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Cerebral white matter lesions and atherosclerosis in the Rotterdam Study

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Cerebral white matter lesions (WML) seen on magnetic resonance imaging scans are associated with cardiovascular disease and vascular risk factors. To assess the association between WML and atherosclerosis, we studied 111 people, aged 65 to 85 years, randomly sampled, and stratified by age and sex, from participants in the Rotterdam Study.

Cerebral T2-weighted magnetic resonance images in the axial plane were obtained for all subjects. Carotid atherosclerosis was ultrasonographically assessed by the presence of stenosis, measurement of intima to media wall thickness (IMT), and the presence of atherosclerotic plaques. A possible or definite myocardial infarction on an electrocardiogram was used as an indicator of coronary atherosclerosis. The ankle to arm systolic blood pressure ratio (ABI) was determined, and peripheral arterial disease was defined as an ABI lower than 0.90 in at least one side.

Carotid atherosclerosis was significantly more pronounced in people with WML. The difference in common carotid IMT was 0.13 mm (95% confidence interval [CI] 0.04-0.21), whereas the odds ratio of WML associated with plaques in the carotid bifurcation was 3.9. The degree of internal carotid artery stenosis was not, however, associated with WML. The mean ABI was significantly lower in people with WML than in those without lesions with a difference of -0.11 (95% CI -0.21 to -0.01). The odds ratio of WML associated with peripheral arterial disease and a possible or definite myocardial infarction was 2.4 and 3.1, respectively. We conclude that atherosclerosis, indicated by increased common carotid IMT, carotid plaques, and a lower ABI, is related to WML.

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Introduction

Cerebral white matter lesions (WML) frequently seen on magnetic resonance imaging (MRI) scans of brains of elderly people¹⁻³ are associated with a history of stroke and coronary heart disease, and with cardiovascular risk factors.⁴⁻⁷ Recently, we have found a positive association between haemostatic factors and WML in an elderly

population.⁶ These findings indicate that some of these lesions in the elderly may be due to atherosclerosis, possibly mediated by cardiovascular risk factors.

Non-invasive techniques for assessing the presence and extent of atherosclerotic vessel wall abnormalities at different arterial sites allow the association between WML and atherosclerosis to be studied more directly. Duplex ultrasonography, combined with doppler spectral analysis, can assess haemodynamically significant stenosis of the carotid artery,⁸ and high resolution B-mode ultrasonography allows accurate detection of early atherosclerosis of the carotid artery wall.⁹⁻¹³ The ratio of systolic blood pressure (BP) in the ankle to systolic BP in the arm (ABI) reflects the presence of atherosclerotic vessel wall abnormalities of the lower leg arteries,^{14,15} whereas myocardial infarction, confirmed by electrocardiography, indicates coronary atherosclerosis.¹⁶ We studied the association of WML and non-invasively assessed atherosclerosis.

Subjects and methods

The Rotterdam Study¹⁷ is a prospective follow-up of people aged 55 years or more to investigate the incidence of, and risk factors for, chronic disabling diseases. The study has been approved by the medical ethics committee of Erasmus University and written informed consent is obtained from all participants. All inhabitants aged 55 years or more, living at one point in time in the Rotterdam suburb of Ommoord, were invited to participate. The study comprises an extensive home interview, followed by two visits to the Rotterdam Study research centre for clinical examinations. The participation rate of the cohort at the time of this analysis was 80%.

Participants aged 65 to 85 years were invited to participate in an additional study of the presence and determinants of WML on MRI scans directly after they had finished the baseline study protocol of the Rotterdam Study.⁶ They were randomly selected, and stratified by 5-year-age groups and gender. Of the 134 subjects initially selected, 6 were excluded: 3 because of a pacemaker, metal prosthesis, or surgical clips; 1 because of a major psychiatric illness; and 2 because they were unable to walk. Of the 128 subjects eligible for MRI scans, 111 (87%) consented to participate.

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Fig 1—Characteristic longitudinal 2-D ultrasound image of distal common carotid artery.

Arrows from top to bottom indicate leading edge of intima/lumen interface of anterior (near) wall, and lumen/intima interface, and media/adventitia interface of posterior (far) wall, respectively.

Carotid artery measurements

Haemodynamically significant stenosis of the right carotid artery was ultrasonographically assessed with a 7.5 MHz sector transducer in combination with a 5 MHz pulsed doppler (ATL UltraMark IV, Advanced Technology Labs, Bethel, Washington, USA).¹⁸ Interpretation of velocity profiles was done on-line.¹⁹ The right internal carotid artery was categorised as normal (no reduction in lumen diameter), minimal lesions (1–15% reduction), moderate stenosis (16–49%), or severe stenosis ($\geq 50\%$).

To assess common carotid intima to media wall thickness (IMT), ultrasonography of both carotid arteries was performed with a 7.5 MHz linear array transducer. On a longitudinal 2-dimensional ultrasound image of the carotid artery, near and far walls of the common carotid artery are displayed as two bright white lines separated by a hypo-echogenic space (fig 1).²⁰ The distance of the leading edge of the second bright line on the near wall (intima/lumen interface) to the leading edge of the first bright line on the far wall (lumen/intima interface) represents the lumen diameter. The distance between the lumen/intima interface and the leading edge of the second bright line (media/adventitia interface) of the far wall indicates the IMT.^{20,21} Studies have indicated that the posterior (far) wall IMT seen with ultrasound reflects the anatomical intima/media layer.^{20,21}

The Rotterdam Study's protocol demands a careful examination of the intima/lumen interface of the near wall, and the lumen/intima and media/adventitia interfaces of the far wall of the distal common carotid artery.¹³ When an optimal longitudinal image is obtained, it is "frozen" on the R wave of the electrocardiogram (ECG) and stored on videotape. This procedure is repeated three times for each left and right side. Subsequently, the common carotid artery is evaluated on-line for the presence (yes/no) of atherosclerotic lesions, defined as focal widening relative to adjacent segments, with protrusion into the lumen of either calcified deposits or of a combination of calcifications and non-calcified material. The actual measurements of lumen diameter and IMT are performed off-line. From the videotape, the frozen images are digitised and displayed on the screen of a personal computer with additional dedicated software.^{13,21} From the average of three frozen images per carotid artery, a mean lumen diameter and a mean IMT ($\frac{1}{2}$ [left plus right]) are taken as measures of current lumen diameter and wall thickness of the distal common carotid artery, respectively.^{13,21} Only data from the IMT of the far wall of the common carotid artery were considered in this analysis.

In a separate reproducibility study, 80 participants of the Rotterdam Study had a second ultrasound scan of both carotid arteries within 3 months of the first scan to measure the posterior

IMT. Mean differences (SD) in IMT between repeated measurements of two sonographers, and of two off-line ultrasound image readers were -0.005 (0.09) and 0.06 (0.05), respectively. Mean difference (SD) in IMT between measurements at the first and second visit was -0.033 (0.12).

Coronary artery measurements

Resting standard 12-lead ECGs were obtained with an ACTA Gnosis IV (EsateBiomedica, Firenze, Italy), and were read and coded.²² The assessment of a possible or definite myocardial infarction was based on the presence of major, moderate, or minor Q/QS abnormalities and an evaluation of the ECG by a cardiologist (Dr H. A. C. M. Kruijsen). The presence of a possible or definite myocardial infarction on the ECG was used as an indicator of atherosclerotic coronary artery disease.¹⁶

Peripheral artery measurements

The presence of atherosclerosis in peripheral arteries was evaluated by measuring the systolic BP of both left and right posterior tibial arteries with an 8 MHz continuous wave doppler probe (Huntleigh 500 D, Huntleigh Technology, East Moor, Cardiff, UK), and a random-zero sphygmomanometer.^{14,15} For each side, one BP reading was taken with the subject in the supine position. The lowest ABI in either leg was used in the analysis,¹⁴ and an ABI less than 0.90 in at least one side was used to select a group with a high probability of having peripheral atherosclerosis.^{15,23}

Cardiovascular risk factor assessment

Information on current health status, medical history, drug use, and smoking behaviour was obtained with a computerised questionnaire. Subjects were categorised into groups of current smokers, former smokers, and those who had never smoked. During two visits to the research centre several cardiovascular risk indicators were measured. Sitting BP was measured in the right upper arm with a random-zero sphygmomanometer. The average of two measurements obtained on one occasion, separated by a count of the pulse rate, was used. Hypertension was defined as a systolic BP of at least 160 mm Hg and/or a diastolic BP of at least 95 mm Hg, and/or current use of antihypertensive drugs. A venepuncture was performed, applying minimal stasis, with a 21-gauge butterfly needle with tube. Serum total and high density lipoprotein (HDL) cholesterol concentrations were determined by an automated enzymatic procedure.²⁴

Cerebral white matter lesions

With MRI (1.5 T Philips Gyroscan), multiple slice spin-echo sequences were performed with a repetition time of 2000 ms, and an echotime of 50 and 100 ms, producing a T2-weighted image. Images were obtained in the axial plane with a slice thickness of 7 mm and a slice increment of 1.4 mm. The MRI scans were assessed blind to any clinical information, or other measurements. We distinguished between WML adjacent to the ventricles (periventricular), and punctate or confluent lesions at some distance from the ventricles (focal). Small caps on the horns of the lateral ventricles and a pencil-thin lining around the ventricles were considered normal.^{1,5,25} Infarcts on MRI scans were recorded, but not included in the rating of WML. The severity of WML was graded as grade 0 (no or slight periventricular hyperintensity, less than 5 punctate lesions, and no confluent lesions); grade 1 (moderate periventricular hyperintensity, or more than 5 punctate lesions, or both, but no confluent lesions); or grade 2 (severe periventricular hyperintensity, or confluent lesions, regardless of the presence of punctate lesions). In addition, for some analyses, subjects with grade 1 or 2 lesions were classified as those with WML, and subjects with grade 0 were classified as without WML.

Data analysis

In 3 subjects, extreme tortuosity of the internal carotid artery prevented reliable measurements. For 5 people, technical failure prevented IMT measurements. For 4 subjects, measurement of vessel wall thickness was not possible because of poor visualisation of stored images. For 102 people (92%), measurements of posterior IMT were available, and data on the presence of plaques in the common carotid artery and the bifurcation were obtained in 94% and 78% of subjects, respectively. ABIs were obtained from all subjects, but no ECGs were available for 6.

The mean common carotid IMT and ABI were compared in people with and without WML. For continuously distributed variables, multiple linear regression analysis was used to assess differences between groups, adjusted for age and gender, and differences are given with a 95% confidence interval (CI). Analyses for trends between groups with increasing severity of WML were done with multiple linear regression analysis. The risk of WML associated with binary variables, such as the presence of plaques in the carotid artery, definite or possible myocardial infarction, and the presence of peripheral arterial disease, was assessed using logistic regression analysis, with the presence of WML being the dependent variable. Measures of the strength of the association are presented as odds ratios (OR) with a 95% CI. Since the prevalence of WML strongly increases with age and varies with gender,⁶ all associations between other variables and these lesions were adjusted for differences in age and gender.

In a separate analysis, a multiple logistic regression model was used to assess whether observed associations between common carotid IMT, myocardial infarction, ABI, and WML, remained after adjustments for cardiovascular risk factors, including hypertension, total serum cholesterol, HDL cholesterol, and current smoking.

Results

Participants without WML were younger than those with lesions and more likely to be male (table 1). As we have found,⁶ these lesions are associated with cardiovascular risk factors.

Indicators of atherosclerosis in those with and without WML are shown in table 1. The IMT of the common carotid artery was significantly higher in people with WML compared to those without lesions, with a difference adjusted for age and gender of 0.13 mm (95% CI 0.04–0.21). The results of the logistic regression analysis indicate that an increase of 0.1 mm in common carotid IMT is associated with a 50% increase in the probability of WML (table II). Furthermore, atherosclerotic plaques in the carotid bifurcation were significantly associated with the presence

TABLE I—CHARACTERISTICS OF SUBJECTS WITH AND WITHOUT CEREBRAL WHITE MATTER LESIONS

	White matter lesions		
	Absent (n = 81)	Present (n = 30)	p
Age (yr)	72.4 [5.8]*	77.7 [5.4]*	<0.01
Women	49%	67%	0.11
Body mass index (kg/m ²)	26.4 [3.6]*	26.5 [3.0]*	0.88
Smoking			
Current	30%	10%	0.04
Former	47%	52%	0.18
Never	23%	38%	0.14
Systolic pressure (mm Hg)†	132 [18]*	141 [19]*	0.08
Diastolic pressure (mm Hg)†	69 [10]*	70 [9]*	0.63
Hypertension‡	28.3%	41.4%	0.20
Cholesterol (mmol/L)			
Total	6.56 [1.34]*	6.83 [1.25]*	0.25
HDL	1.29 [0.32]*	1.24 [0.30]*	0.40
Carotid arteries			
Stenosis (%)			
0	74%	75%	0.97
1–16	22%	21%	0.80
≥16	4%	4%	0.84
IMT (mm)	0.81 [0.16]*	0.96 [0.24]*	<0.01
Plaques§			
Common carotid artery	14%	11%	0.74
Carotid bifurcation	57%	83%	0.02
Coronary arteries			
Definite myocardial infarction	7%	19%	0.24
Possible myocardial infarction	3%	8%	0.26
Combined	10%	27%	0.03
Peripheral arteries			
ABI	1.13 [0.21]*	1.03 [0.25]*	0.03
Peripheral arterial disease	14%	30%	0.05

*Mean [SD].

†Subjects on antihypertensive drugs excluded.

‡Systolic pressure ≥ 160 mm Hg, and/or diastolic pressure ≥ 95 mm Hg, and/or on antihypertensive drugs.

§Plaques located in at least one carotid artery in anterior or posterior wall of common carotid artery and bifurcation.

of WML. The prevalence of a minimal, or moderate to severe, haemodynamic stenosis of the right carotid artery did not differ between the two groups.

The ABI was significantly reduced in subjects with WML with a difference adjusted for age and gender of –0.11 (95% CI –0.21 to –0.01). A decrease of 0.1 in ABI was associated with a 20% increase in probability of WML. Similar results were observed when the left or right carotid

TABLE II—ATHEROSCLEROSIS AND CEREBRAL WHITE MATTER LESIONS

	Odds ratio (95% CI) of having cerebral white matter lesions	Odds ratio adjusted for age and gender (95% CI) of having cerebral white matter lesions
Carotid arteries		
Stenosis (%)		
0	1.0	1.0
1–16	0.9 (0.3–2.7)	0.7 (0.2–2.3)
≥16	2.1 (0.2–10.4)	5.3 (0.7–46.3)
IMT (mm)*	1.5 (1.2–1.9)	1.5 (1.1–2.1)
Plaques†		
Common carotid artery	0.8 (0.2–3.2)	0.9 (0.2–4.1)
Carotid bifurcation	3.8 (1.1–12.5)	3.9 (1.0–14.5)
Coronary arteries		
Definite myocardial infarction	3.3 (0.9–12.8)	2.1 (0.5–9.2)
Possible myocardial infarction	3.0 (0.4–23.4)	6.9 (0.7–70.0)
Combined	3.6 (1.1–11.6)	3.1 (0.8–11.4)
Peripheral arteries		
ABI‡	1.2 (1.0–1.5)	1.2 (1.0–1.5)
Peripheral arterial disease	2.7 (1.0–7.6)	2.4 (0.8–7.6)

*Per 0.1 mm increase.

†Plaques located in at least one carotid artery in anterior or posterior wall of common carotid artery and bifurcation.

‡Per 0.1 decrease.

Fig 2—Measures of atherosclerosis across groups with increasing severity of cerebral white matter lesions.

Top = mean IMT (SE) of common carotid arteries (mm), test for linear trend across groups ($p < 0.01$); middle = mean ABI (SE) of tibial posterior arteries, test for linear trend across groups ($p = 0.05$); bottom = prevalence of combined definite and possible myocardial infarction (SE), test for linear trend across groups ($p = 0.19$). All adjusted for age and gender.

artery, and the left or right ABI, were used in the analysis. Peripheral arterial disease was found in 30% of subjects with WML compared to 14% of subjects without lesions.

The prevalence of definite or possible myocardial infarction, based on ECGs, was 27% in subjects with WML compared to 10% in those without lesions. The observed associations for peripheral arterial disease and prevalence of myocardial infarction did not, however, reach significance.

Significant trends were found for carotid IMT (fig 2, top) and ABI (fig 2, middle) between groups with increasing severity of WML. Although myocardial infarction was more common among subjects with grade 1 or grade 2 lesions, a significant gradual increase in the prevalence of myocardial infarction with increasing severity of WML was not demonstrated (fig 2, bottom). For subjects aged 65 to 74 years, the association between WML and carotid IMT was stronger than in subjects aged 75 to 84 years. Mean differences between groups were 0.16 mm (95% CI 0.03–0.27) and 0.09 mm (95% CI –0.04 to 0.22), respectively. Similar results were obtained for ABI. The strength of the association between myocardial infarction and WML, however, increased with age. For those aged 75 to 84 years, an odds ratio of 5.1 (95% CI 0.8–31.5) was observed, compared to an odds ratio of 1.5 (95% CI 0.1–7.6) for subjects aged 65 to 74 years. The magnitude of the association between WML and IMT did not differ between

TABLE III—ATHEROSCLEROSIS AND CEREBRAL WHITE MATTER LESIONS WITH AND WITHOUT ADJUSTMENT FOR CARDIOVASCULAR RISK FACTORS

Adjustment	Odds ratio (95% CI) per 0.1 mm increase in IMT	Odds ratio (95% CI) of myocardial infarction*	Odds ratio (95% CI) per 0.1 decrease in ABI
No adjustment	1.5 (1.2–1.9)	3.6 (1.1–11.6)	1.2 (1.0–1.5)
Age and gender	1.5 (1.1–2.1)	3.1 (0.8–11.4)	1.2 (1.0–1.5)
Hypertension†	1.4 (1.1–2.1)	2.9 (0.8–10.9)	1.2 (1.0–1.5)
Total cholesterol†	1.5 (1.1–2.2)	3.0 (0.8–11.3)	1.2 (1.0–1.5)
HDL cholesterol†	1.5 (1.1–2.1)	2.8 (0.7–10.6)	1.2 (1.0–1.5)
Current smoking†	1.5 (1.1–2.2)	3.3 (0.9–12.5)	1.3 (1.0–1.6)
All‡	1.4 (1.0–2.1)	2.9 (0.7–11.6)	1.2 (0.9–1.6)

*Combined definite and possible myocardial infarction diagnosed on ECG.

†Results obtained by multivariate logistic regression; each risk factor entered separately in model in which age and gender included.

‡All risk factors used in the logistic regression model.

elderly men and women. A difference in ABI of –0.14 (95% CI –0.03 to –0.025) was observed between women with and without lesions, whereas for men the difference was –0.04 (95% CI –0.24 to 0.20). For myocardial infarction, an opposite association was found with a stronger association in men.

The results of additional multivariate adjustment of cardiovascular risk factors on the size of the odds ratios for IMT, ABI, and presence of possible or definite myocardial infarction in subjects with WML are presented in table III. Adjustment for differences in risk factors slightly reduced the magnitude of the association with carotid IMT without changing the direction of the association between carotid atherosclerosis and WML. Similar results were found for myocardial infarction. No change was observed in the magnitude of the association between these lesions and ABI after additional adjustment for cardiovascular risk factors.

Discussion

Our findings, in a population-based study of MRI scans of brains of elderly people, provide evidence that WML are associated with atherosclerosis as non-invasively demonstrated by increased common carotid IMT and reduced ABI. Atherosclerotic plaques in the carotid bifurcation, evidence of myocardial infarction on ECG, and peripheral arterial disease are more common in subjects with WML. Trend analyses suggest that a gradual increase in the severity of these lesions is associated with an increase in IMT and a decrease in ABI. Haemodynamically significant stenosis of the right internal carotid artery was, however, not associated with WML.

Before these findings can be accepted, some aspects of the study need to be considered. First, increased common carotid IMT may not necessarily be atherosclerosis and is not in itself a precursor of atherosclerosis. It may merely reflect an adaptive response of the vessel wall to changes in shear stress and tensile stress.²⁶ Furthermore, atherosclerosis is viewed as a disorder restricted to the intima of the arterial vessel wall, and ultrasound imaging cannot discriminate between the intima and the media. Ultrasonographically determined increased IMT of the common carotid artery has been associated with cardiovascular risk factors.^{10,13,27,28} In addition, progression of common carotid IMT has been associated with risk factors for atherosclerosis.¹¹ These results support the view that non-invasively assessed IMT of the common carotid artery may be regarded as a measurement of atherosclerosis. Second, ABI was based on a single BP reading at the ankle

and the arm. Some misclassification may have occurred, which may have reduced the observed difference between the groups, provided a true association exists and misclassification occurred to the same extent among subjects with and without WML. Similarly, misclassification in the assessment of coronary atherosclerosis may have occurred as the diagnosis was based on ECG findings only. This may have resulted in some dilution of the observed association.

In several studies, WML have been found to be related to established cardiovascular risk factors.^{1,4-6} In addition, haemostatic and rheological factors have been associated with these lesions.^{6,7} Postmortem studies have indicated that WML seen on MRI scans are associated with degenerative changes in arterioles which are related to atherosclerosis.²⁹⁻³¹ Our observation of an association between WML and carotid, coronary, and peripheral atherosclerosis in an ageing population supports these findings.

In the present study, the frequency of haemodynamically important stenosis of the right internal carotid artery among subjects with WML did not differ from those without lesions. This finding can probably not be explained by the fact that only the right carotid artery was evaluated for stenosis, as stenosis of the internal carotid artery appears to be randomly distributed in both left and right sides.³² Our finding contrasts with the unilateral or bilateral stenosis found in 8 out of 53 volunteers with WML.³³ Postmortem studies have indicated, however, that WML are predominantly associated with arteriolosclerosis, a type of small artery disease. Furthermore, our findings are in accordance with others who have observed a relatively low prevalence of carotid artery stenosis in subjects with lacunar infarcts, another type of small artery disease.^{34,35} These results may indicate that the haemodynamic consequences of stenosis of the carotid artery may not be responsible for the development of WML, and support the view that these lesions represent generalised vascular disease.

Adjustment for differences in smoking, hypertension, and raised serum lipids, only partly attenuated the observed associations between WML, carotid atherosclerosis, and coronary atherosclerosis, whereas the association between these lesions and peripheral arterial atherosclerosis remained unchanged. These findings suggest that the association between WML and large vessel atherosclerosis cannot be entirely attributed to confounding by common cardiovascular risk factors, and favours the hypothesis that these lesions are partly a direct consequence of atherosclerotic vessel wall disease, which in itself is related to increased cardiovascular risk factors. Alternative explanations are that other unknown factors play a role in the development of atherosclerosis of the carotid, coronary, and peripheral arteries, and WML, or that the effect of these risk factors on both atherosclerosis and WML may be different in different arteries. A time-dependent relation between WML and atherosclerosis cannot be determined on the basis of these cross-sectional data.

Whether WML cause dementia is still debated. Conflicting associations between cognitive impairment and these lesions have been reported.^{2-4,25,36,37} The type of WML on MRI scans may also be important. Periventricular hyperintensities were found more often in demented patients than in age-matched controls in most studies.^{25,38} The extent and the location of lesions may also partly explain some of the negative results.³⁹ In addition, differences between studies of their association with dementia may be attributed to differences in selection of subjects, sample sizes, classification of the presence or absence of WML, and

the assessment of cognitive functioning. Finally, as our findings and those of others suggest that WML are clearly associated with atherosclerosis, differences in the aetiology of these lesions may contribute to the contrasting results.

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Human parvovirus infection in homozygous sickle cell disease

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We studied the epidemiology of human parvovirus B19 infection in 308 children with homozygous sickle cell (SS) disease and 239 controls with a normal haemoglobin (AA) genotype followed from birth in a cohort study. Annual serum samples identified the time and frequency of B19 infection, which did not differ between SS and AA children, about 40% of each group developing specific IgG by age 15. B19 infection followed an epidemic pattern similar to that observed for aplastic crises; accounted for all 91 aplastic crises that occurred; and was found in an additional 23 SS patients, of whom 10 showed mild haematological changes and 13 no changes. The magnitude or duration of IgG response did not differ between these groups. No patient had 2 attacks of aplasia and no patient nor control had 2 attacks of B19 infection. Following B19 infection, serial specific IgG concentrations remained high after 5 years in only 45% of SS patients, although the rarity of recurrent aplasia suggests lifelong immunity. B19 infection accounts for most if not all aplastic crises in SS disease, but at least 20% of infections do not result in aplasia. An effective vaccine against B19 might make an important contribution to the management of sickle cell disease.

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Introduction

In the rapid cell destruction of sickle cell disease, haemoglobin is maintained by increased erythropoiesis.

Destruction of red-cell precursors, as occurs in aplastic crisis, results in disappearance of reticulocytes from the peripheral blood and a fall in haemoglobin. Aplastic crisis principally affects children under 15,¹⁻³ clusters in families,^{1,4,5} and occurs in epidemics.³ These characteristics are consistent with an infection but early studies did not find a common single agent.⁴⁻⁷ Human parvovirus infection has been found at the same time as aplastic crisis in homozygous sickle cell (SS) disease by researchers in Jamaica³ and elsewhere,^{8,9} and in other haemolytic diseases.^{8,10,11} We have studied the characteristics of human parvovirus (B19) infection in Jamaica to determine its incidence in SS disease and in controls with normal haemoglobin (AA).

Patients and methods

Patients

Patients were from a cohort study which included all cases of sickle cell disease detected in 100 000 consecutive normal deliveries at the Victoria Jubilee Hospital, Kingston, Jamaica between June, 1973 and December, 1981. 315 children with an SS genotype were identified of whom 308 were followed up. Between June, 1973, and January, 1976, each baby with SS was matched with 2 controls of the same sex, born closest in time to the patient but with a normal haemoglobin (AA). 4 of the 250 AA controls were found to have the

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