ORIGINAL ARTICLE

C-reactive protein is elevated in the offspring of parents with essential hypertension

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Arch Dis Child 2007;92:304–308. doi: 10.1136/adc.2006.094672

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Accepted 27 November 2006
Published Online First
6 December 2006

Background: Hypertension is a risk factor for cardiovascular disease (CVD). Studies in adults have shown that high sensitivity C-reactive protein (CRP) levels are associated with increased risk of CVD and essential hypertension (EHT). Genetic background is widely accepted as a risk factor for CVD. The aim of the present study was to analyse the association of high sensitivity CRP levels with other cardiovascular risk factors in children and young adults with at least one parent with EHT.

Methods: Fifty one healthy children and young adults (28 boys) with at least one parent with hypertension and 69 (41 boys) whose parents did not have hypertension were recruited prospectively from primary care centres. High sensitivity CRP, fasting lipid profile, blood pressure (BP) and anthropometric variables were obtained for all participants.

Results: CRP values were higher in the study group than in controls (logCRP mean difference: -0.69 ; 95% confidence interval: -1.05 to -0.33), even when differences were adjusted for age, gender, body mass index (BMI) and triglyceride levels ($p=0.01$). No differences were observed in BP values between groups. In the study group, 35.3% of the participants had a CRP level ≥ 1 mg/l compared to 14.5% in the control group ($p=0.009$). CRP showed a significant correlation with body weight ($\rho=0.28$, $p=0.04$), BMI ($\rho=0.32$; $p=0.02$) and ponderosity index ($\rho=0.28$; $p<0.05$).

Conclusions: CRP is significantly higher in the offspring of parents with EHT. A significant positive relationship exists between BMI and serum CRP levels in this high risk group of children and young adults.

Hypertension is a risk factor for cardiovascular disease (CVD) and is the most important risk factor for stroke.¹ Essential hypertension (EHT) is known to be a multifactorial process with a genetic component.² Hypertension is about twice as common in subjects with one or both parents with hypertension, and many epidemiological studies suggest that genetic factors account for approximately 30% of the variation in blood pressure (BP) in various populations.³

C-reactive protein (CRP) is a non-specific inflammatory marker commonly used in paediatrics in the diagnosis and monitoring of inflammation and active infection, as CRP values increase markedly during these acute processes. High sensitivity methods have recently been developed and permit the determination of CRP levels far below those found in inflammatory processes.⁴ Prospective studies in adults have shown that these high sensitivity CRP levels are associated with an increased risk of several manifestations of CVD, including myocardial infarction,⁵ stroke,⁶ sudden cardiac death⁷ and peripheral artery disease.⁸

CRP levels are also associated with EHT in adults.^{9–10} There are also several studies which analyse the association between CRP levels and cardiovascular risk factors in children.¹¹ Recently, it has been reported that high serum levels of CRP and arterial structural changes coexist at an early age in subjects with a family history of premature myocardial infarction.¹² To our knowledge, none of these studies dealt with this relationship in the offspring of subjects with EHT.

The aim of this study was therefore to compare CRP levels in the offspring of subjects with hypertension to those in a control population and to analyse the relationship between CRP levels and other cardiovascular risk factors.

METHODS

EHT offspring group

These individuals were recruited from three primary care centres, two in urban regions and one in a rural area. Primary care doctors agreed to collaborate in the study and were responsible for contacting patients with hypertension, asking for their consent for participation and fixing a date for the examination of their offspring. Subjects were submitted for examination by their respective primary care doctors.

Primary care doctors were asked to submit only the offspring of parents with EHT. The diagnosis of EHT was established according to standard diagnostic investigation (medical history, physical examination and routine laboratory tests). Therefore, the offspring of patients with secondary hypertension were not included in this study.

The first 51 subjects (children and young adults) attending the office who fulfilled the following criteria were included in this study: (a) at least one parent with EHT, defined as having systolic BP (SBP) or diastolic BP (DBP) equal to or higher than 140 mm Hg or 90 mm Hg, respectively, according to current recommendations¹³; (b) age in the range of 5–25 years.

Twenty eight boys and 23 girls with a median age of 18.4 years (age range 5–25 years) were studied.

Abbreviations: BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; EHT, essential hypertension; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PI, ponderosity index; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglycerides

Table 1 Gender composition, anthropometric measures, lipid profile, C-reactive protein levels and blood pressure values

	Control group (n=69)	EHT offspring group (n=51)	p Value
Gender (male/ female)	41/28	28/23	0.62
Age (years)†	17.5 (9–21)	18.4 (5–25)	0.22
Weight (kg)	59.2±11.6	63.1±20.0	0.21
Height (cm)	167.5±10.5	164.0±13.9	0.13
BMI (kg/m ²)	20.9±2.7	23.0±5.0	0.009
PI (kg/m ³)	12.5±1.6	14.0±2.8	0.001
SBP (mm Hg)	111.9±10.9	112.7±12.1	0.35
DBP (mm Hg)	70.3±8.1	68.9±8.0	0.72
TC (mg/dl)	156.7±24.8	157.8±31.0	0.84
HDL-C (mg/dl)	53.7±10.3	56.0±13.8	0.32
LDL-C (mg/dl)	90.0±21.9	83.8±24.2	0.14
TG (mg/dl)	51.8±21.8	71.9±44.4	0.004
CRP (mg/l)*	0.60 (0.15–8.4)	1.16 (0.15–9.0)	0.001
LogCRP	−1.14±0.9	−0.45±1.1	0.0001

BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; EHT, essential hypertension; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LogCRP, log transformed C-reactive protein; PI, ponderosity index; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

*Median (range); all other data are presented as mean±standard deviation.

Control group

The subjects in this group attended the follow-up visits of a longitudinal project in which reference values and determinants of casual BP were assessed. In 1992 a Spanish multicentre study (the RICARDIN study) including 14 000 children and adolescents between 6 and 18 years of age was conducted in 14 different locations in Spain.¹⁴ The contribution of our group in Asturias, northern Spain, consisted of 1200 subjects. Later, between 1995 and 1997, a subset sample of 270 subjects from this cohort from our region was included in a follow-up study. The 69 healthy children and young adults (41 boys) previously reported to have had parents without EHT, who completed the follow-up visits of the study, were recruited and comprised the control group in the present study. The age range was 9–21 years (median 17.5 years).

In both groups, parental informed consent or personal consent in the case of individuals over 18 years of age was required for inclusion in the study. Those individuals with symptoms of acute illness on the day of the examination were excluded. None of the subjects included in the study were taking non-steroidal anti-inflammatory drugs or statins. Approval of the study protocol was obtained from the research ethics board of our institution.

BP was measured by certified observers using a standardised technique according to the American Academy of Pediatrics recommendations for BP measurement,¹⁵ calculating the average of two determinations obtained with the subject seated and after a resting period of 15 min, using an ERKAMETER Hg sphygmomanometer (Erka, Bad Toelz, Germany). Body weight was obtained for each individual by experienced personnel using a standard balance scale with subjects barefoot and wearing light indoor clothing, to an accuracy of 0.1 kg. Body height was recorded to the nearest 0.5 cm using a ruler attached to the same scale. Body mass index (BMI; body weight (kg)/height²(m²)) and ponderosity index (PI; body weight(kg)/height³(m³)) were calculated afterwards. An overnight fasting blood sample was drawn. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) levels were determined with a Hitachi 717 analyser (Hitachi, Tokyo, Japan) using a standard technique. As no TG value was above 400 mg/dl, low-density lipoprotein cholesterol

Table 2 Distribution of participants according to American Heart Association CRP risk stratification levels

	Risk stratification level ¹⁹		
	Low <1 mg/l (%)	Intermediate 1–3 mg/l (%)	High >3 mg/l (%)
Control group, n=69	59 (85.5)	8 (11.6)	2 (2.9)
EHT offspring group, n=51	33 (64.7)	14 (27.5)	4 (7.8)

EHT, essential hypertension. $\chi^2=7.0$; $p=0.029$.

(LDL-C) was estimated by Friedewald's formula (LDL-C = TC − HDL-C − (TG/5)).¹⁶

CRP was determined by end-point nephelometry using a BN-II system (Dade-Behring, Deerfield, Illinois, USA). The assay was performed according to the manufacturer's protocol. We assessed the intra-individual variability of serum CRP concentrations both in offspring of parents with hypertension and in healthy subjects. The mean intra-assay coefficients of variance were 3.21% and 2.96%, respectively. Two levels of control samples were used for quality control purposes, and day-to-day coefficients of variation (CVs) ranged from 4.93% to 7.84%. The CRP levels of each patient were measured twice using the same samples to check for machine accuracy. Values equal to or higher than 10 mg/l were assumed to be secondary to unapparent or occult underlying disease and were excluded from the study. This high sensitivity assay does not discriminate values below 0.15 mg/l, so all lower values were included in the analysis as 0.15 mg/l. According to the method described elsewhere,¹⁷ CRP values were grouped in three different risk categories: low (<1 mg/l), intermediate (1–3 mg/l) and high (>3 mg/l).

Statistical analysis

Values are presented as mean±standard deviation (SD). Comparisons were performed using Student's unpaired *t* test and Mann-Whitney U test in those cases where values were not normally distributed. Fisher's exact test and χ^2 test were used to analyse qualitative variables. Pearson and Spearman correlation coefficients were applied to establish the association between quantitative variables. Multiple regression analysis was employed to obtain adjusted coefficients eliminating the effect of possible confounding variables; since CRP values were skewed to the right, these values were log-transformed to achieve a normal distribution and then introduced as the dependent variable in the regression analysis. A Jonckheere-Terpstra test, appropriate if the alternatives to the null hypothesis of equality of the different populations are ordered,¹⁸ was used to assess the presence of a significant linear trend between BMI and CRP categories. A two-tailed *p* value of 0.05 was deemed statistically significant. Data were collected in a database created ad hoc for the study, with range and logic filters to avoid incorrect data input and analysed on a PC with the SPSS 11.0 program (SPSS, Chicago, Illinois, USA).

RESULTS

As shown in table 1, both groups were similar in gender composition, age distribution, BP, and TC, HDL-C and LDL-C values. The EHT offspring group showed significantly higher BMI, PI and TG levels.

All CRP values below the lower detection limit of 0.15 mg/l were included in the database as being equal to 0.15 mg/l. No values higher than 10 mg/l were found. Due to the resulting skewness of the distribution, groups were compared using a non-parametric test. Moreover, the analysis was repeated using

Table 3 Spearman correlation coefficients between CRP and other cardiovascular risk factors in offspring of parents with essential hypertension

	Coefficient	p Value
Body weight	0.28	0.04
Body height	0.11	0.45
BMI	0.32	0.02
PI	0.28	<0.05
SBP	-0.05	0.73
DBP	0.19	0.19
TC	-0.23	0.10
HDL-C	-0.16	0.26
LDL-C	-0.15	0.30
TG	0.18	0.21

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PI, ponderosity index; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

for these “uncertain” cases the mean value of the interval between 0 and the detection limit. As expected, no differences were observed whether CRP values were introduced as 0.15 or as 0.075 mg/l (data not shown).

CRP values were significantly higher in the EHT offspring group (table 1) than in controls (logCRP mean difference: -0.69; 95% confidence interval: -1.05 to -0.33). This difference remained statistically significant when adjusted for age, gender, BMI and TG level ($p = 0.01$). More than 35% of the participants in the EHT offspring group but only 15% of the participants in the control group had a CRP level equal to or higher than 1 mg/l (Fisher's exact test, $p = 0.009$) (table 2).

CRP levels in the EHT offspring group were specifically studied and Spearman's correlation coefficients between CRP levels and all other cardiovascular risk factors analysed were obtained (table 3). CRP levels showed a significant correlation with body weight, BMI and PI.

When CRP risk stratification groups were compared (fig 1), BMI showed a significant positive tendency ($p = 0.031$), with the highest BMI levels observed in the high-risk CRP group.

Figure 1 Body mass index distribution in offspring of parents with essential hypertension by C-reactive protein risk categories. Jonckheere-Terpstra test, $p = 0.03$. Upper and lower box sides represent 75th and 25th percentiles, respectively. Thick line: median. Whiskers: values lower than 1.5 times the interquartile range (IQR) away from the nearest edge of the box. Outlier: value between 1.5 and 3.0 times the IQR away from the nearest edge of the box. BMI, body mass index; CRP, C-reactive protein.

DISCUSSION

Plasma CRP levels are commonly used in the diagnosis and monitoring of inflammatory and acute infectious diseases in children and adults. Under these circumstances CRP levels may increase by up to 100 times their normal value in hours or days and then steadily decrease when the problem resolves. Conventional CRP assays are not able to detect blood levels <1 mg/l. The development of high sensitivity CRP assays, such as that used throughout this study, has permitted detection of low-grade inflammation in healthy individuals.^{17–19} Several studies have observed the relationship of CRP with CVD, raising the hypothesis that atherosclerosis could in part be an inflammatory disorder.^{6–8} In this study, we show that CRP is significantly elevated in a sample of children and young adults with at least one parent with EHT. Moreover, CRP levels are clearly positively correlated with BMI and PI in these subjects.

There is a positive association between elevated CRP levels and higher BP in adults, mainly higher SBP.²⁰ Moreover, in a recent prospective study,¹⁰ elevated CRP levels were associated with increased risk of developing hypertension. These observations may also indicate that, like atherosclerosis, hypertension could in some way be considered an inflammatory disorder. A chronic inflammatory state may induce endothelial dysfunction, impairing the ability of the endothelium to produce nitric oxide and prostacyclin, which can contribute to the development of hypertension.²¹

CRP and SBP levels in children showed a positive but weak correlation in an extensive study which included 699 healthy boys.²² However, there was no association between higher CRP levels and high SBP in the children and young adults in our study. Although both studies were carried out on a healthy population, the limited number of subjects in our study could account for this disparity.

Nevertheless, development of hypertension in susceptible patients, such as the offspring of patients with EHT, generally occurs in late childhood or adulthood. Our observation of elevated CRP values without consistent elevation of current BP levels does not exclude a possible role in hypertension and could indicate that CRP elevation is a phenomenon that takes place before actual hypertension occurs. In addition, it has been reported that CRP levels are elevated in overweight youths.²³ In our study, CRP levels were significantly higher in the EHT offspring group than in controls. We have found a positive association between body weight, BMI, PI and CRP levels. Moreover, when CRP levels were grouped according to the risk levels proposed for the clinical use of CRP levels in adults, BMI showed a significant positive linear trend (BMI values increasing as CRP risk increased). A consistent association between CRP and adiposity has been observed in several studies in adults²⁴ and children.²² It has been hypothesised that adipose tissue releases tumour necrosis factor, which induces interleukin-6 production,²⁵ which in turn stimulates hepatic production of CRP.

In order to control statistical confusion, CRP-adjusted differences between groups were determined by multiple regression analysis, in which age, gender, TG and BMI were included as potential confounding factors. CRP levels remained significantly higher in the EHT offspring group after adjustment for age, gender and BMI.

CRP increases cardiovascular risk independently of lipoprotein levels, and in adults CRP correlates weakly with TC, HDL-C or LDL-C.²⁶ Our data showed no association between CRP and lipoprotein levels.

It is not clear whether CRP is only a marker of the underlying inflammatory process that leads to atherosclerosis, with no pathogenic involvement, or is a real cardiovascular risk factor in itself. It has been observed that CRP has direct proinflammatory and atherogenic effects in adults.²⁷ A recent study in 79

What is already known on this topic

- C-reactive protein (CRP), an inflammatory marker, is associated with cardiovascular disease in adults.
- Higher CRP values are associated with higher blood pressure and higher body mass index values.
- Obesity is associated with hypertension in adults and children.

What this study adds

- Compared with controls, the offspring of parents with essential hypertension showed higher C-reactive protein (CRP) and body mass index values while no differences in blood pressure were observed.
- In this group of subjects, CRP elevation is independent of BMI values.

healthy Finnish children demonstrated that CRP levels were significantly associated with decreased endothelial vasodilatory function and increased carotid artery intima-media thickness.²⁸

The American Heart Association in a recent position paper¹⁹ highlights the need to understand the distribution of inflammatory markers in selected population subgroups, especially children, and the need to evaluate the significance of elevated CRP values in children and young adults. Our study throws some light on a special subgroup of children and young adults, the offspring of EHT parents, with special familial risks (genetic, environmental or both) of CVD, which to our knowledge has not previously been studied. Moreover, we have observed that, in this group, CRP and BMI were significantly higher than in controls, while BP values were not. This observation could indicate that elevation of CRP values and being overweight precedes the development of hypertension in the offspring of subjects with EHT. If sustained high CRP values are associated with the development of future hypertension, detection of high CRP values in a normotensive subject with a familial risk of developing EHT, could indicate a need for early preventive measures.

The cross-sectional design of our study does not allow us to infer any causal relationship between variables. It may be difficult for a single regional group to design a prospective study with a sufficient number of descendants of subjects with hypertension. It is not clear from the literature^{5 19 26} whether CRP levels are regulated by genetic or environmental factors. If CRP levels are genetically controlled, there should be larger differences compared to controls when both parents have EHT. This possibility has not been investigated in this paper. On the other hand, parents who develop EHT later in life after having children, have already passed their genes onto their children possibly altering their CRP levels. This may bias the results towards the null hypothesis since some of the subjects in the control group may actually have parents whose EHT has not yet presented. Therefore, well-designed multicentre trials are necessary to confirm these observations and to develop preventive strategies in this age group.

In conclusion, there are significant increases in BMI, PI, TG and CRP levels in the offspring of patients with EHT. There is a significant positive relationship between adiposity and CRP levels in this high-risk group once they reach adolescence and young adulthood. However, this elevation in CRP levels cannot be accounted for by increased adiposity alone.

ACKNOWLEDGEMENTS

We wish to thank Penny Metcalfe for revision of the English translation and the medical and nursing staff of primary care centres and the Hospital Universitario Central de Asturias (Spain), who in one way or another contributed to the study. Overall, we are indebted to all the subjects and families who voluntarily participated in this research.

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The present study has been supported by the following grants: (1) University of Oviedo, reference: MA-03-519-1; (2) Ernesto Sánchez Villares Foundation Research Grant, 2003; (3) Instituto de Salud Carlos III, PI-030350.

Competing interests: The authors declare that they have no involvement that might raise the question of bias in the work reported or in the conclusions, implications or opinions stated.

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