

This work was supported by the Danish Heart Foundation and Bloddonorernes Forskningsfond.

References