Hypertension and cerebral white matter lesions in a prospective cohort study

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Summary

White matter lesions are frequently found on cerebral MRI scans of elderly people and are thought to be important in the pathogenesis of dementia. Hypertension has been associated with the presence of white matter lesions but this has been investigated almost exclusively in cross-sectional studies. We studied prospectively the association of these lesions with the duration and treatment of hypertension. We randomly sampled 1077 subjects aged between 60 and 90 years from two prospective population-based studies. One-half of the study subjects had their blood pressure measured between 1975 and 1978 and the other half between 1990 and 1993. All subjects underwent 1.5 T MRI scanning; white matter lesions in the subcortical and periventricular regions were rated separately. Subjects with hypertension had increased rates of both types of white matter lesion. Duration of hypertension was associated with both periventricular and subcortical white matter lesions. This relationship was influenced strongly by age. For participants with >20 years of hypertension and aged between 60 and 70 years at the time of follow-up, the relative risks for subcortical and periventricular white matter lesions were 24.3 [95% confidence interval (CI) 5.1–114.8] and 15.8 (95% CI 3.4–73.5), respectively, compared with normotensive subjects. Subjects with successfully treated hypertension had only moderately increased rates of subcortical white matter lesions and periventricular white matter lesions (relative risk 3.3, 95% CI 1.3–8.4 and 2.6, 95% CI 1.0–6.8, respectively) compared with normotensive subjects. For poorly controlled hypertensives, these relative risks were 8.4 (95% CI 3.1–22.6) and 5.8 (95% CI 2.1–16.0), respectively. In conclusion, we found a relationship between long-standing hypertension and the presence of white matter lesions. Our findings are consistent with the view that effective treatment may reduce the rates of both types of white matter lesion. Adequate treatment of hypertension may therefore prevent white matter lesions and the associated cognitive decline.

Keywords: MRI; hypertension; longitudinal studies; aged; white matter lesions

Abbreviations: CI = confidence interval; PD = proton density

Introduction

Cerebral white matter lesions are observed frequently on MRI scans of elderly, non-demented people (Breteler *et al.*, 1994; Liao *et al.*, 1996; de Leeuw *et al.*, 1999). In cross-sectional studies, it has been suggested that these white matter lesions may play a role in cognitive decline and dementia (Breteler *et al.*, 1994; Skoog *et al.*, 1996; de Groot *et al.*, 1998, 2000). The pathogenesis of white matter lesions remains largely unknown, but it is generally thought that hypertension and other vascular risk factors are involved (Breteler *et al.*, 1994; Ylikoski *et al.*, 1995; Liao *et al.*, 1996; de Leeuw *et al.*, 1999, 2000). The longitudinal relationship between hypertension and white matter lesions has not been investigated until now except in two studies with a follow-up of 6 and 4 years, respectively (Liao *et al.*, 1996; Dufouil *et al.*, 2001), and in a male cohort from the NHBLI (National Heart, Lung and Blood Institute) twin study, with 25 years of follow-up (Swan *et al.*, 1998). Results from one of these studies suggested that successful treatment of hypertension may reduce the risk of white matter lesions (Liao *et al.*, 1996) and recently the Syst-Eur investigators reported that, in subjects with isolated systolic hypertension, antihypertensive treatment significantly reduced the incidence of dementia (Forette *et al.*,

1998). Hypertension in the elderly may have been present for a long period. If hypertension early in life is related to white matter lesions later in life, effective treatment of hypertension may prevent or delay the emergence of white matter lesions and of cognitive impairment.

We investigated prospectively the associations between the duration and treatment of hypertension and the presence of cerebral white matter lesions.

Methods
Study population
The Rotterdam Scan Study was designed to study the determinants and consequences of age-related brain abnormalities in the elderly. In 1995/1996, 1904 subjects aged between 60 and 90 years were selected randomly in strata of age (5 years) and sex from two large, ongoing prospective follow-up studies, the Zoetermeer Study and the Rotterdam Study. The Zoetermeer Study had its baseline data collection during 1975–1978; the mean follow-up period was 19.6 years. The Rotterdam Study had its baseline data collection during 1990–1993; the mean follow-up period was 4.8 years. Both studies have been described in detail elsewhere (Hofman *et al.*, 1979, 1991). In brief, the Zoetermeer Study is a prospective, population-based study involving 10 361 subjects who were aged between 5 and 91 years at baseline. The study originally addressed the determinants of chronic diseases. The Rotterdam Study is a population-based prospective cohort study involving 7983 elderly subjects aged ⩾55 years, which is investigating the determinants of neurological, cardiovascular, locomotor and ophthalmological diseases in the elderly.

For the follow-up examination in the Rotterdam Scan Study, subjects were invited initially by letter and contacted subsequently by telephone. Upon their agreement to participate in the study, a list of contra-indications was reviewed in order to assess eligibility (dementia; blindness; or the presence of MRI contra-indications, including prosthetic valves, pacemaker, cerebral aneurysm clips and a history of intraocular metal fragments, cochlear implants or claustrophobia). Of the 1904 subjects who were invited to participate, 1717 were eligible for the study. Complete information was obtained, including a cerebral MRI scan, from 1077 persons (response 63%); 563 from the Rotterdam Study (response rate 68%) and 514 from the Zoetermeer Study (response rate 58%). The response rate declined from 73% in individuals aged between 60 and 70 years to 48% for participants aged between 80 and 90 years (in 1995/1996). Each participant signed an informed consent form. The study was approved by the medical ethics committee of Erasmus University.

Measurement of risk factors
Physical examinations and standardized questionnaires were administered in a similar way both at baseline and at follow-up in the two subpopulations of the Rotterdam Scan Study. At baseline and follow-up, blood pressure was measured twice on the right arm with a random zero sphygmomanometer and the participant in the sitting position. The average of the two blood pressure measurements was used in the analysis. Hypertension was defined as a systolic blood pressure ⩾160 mmHg and/or a diastolic blood pressure ⩾95 mmHg and/or the self-reported use of blood pressure-lowering medication. Information on blood pressure-lowering medication was obtained from a computerized, structured questionnaire, which was checked by a physician.

Height and weight were measured with the participant in light clothing. The body mass index was calculated as weight divided by height squared. Information on smoking behaviour was obtained by the use of a standardized questionnaire, which was checked by a physician during the interview. Diabetes mellitus was considered to be present if the participant was taking oral antidiabetic drugs or insulin.

MRI scanning protocol
For all participants, an axial T_1-, T_2- and proton density (PD)-weighted cerebral MRI scan was made on a 1.5 T MRI scanner. Subjects recruited from the Zoetermeer Study were scanned with a 1.5 T MR Gyroscan (Philips, Best, The Netherlands) and participants from the Rotterdam Study with a 1.5 T MR Vision (Siemens, Erlangen, Germany). In a uniform protocol, the following pulse sequences were applied: Gyroscan, T_1 [TR (repetition time) 485 ms, TE (echo time) 14 ms], T_2 (TR 2236, TE 90 ms) and PD (TR 2236 ms, TE 20 ms); Vision, T_1 (TR 700 ms, TE 14 ms), T_2 (TR 2200 ms, TE 80 ms) and PD (TR 2200 ms, TE 20 ms). Slice thickness was 6 and 5 mm, respectively, with an interslice gap of 20.0%. The images were printed as hard copy with a reduction factor of 2.7.

White matter lesion rating scale
White matter lesions were considered to be present if there was hyperintensity on both the PD- and the T_2-weighted image without prominent hypointensity on the T_1-weighted image. White matter lesions were classified into those in the subcortical and periventricular regions (de Groot *et al.*, 2000). The number and size of subcortical white matter lesions was rated on hard copy according to their largest diameter in categories of small (<3 mm), medium (3–10 mm) and large (>10 mm). In order to calculate the volume of subcortical white matter lesions on hard copy, they were considered to be spherical with a fixed diameter for each size category. Periventricular white matter lesions were rated semiquantitatively for each region [adjacent to the frontal horns (frontal capping); adjacent to the lateral wall of the lateral ventricles (bands); and adjacent to the occipital horns (occipital capping)] on a four-point scale: 0 = no white matter lesions; 1 = pencil-thin periventricular lining; 2 = smooth halo or thick lining; 3 = large confluent white matter lesions. The overall

amount of periventricular white matter lesion was calculated by summing the scores for the three separate regions to give a total in the range 0–9. All MRI scans were examined by two raters from a pool of four experienced raters. In case of disagreement by more than one point, a consensus reading was held; in all other cases the readings of the two readers were averaged. The inter- and intra-rater studies showed good to excellent agreement. Weighted κ values for grading the periventricular white matter were between 0.79 and 0.90. For total subcortical white matter volume, the inter- and intra-rater intraclass correlation coefficients were 0.88 and 0.95, respectively.

Statistical analysis

The relationships among hypertension, its duration and treatment, and white matter lesions were assessed by age- and sex-adjusted logistic regression with the presence of severe white matter lesions as the outcome variable. The strength of the association was expressed as the relative risk, as estimated by the odds ratio, and is presented with a 95% confidence interval (CI). White matter lesions were dichotomized at the upper quintile. The upper quintile was taken to represent severe white matter lesions. Subjects without severe white matter lesions were taken as the reference group (lower four quintiles). Additional adjustments were made for the following possible confounding factors: body mass index, smoking behaviour (never, former, current) and diabetes mellitus.

The duration of hypertension was studied in each of the two subpopulations separately by introducing dummy variables into the model for the duration of hypertension. In participants originating from the Rotterdam Study, duration was defined as <5 years (hypertension present in 1995/1996 but not in 1990–1993) or >5 years (hypertension present in 1990–1993 and in 1995/1996). In participants from the Zoetermeer Study, the duration was estimated as <20 years (hypertension present in 1995/1996 but not in 1975–1978); or >20 years (hypertension present in 1975–1978 and in 1995/1996). Subjects without hypertension at baseline and at follow-up were taken as the reference group. Subjects who were hypertensive at baseline (1990–1993 or 1975–1978) but not during the 1995/1996 data collection were excluded from the analysis (*n* = 22 and *n* = 19, respectively).

The relationship between duration of hypertension and the presence of white matter lesions may be biased by selective survival because hypertension is related to mortality (Hansson *et al.*, 1998). In particular, increased mortality might occur with long-standing hypertension and in elderly subjects. We addressed this issue by age-stratified analysis because we expected a smaller effect of selective mortality in the youngest age category. In addition, we compared the baseline prevalence of hypertension between survivors and those who died before the follow-up assessment, by means of age- and sex-adjusted analysis of covariance.

Previous studies indicated the importance not only of differentiating between treated and untreated hypertensives but also of distinguishing between successfully treated and poorly controlled hypertension in the treated hypertensives. It has been shown that there is an excess risk of white matter lesions in poorly controlled hypertensives but a reduction in risk in successfully treated hypertensives (Liao *et al.*, 1996). Participants who were identified as hypertensive during the data collection of the Rotterdam Scan Study (1995/1996) were considered as treated if they reported the use of blood pressure-lowering medication, otherwise they were classified as untreated. Subjects were considered as successfully treated if they reported the use of blood pressure-lowering medication and their systolic and diastolic blood pressures were <160 and <95 mmHg, respectively. If their blood pressure still fulfilled criteria of hypertension despite blood pressure-lowering medication, they were classified as poorly controlled. Subjects without hypertension at follow-up served as the reference group. The association between treatment status at follow-up and white matter lesions was studied by the introduction of dummy variables for treatment status into the model.

Results

Table 1 presents baseline and follow-up characteristics of the participants and non-participants in the two subpopulations of the Rotterdam Scan Study. In the 60–70, 70–80 and 80–90 year age groups, 213, 204 and 146 participants, respectively, originated from the Rotterdam Study and 253, 211 and 50 from the Zoetermeer Study. Of all subjects, 20% had no periventricular white matter lesions, whereas 8% of all subjects were free of subcortical white matter lesions. The median volume of subcortical white matter lesions on hard copy was 3.9 ml and the median grade of periventricular white matter lesions was 2 (range 0–9).

In both subpopulations of the study, non-participants were significantly older than participants. Non-participants from the Zoetermeer Study had a significantly higher systolic blood pressure at baseline assessment than participants (137.2 versus 131.4 mmHg, *P* = 0.04). The proportion with hypertension was ~25% larger in participants than in non-participants in both subpopulations of the study, but the difference was not statistically significant.

Cumulative mortality until follow-up among eligible subjects from the Zoetermeer subpopulation in the age groups 40–50, 50–60 and 60–70 years at baseline (1975–1978) was 8, 17 and 47%, respectively. For eligible subjects from the Rotterdam subpopulation who were aged between 55–65, 65–75 and 75–85 years at baseline (1990–1993), cumulative mortality for the relevant age category until follow up was 10, 28 and 62%, respectively.

The difference in the prevalence of hypertension between those who died before follow-up and those who were eligible for the study was not significant in the youngest age category

Table 1 *Characteristics at baseline and follow-up of subjects eligible for the Rotterdam Scan Study**

Characteristic	Subjects originating from Zoetermeer Study			Subjects originating from Rotterdam Study		
	Baseline (1975-1978)		Follow-up (1995/1996)	Baseline (1990-1993)		Follow-up (1995/1996)
	Participants (*n* = 514)	Non-participants (*n* = 371)		Participants (*n* = 563)	Non-participants (*n* = 269)	
Mean age (years)	51.2 (6.7)	56.1 (7.1)	70.8 (6.5)	68.9 (8.0)	72.0 (8.0)	73.5 (8.0)
Women (%)	53.3	59.7	53.3	49.9	58.5	49.9
Systolic BP (mmHg)	131.4 (17.0)	137.2 (18.0)	148.7 (22.8)	136.7 (20.5)	139.3 (20.2)	146.1 (20.4)
Diastolic BP (mmHg)	81.3 (10.9)	83.0 (11.5)	81.1 (11.6)	73.2 (10.9)	71.3 (10.9)	76.6 (11.4)
Body mass index (kg/m^2)	25.0 (3.0)	25.3 (3.1)	27.0 (3.7)	26.3 (3.4)	26.3 (3.4)	26.3 (3.5)
Hypertension (%)	25.3	31.4	51.6	39.2	48.6	52.6
Diabetes mellitus (%)	0.8	0.2	6.4	6.8	11.9	5.3
Smokers (%)						
Current	37.0	38.3	15.4	20.1	18.8	16.1
Former	35.0	25.1	47.1	45.8	38.4	53.9
Never	28.0	36.6	37.5	34.1	42.7	30.0

*Values are unadjusted means (standard deviation) or percentages; BP = arterial blood pressure.

Table 2 *Relative risks (with 95% confidence interval) of duration of hypertension and severe cerebral white matter lesions**

White matter lesions[†] and age category (years)	Duration of hypertension[‡]					
	Zoetermeer Study			Rotterdam Study		
	No hypertension[§] (*n* = 230)	<20 years (*n* = 153)	>20 years (*n* = 111)	No hypertension[§] (*n* = 238)	<5 years (*n* = 97)	>5 years (*n* = 194)
Subcortical						
60–70	1.0 (reference) **1.3**	6.2 (1.5–25.4) **10.7**	24.3 (5.1–114.8) **23.5**	1.0 (reference) **7.4**	3.7 (1.2–11.7) **20.5**	1.5 (0.5–4.9) **13.2**
70–80	1.0 (reference) **8.6**	2.8 (1.0–7.6) **21.9**	1.3 (0.4–4.0) **15.0**	1.0 (reference) **16.7**	0.9 (0.3–2.5) **17.4**	2.0 (1.3–6.8) **41.7**
80–90	1.0 (reference) **31.3**	1.6 (0.3–8.8) **35.7**	0.8 (0.1–4.8) **23.5**	1.0 (reference) **47.4**	1.3 (0.4–4.0) **59.1**	1.1 (0.5–2.4) **52.5**
Overall	1.0 (reference) **6.6**	2.9 (1.5–5.8) **17.6**	2.6 (1.2–5.6) **18.9**	1.0 (reference) **17.4**	1.6 (0.9–2.9) **28.1**	1.8 (1.1–3.0) **38.3**
Periventricular						
60–70	1.0 (reference) **1.7**	1.9 (0.4–8.6) **5.3**	15.8 (3.4–73.5) **20.6**	**5.5**	3.4 (0.9–13.0) **15.4**	2.1 (0.5–8.0) **9.4**
70–80	1.0 (reference) **22.8**	0.9 (0.4–2.1) **20.3**	1.5 (0.6–3.4) **31.7**	1.0 (reference) **14.3**	1.1 (0.4–3.4) **17.1**	2.8 (1.1–6.9) **31.7**
80–90	1.0 (reference) **58.8**	0.8 (0.2–3.9) **57.1**	0.2 (0.0–1.1) **29.4**	1.0 (reference) **47.4**	0.9 (0.3–2.6) **43.5**	1.2 (0.5–2.7) **51.3**
Overall	1.0 (reference) **13.9**	1.1 (0.6–2.1) **16.3**	1.7 (0.9–3.3) **27.9**	1.0 (reference) **15.5**	1.5 (0.8–2.8) **22.7**	1.8 (1.1–3.1) **33.7**

Data are adjusted for age, sex, diabetes mellitus, body mass index, smoking behaviour. [†]Upper quintile of the distribution of white matter lesion severity; [‡]hypertension: systolic blood pressure $\geqslant$160 mmHg and/or diastolic blood pressure $\geqslant$95 and/or the use of blood pressure-lowering drugs; [§]reference group (subjects without hypertension at either baseline or follow-up). Numbers in bold type in each cell are the percentages of individuals with severe white matter lesions.

in the Zoetermeer Study and differed with borderline significance in subjects in the age categories of 70–80 and 80–90 years (*P* = 0.06 and *P* = 0.09, respectively). In participants from the Rotterdam Study, the prevalence of hypertension was significantly higher in those who had died before follow-up than in eligible subjects for the youngest and middle age categories (*P* = 0.008 and *P* = 0.02, respectively), but not the category 80–90 years.

Table 2 presents the association between the duration of hypertension and the presence of white matter lesions. For participants with >20 years of hypertension and aged between 60 and 70 years at the time of follow-up, the relative risks of

Table 3 *Relative risk (with 95% confidence intervals) of severe cerebral white matter lesions* by treatment status*

White matter lesions[†] and age category	Hypertension (all)	Hypertension treatment status[‡]		
		Untreated (*n* = 187)	Treated successfully (*n* = 231)	Poorly controlled (*n* = 143)
Subcortical				
60–70 years	4.6 (2.2–9.7)	4.3 (1.7–10.8)	3.3 (1.3–8.4)	8.4 (3.1–22.6)
	15.2	**14.7**	**12.2**	**22.7**
70–80 years	1.8 (1.1–3.1)	1.5 (0.8–3.1)	1.8 (0.9–3.4)	2.3 (1.1–4.8)
	25.1	**21.3**	**25.8**	**28.6**
80–90 years	1.2 (0.6–2.3)	(0.5–2.6)	(0.5–2.4)	1.4 (0.6–3.4)
	48.5	**45.9**	**45.5**	**54.8**
Overall	2.1 (1.5–2.9)	1.9 (1.2–3.0)	1.8 (1.2–2.8)	2.8 (1.8–4.5)
	27.1	**23.5**	**25.7**	**34.5**
Periventricular				
60–70 years	2.9 (1.3–6.4)	2.0 (0.7–5.9)	2.6 (1.0–6.8)	5.8 (2.1–16.0)
	10.8	**8.0**	**9.8**	**18.2**
70–80 years	1.5 (0.9–2.4)	(0.6–2.5)	1.1 (0.6–2.2)	2.5 (1.3–4.9)
	26.0	**22.7**	**22.5**	**35.7**
80–90 years	0.9 (0.5–1.8)	0.7 (0.3–1.7)	(0.5–2.2)	(0.4–2.3)
	48.1	**40.5**	**51.8**	**50.0**
Overall	1.5 (1.0–2.1)	(0.7–1.9)	(0.9–2.1)	2.2 (1.4–3.6)
	25.8	**20.3**	**25.1**	**34.5**

*Adjusted for age, sex, diabetes mellitus, body mass index and smoking behaviour; [†]upper quintile of the distribution of white matter lesion severity; [‡]hypertension: systolic blood pressure ⩾160 mmHg and/or diastolic blood pressure ⩾95 and/or the use of blood pressure-lowering drugs. The numbers in bold type in each cell are percentages of individuals with severe white matter lesions.

having subcortical and periventricular white matter lesions were 24.3 (95% CI 5.1–114.8) and 15.8 (95% CI 3.4–73.5), respectively, compared with non-hypertensives. For participants with <20 years of hypertension and aged between 60 and 70 years at the time of follow-up, the relative risks of having subcortical and periventricular white matter lesions were 6.2 (95% CI 1.5–25.4) and 1.9 (95% CI 0.4–8.6), respectively. This observation suggests a relationship between the duration of hypertension and the presence of either type of white matter lesion, because the relative risk increased as the duration of the hypertension extended. A marked modification of the effect according to age was observed, in that the relative risk was highest in the group aged 60–70 years and lowest in those aged 80–90 years.

Table 3 shows the cross-sectional association between hypertension treatment and the presence of cerebral white matter lesions. Because these associations were similar in the two subpopulations, they are presented together. For hypertensive participants who were treated successfully and aged between 60 and 70 years at follow-up, the relative risks of having subcortical and periventricular white matter lesions were 3.3 (95% CI 1.3–8.4) and 2.6 (95% CI 1.0–6.8), respectively, compared with non-hypertensives. However, for participants in whom blood pressure was poorly controlled and who were aged between 60 and 70 years at follow-up, the relative risks of having subcortical and periventricular white matter lesions were 8.4 (95% CI 3.1–22.6) and 5.8 (95% CI 2.1–16.0), respectively, compared with non-hypertensive individuals. Again, a similar modification of the effect according to age was noticed.

Discussion

The main finding in this prospective, population-based study among elderly participants was that current hypertension and hypertension established 5 or 20 years previously are both associated with the presence of white matter lesions in subcortical and periventricular regions. In addition, we found a relationship between the duration of hypertension and the presence of white matter lesions. Individuals with successfully treated hypertension had a lower risk of white matter lesions than poorly controlled hypertensives. Our observations are compatible with the view that antihypertensive treatment may reduce the risk of both types of white matter lesion.

Before these findings can be accepted, some methodological aspects need to be considered. Hypertension is associated with increased mortality (Hansson *et al*., 1998), and therefore the association between hypertension earlier in life and white matter lesions later in life is likely to be biased by selective mortality, especially with advancing age. This selective mortality was of particular concern in the Zoetermeer Study subpopulation, in which follow-up was longest. We addressed this issue by comparing the prevalence of hypertension in three age strata between survivors and those who had died before the follow-up. In the youngest age stratum in the Zoetermeer Study (60–70 years at the time of follow-up) there was no significant difference in the proportion of participants with hypertension between survivors and those who had died before the follow-up. However, this difference was significant in the youngest age stratum in the Rotterdam Study and in the oldest age categories of both

subpopulations. Therefore, it seems plausible that relative risks in the youngest age category represent the most unbiased risk estimates. In the Rotterdam Study, selective survival plays a smaller part because baseline data collection took place relatively late in life (≥55 years) and the follow-up period was short (5 years). Another potential source of bias is selection of participants, especially in the oldest age category, in which the response rate was lowest. The subjects who refused to participate had higher systolic blood pressures than the participants at baseline and were therefore likely to have more severe white matter lesions than the participants. Both these factors—decreased susceptibility to the effects of hypertension among survivors and selective non-participation of survivors with white matter lesions and cognitive impairment—probably led to underestimation of the relative risk of white matter lesions with hypertension in the two upper age strata. To our knowledge, there are no reports of other population-based studies of age-stratified associations between hypertension and white matter lesions.

The difference in the duration of hypertension between the untreated and the two treated groups may also have led to bias. A hypertensive individual who does not receive blood pressure-lowering drugs (i.e. an untreated individual) may have an elevated blood pressure for only a relatively short period compared with an individual whose hypertension is treated, and therefore may be at lower risk of having white matter lesions. This is in line with our finding that, among untreated hypertensives, the proportion of subjects with a shorter duration of hypertension was higher than in the treated hypertensives (data not shown). However, we think that the higher relative risks of both types of white matter lesions among subjects with poorly controlled hypertension compared with those with successfully controlled hypertension cannot be explained by a difference in the duration of hypertension since additional analyses revealed no major difference in this duration between subjects with successfully and poorly controlled hypertension (data not shown).

The white matter lesion rating scale that we used was different from that used by others, especially with respect to the distinction between periventricular and subcortical white matter lesions. However, our rating scale is compatible with that of others in terms of the severity of the white matter lesions, although the number of categories may vary among the different rating scales. We therefore think that the use of another rating scale would lead to an evaluation of the strength of the association between hypertension and white matter lesions similar to that found in our study and would not introduce any additional bias.

In our study, hypertension was defined as a systolic blood pressure ≥160 mmHg and/or a diastolic blood pressure ≥95 mmHg and/or the self-reported use of blood pressure-lowering medication. However, the WHO guidelines nowadays advise that hypertension should be treated if systolic blood pressure is ≥140 mmHg and/or diastolic blood pressure is ≥90 mmHg. Since there is a linear relationship between blood pressure and white matter lesions, one could argue that lowering the blood pressure that defines hypertension would result in a lower mean blood pressure in the hypertension group. This would lead to more people with fewer white matter lesions in this group. On the other hand, the same process would occur in the reference group, resulting in a relative risk of white matter lesions of about the same magnitude among hypertensives according to either the 160/95 mmHg or the 140/90 mmHg criteria. This is supported by previous studies (Liao *et al.*, 1996).

How hypertension contributes to white matter lesions is not entirely clear. A possible explanation is that long-standing hypertension results in a decrease in cerebral blood flow by impairment of cerebral autoregulation (Paulson *et al.*, 1990). In healthy subjects, cerebral blood flow is maintained at a constant level as long as mean arterial blood pressure remains between 60 and 150 mmHg (Paulson *et al.*, 1990). However, these limits shift upwards in subjects with chronic hypertension, and this may lead to transient falls in cerebral blood flow during periods of lower blood pressure, even at levels considered normal for normotensive subjects (Moody *et al.*, 1991; Matsushita *et al.*, 1994; Pantoni and Garcia *et al.*, 1995). Most vulnerable are areas with a blood supply that is already marginal under physiological conditions, such as the subcortical and periventricular white matter (De Reuck, 1971; Pantoni and Garcia, 1997). Consequently, the white matter of chronic hypertensives might become ischaemic during episodes of relatively low blood pressure. This is in line with the observation of severe periventricular white matter lesions in hypertensive subjects with impaired cerebral autoregulation (Matsushita *et al.*, 1994) and with our observation of the strongest association in subjects with the longest duration of hypertension.

An alternative explanation of the presence of white matter lesions in hypertensives may be that (long-standing) hypertension leads to structural changes of the arterioles in the white matter, such as hyalinization, tortuosity, elongation and narrowing, leading ultimately to a decrease in blood flow and subsequent ischaemia (Moody *et al.*, 1991; Pantoni and Garcia, 1997).

Notwithstanding the fact that hypertension is a strong risk factor for white matter lesions, the occurrence of white matter lesions has been described in normotensive individuals, indicating that other risk factors may be involved in the pathogenesis of these lesions. A possible candidate is (familial) cerebral amyloid angiopathy, which leads to weakening of the small and medium-sized arteries by the deposition of amyloid deposits in the vessel wall (Maat-Schieman *et al.*, 1996; Bornebroek *et al.*, 1997). Hereditary forms of cerebral amyloid angiopathy are rare, whereas the prevalence of the sporadic form increases from 10% in persons aged 60–70 years to 50% for those aged >90 years (Masuda *et al.*, 1988). White matter lesions are also observed frequently among non-hypertensives with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy). However, these patients usually present with their symptoms at an age below the age

categories included in our study (Chabriat *et al.*, 1998). Mutations of the Notch3 gene, located on chromosome 19, lead to thickening of the cerebral arterioles and subsequent reduction in blood flow, and consequently to cerebral ischaemia (Chabriat *et al.*, 1998).

A possible explanation of our finding that poorly controlled hypertensives have the highest risk of either type of white matter lesion is that adequate control of hypertension may lead to a lesser degree of cerebral arteriolosclerosis and thereby prevent the occurrence of cerebral ischaemia (Liao *et al.*, 1996; Pantoni and Garcia, 1997). A clinical trial of antihypertensive drugs in systolic hypertension showed a reduced incidence of dementia in the treated group (Forette *et al.*, 1998); this may have occurred through sparing of the white matter.

In conclusion, we found that a 20-year duration of hypertension increased the risk of white matter lesions about 20-fold, especially among middle-aged individuals. Successful control of hypertension is related to a reduced risk of white matter lesions. This may offer potential therapeutic possibilities in preventing and reducing the attendant cognitive decline or dementia. However, it should be borne in mind that this was an observational study, and it cannot be deduced from the results that effective treatment of hypertension will reduce the development of white matter lesions. A double-blind, randomized clinical study would be needed to evaluate the effect of treatment of hypertension on the development of white matter lesions.

Acknowledgements

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