The Association Between Retinal Vessel Abnormalities and H-type Hypertension

Kuankuan Huang
Changzhou NO.2 People's Hospital Affiliated to Nanjing Medical University
Wenwei Yun
Changzhou NO.2 People's Hospital Affiliated to Nanjing Medical University
Shan Huang
Changzhou NO.2 People's Hospital Affiliated to Nanjing Medical University
Yanwen Jia
Changzhou NO.2 People's Hospital Affiliated to Nanjing Medical University
Zhixiang Zhang
Changzhou NO.2 People's Hospital Affiliated to Nanjing Medical University
Min Zhang (zhangjueming11@163.com)
Changzhou NO.2 People's Hospital Affiliated to Nanjing Medical University https://orcid.org/0000-0003-3568-7351

Research article

Keywords: retinal vessel abnormality, homocysteine, hypertension

Posted Date: August 19th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-56407/v1

Version of Record: A version of this preprint was published on January 6th, 2021. See the published version at https://doi.org/10.1186/s12883-020-02029-z.

Abstract

Introduction: This study aimed to investigate the relationship between H-type hypertension and retinal vessel abnormalities.

Methods: Hypertensive patients were retrospectively enrolled in this study. According to serum homocysteine (HCY), patients were divided into isolated hypertension and H-type hypertension group. Retinal fundus photography was used to evaluate the diameter of retinal vessels and retinopathy. Univariate and multivariate regression were used to investigate difference of retinal vessel abnormalities between H-type hypertension and isolated hypertension patients.

Results: A total of 191 hypertensive patients were included, of which 85 were isolated hypertension and 106 were H-type hypertension. H-type hypertension patients had a higher ratio of retinopathy(*P*=0.004) and higher degree of retinal arteriosclerosis (*P*=0.005). CRAE(*P*=0.002) and AVR(*P*=0.001) were smaller in H-type hypertension group. Multivariate analysis showed that after adjusting for age, sex, course of hypertension and diabetes, H-type hypertension were still risk factor of retinopathy(OR, 2.259; 95%CI, 1.165—4.378; *P*=0.016), CRAE (B=-5.669; 95%CI, -9.452—-1.886; *P*=0.004), and AVR(B=-0.023; 95%CI,-0.039—-0.007; *P*=0.005).

Conclusion: H-type hypertension may aggravate retinal vessel abnormalities compared with isolated hypertension.

Background

H-type hypertension is defined as subject concomitant with hypertension and hyperhomocysteinemia (HHCY ≥ 10 μmol/L). Homocysteine (HCY) is a sulfur-containing amino acid, an important intermediate product in methionine metabolism. As we all know, hypertension can cause small vascular lesions throughout the body, especially the retinal vessels. Recently, many studies have already investigated in the relationship between HCY and cardiovascular or cerebrovascular diseases[1–3]. Retinal vessels are the only visible microvascular in the human body. There are many similarities of retinal and cardio-cerebro- vessels. The mechanism that the effect on cardiovascular and cerebrovascular diseases of HCY may also affect retinal vessels. Besides, a study had already found that HCY may be a potential biomarker of diabetic retinopathy[4].

However, research on the relationship between H-type hypertension and retinal vessels remains scarce. Therefore, we used retinal fundus photography as a non-invasive examination to evaluate retinal vessel abnormalities. Diameters of the retinal vessels were measured, and the degree of retinal arteriosclerosis and other retinal lesions were visually rated though retinal fundus photographs. This study aimed to investigate the relationship of H-type hypertension and retinal vessel abnormalities.

Methods

Patients

The institutional review board of our hospital approved this study and informed consent was obtained from all participants. All the patients were recruited from February 2019 to August 2019 through the Department of Neurology at Changzhou No.2 People's Hospital Affiliated to Nanjing Medical University. Patients diagnosed essential hypertension were enrolled. Exclusion criteria were as follows: (1) patients who were not able to provide informed consent. (2) unavailable or unreliable retinal fundus photographs (e.g. due to poor imaging quality);(3)patients with serious complications such as organ failure, serious infections and so forth; (4)patients who had undergone eye surgery (such as cataract extraction, laser surgery, glaucoma surgery, pseudo eyeball replacement, etc.) in the past six months.

H-type hypertension diagnosis

H-type hypertension were patients diagnosed with both HHCY and hypertension. Patients had been diagnosed with hypertension according to their past medical history or blood pressure ≥ 140 mmHg SBP and/or ≥ 90 mmHg DBP without medicine. HHCY is defined as serum HCY more than or equal to 10 μmol per liter. A noninvasive ambulatory blood pressure monitor (model 6100) was used to measure blood pressure. The purpose and precautions of the examination were explained to the patients and their families, and their informed consents were obtained. The effective measurement was more than 80 percent of the measurement times. The monitoring starts and ends at 06:00–06:00 of the next day, 15 min/time in the daytime (06:00–22:00), and 30 min/time at night (22:00–06:00 of the next day). The 24-hour mean systolic and diastolic pressures were calculated by a computer. To measure serum HCY, 4 ml peripheral venous blood was collected in the morning and placed in the heparin anticoagulant tube (Shanghai Hengyuan biological technology co., LTD.). The serum was centrifugated at 4000r/min (ebende ag., Germany) for 5 min to separate the serum. The serum HCY was detected by Siemens ADVIA2400 automatic biochemical analyzer. Other related clinical characteristics and demographics were collected in the hospital. More information including demographic and clinical factors and laboratory factors were collected.

Retinal fundus photograph assessment

Several classic abnormalities of hypertensive ophthalmopathy were used to evaluate retinal lesions through retinal photographs. Retinopathy was defined as present if any of the following retinal vascular abnormalities were detected through retinal fundus photographs: retinal hemangioma, hemorrhages, hard and soft exudates. Arteriovenous nicking (AVN), the curvature of vessels and arteriosclerosis grades had also been rated. Retinal arteriosclerosis grades were assessed according to Scheie grading method[5]. And diameters of retinal vessels were also measured (Fig. 1).

All patients received 45-degree color photos of the retinal fundus with Kowa nonmyd Wx nonmydriatic fundus camera. Make sure that the optic disc was in the center, and retinal fundus photography was performed. The pictures were saved in TIFF format (pixels: 2992 × 2000). Image J software was used to measure the diameter of six retinal vessels. First, we magnified the fundus photograph obtained by the

same multiple, and then circled the range of 1/2–1 papilla disc (PD) from the edge of the optic disc. Third, we selected the edge of the blood vessel wall with the mouse, measuring the diameter of the blood vessel vertically. The software automatically displayed the measurement results[5–7]. Repeat the above operation to get the average value of each vessel diameter to reduce the artificial errors. Thus, we got the diameter of six retinal arteries (Wa1–Wa6) and retinal veins (Wv1–Wv6) together with the vertical diameter (PD1) and horizontal diameter (PD2) of the optic disc at the same time. PD is equal to half of the sum of PD1 and PD2. The whole measurement process was completed by a graduate student. When measuring, try to avoid the vascular bifurcation. After that, the measured data unit was a pixel. The average diameter of the optic disc is close to 1850 micrometers (μm). We had to convert its' unit from pixel into μm.

W (actual) = 1850/PD × W (measurement)

Thus, the actual diameters of six retinal arteries and retinal veins were obtained respectively. Then, we used an iterative operation formula named Parr-Hubbard formula to get central retinal vein equivalent (CRVE), central retinal artery equivalent(CRAE) and arteriole-to-venule ratio(AVR)[6]. The formula is as follows:

$CRVE = 0.95\times(W_{min}^2+W_{max}^2)^{1/2}$

$CRAE = 0.88\times(W_{min}^2+W_{max}^2)^{1/2}$

AVR = CRAE /CRVE

Statistical analysis

Statistical analysis was performed by SPSS Statistics Version 25. Continuous variables with normal distribution were expressed as mean ± SD. Those with non-normal distribution were expressed as median (interquartile range). Categorical variables were expressed as the number of cases (proportion). The differences of baseline characteristics between H-type hypertension and isolated hypertension group were described. All patients were divided into two groups according to the presence of retinopathy. Differences were determined by χ^2, T test, or Mann Whitney U where appropriate. Univariable and multivariable logistic regression were used to estimate the association between H-type hypertension and retinopathy. We also used univariable and multivariable linear regression to explore the relation between H-type hypertension and CRAE, H-type hypertension and AVR.

Results

Baseline characteristics of isolated and H-type hypertension

A total of 191 hypertension patients were enrolled in this study. Table 1 outlines relevant characteristics of hypertension and H-type hypertension groups. H-type hypertension group had a higher proportion of

retinopathy(P = 0.004) and higher grades of retinal arteriosclerosis (P = 0.005). There was a significant difference in arterial diameter between the two groups. CRAE(P = 0.002) and AVR(P = 0.001) were smaller in H-type hypertension group (Table 1).

Table 1
Baseline characteristics of patients of two groups(N = 191)

Variable	Isolated hypertension (86)	H-type hypertension (105)	*P* value
Characteristics			
Age, y, mean ± SD	64.62 ± 10.97	66.29 ± 12.35	0.328
Sex, male, n (%)	63(73.3%)	76(72.4%)	0.892
Smoking currently, n (%)	41(47.7%)	53(50.5%)	0.700
Alcohol use, n (%)	17(19.8%)	29(27.6%)	0.207
Atrial fibrillation, n (%)	8(9.3%)	4(3.8%)	0.120
Coronary heart disease, n (%)	8(9.3%)	12(11.4%)	0.633
Diabetes, n (%)	23(26.7%)	39(37.1%)	0.127
Hypertension duration, median (IQR)	10.00(5.0,13.00)	12.00(6.00,15.00)	0.145
Laboratory examination, Mean ± SD			
Total cholesterol, mmol/L	3.92 ± 1.03	4.01 ± 0.78	0.489
Total cholesterol, mmol/L	2.07 ± 3.73	1.75 ± 0.87	0.400
LDL, mmol/L	2.09 ± 0.75	2.21 ± 0.64	0.215
HDL, mmol/L	1.05 ± 0.31	1.05 ± 0.25	1.000
Serum creatinine, mmol/L	69.90 ± 19.95	70.75 ± 17.41	0.755
Retinal vessel abnormalities			
Retinopathy, n (%)	19 (22.1%)	44 (41.9%)	0.004
Hemangioma, n (%)	14(16.3%)	26 (24.8%)	0.152
Hemorrhages, n (%)[a]	1(1.2%)	5 (4.8%)	0.316
Hard exudates, n (%)	9(10.5%)	21(20.0%)	0.072
Soft exudates, n (%)	6(7.0%)	11(10.5%)	0.398
Arteriovenous nicking, n (%)	32(37.2%)	53(50.5%)	0.066

Abbreviations: SD, standard deviation; IQR, interquartile range; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRVE, central retinal vein equivalent; CRAE, central retinal artery equivalent; AVR, arteriole-to-venule ratio.

[a] Continuity correction were used.

Variable	Isolated hypertension (86)	H-type hypertension (105)	*P* value
Vascular curvature, median (IQR)	1.00(1.00,1.00)	1.00(1.00,1.50)	0.511
Arteriosclerosis grades, median (IQR)	1.00(0.00,1.00)	1.00(0.00,2.00)	0.005
CRVE,μm	195.98 ± 21.19	194.07 ± 19.10	0.515
CRAE,μm	113.49 ± 11.72	107.47 ± 13.99	0.002
AVR	0.58 ± 0.06	0.55 ± 0.06	0.001
Abbreviations: SD, standard deviation; IQR, interquartile range; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRVE, central retinal vein equivalent; CRAE, central retinal artery equivalent; AVR, arteriole-to-venule ratio.			
[a] Continuity correction were used.			

Baseline characteristics of factors of retinopathy

Table 2 shows the results of related risk factors of retinopathy. The proportion of patients with H-type hypertension in retinopathy group [44(69.8%)] was higher than that in the group without retinopathy [61(47.7%)]. The difference was significant(P = 0.004). Other risk factors such as history of diabetes(P = 0.013), courses of hypertension(P = 0.032) and age(P = 0.024) were also the decisive factors leading to the probability of retinopathy.

Table 2
Baseline characteristics of retinopathy

Variable	Without Retinopathy (128)	With Retinopathy (63)	*P* value
Age, y, mean ± SD	64.20 ± 12.09	68.25 ± 10.47	0.024
Group, n (%)	61(47.7%)	44(69.8%)	0.004
male, n (%)	98(76.6%)	41 (65.1%)	0.094
Smoking currently, n (%)	67(52.3%)	27 (42.9%)	0.218
Alcohol use, n (%)	32(25.0%)	14 (22.2%)	0.673
Atrial fibrillation, n (%)	7(5.5%)	5 (7.9%)	0.509
Coronary heart disease, n (%)	11 (8.6%)	9 (14.3%)	0.227
Diabetes, n (%)	34(26.6%)	28 (44.4%)	0.013
Hypertension duration, median (IQR)	10.00(5.00,13.00)	12.00(8.00,16.00)	0.032
Total cholesterol, mmol/L	3.95 ± 0.92	4.00 ± 0.87	0.732
Total cholesterol, mmol/L	2.02 ± 3.11	1.65 ± 0.76	0.352
LDL, mmol/L	2.14 ± .70	2.19 ± 0.68	0.690
HDL, mmol/L	1.05c0.29	1.05 ± 0.24	0.932
Serum creatinine, mmol/L	69.54 ± 18.48	72.06 ± 18.73	0.379

Abbreviations: SD, standard deviation; IQR, interquartile range; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Retinopathy was defined as present if any of the following retinal vascular abnormalities were detected through retinal fundus photographs: retinal hemangioma, hemorrhages, hard exudates and soft exudates.

Logistic regression between H-type hypertension and retinopathy

Univariable logistic analysis showed that H-type hypertension was related to retinopathy (OR, 2.544; 95%CI, 1.341—4.825; *P* = 0.004, Table 3). After adjusting for age, sex, history of diabetes and course of hypertension, presence of H-type hypertension were still significantly associated with retinopathy (OR, 2.259; 95%CI, 1.165—4.378; *P* = 0.016).

Table 3
Univariable and multivariable logistic regression between H-type hypertension and retinopathy

Variable	OR (95%CI)	*P* value
Crude	2.544(1.341,4.825)	0.004
Model 1	2.477(1.293,4.745)	0.006
Model 2	2.259(1.165,4.378)	0.016
Crude: Univariable logistic regression analysis of H-type hypertension and retinopathy.		
Model 1: Adjusting for age, sex		
Model 2: Adjusting for age, sex, history of diabetes, courses of hypertension.		

Linear regression between H-type hypertension and diameters of retinal vessels

In univariate linear analysis, H-type hypertension was associated with CRAE (B, -6.023;95%CI, -9.759—-2.288; *P* = 0.002, Table 4). After adjusting for age, sex, history of diabetes and courses of hypertension step by step, H-type hypertension was independent risk factor of CRAE (B, -5.669;95%CI, -9.452—-1.886; *P* = 0.004). As for the relation of H-type hypertension and AVR. The results showed that, after the multivariate adjustment for age, sex, diabetes and courses of hypertension, H-type hypertension could decrease AVR (B, -0.023;95%CI, -0.039—-0.007; *P* = 0.005).

Table 4
Univariable and multivariable linear regression between H-type hypertension and retinal vessel calibers

Variable	CRAE			AVR		
	B	59%CI	*P* value	B	59%CI	*P* value
Crude	-6.023	-9.759, -2.288	0.002	-0.027	-0.044, -0.011	0.001
Model 1	-5.934	-9.690, -2.178	0.002	-0.027	-0.043, -0.010	0.002
Model 2	-5.669	-9.452, -1.886	0.004	-0.023	-0.039, -0.007	0.005
Crude: Univariable linear regression analysis of H-type hypertension and retinal vessel calibers.						
Model 1: Adjusting for age, sex						
Model 2: Adjusting for age, sex, history of diabetes, courses of hypertension.						
Abbreviations: CRAE, central retinal artery equivalent; AVR, arteriole-to-venule ratio.						

Discussion

This study found that H-type hypertension tended to have more severe retinal vessel abnormalities. Patients with H-type hypertension had smaller retinal arteries and more severe retinal arteriosclerosis.

H-type hypertension was first proposed by a Chinese research team in 2008[8]. It refers to patients with hypertension and HHCY at the same time. H-type hypertension accounts for 75% of total hypertension. They found that HCY is another major risk factor for stroke in addition to hypertension. A meta-analysis had identified potentially relevant researches up to August 1, 2019. The conclusion was that hypertension was closely associated with HCY[9]. According to previous findings, a high level of HCY did harm to systemic vascular endothelial cells [10, 11]. Elsherbiny et al further demonstrated that HHCY can undermine inner and outer blood–retinal barriers[12]. We doubt that H-type hypertension may cause more serious retinal vessel lesions. Our study found that patients with H-type hypertension had a higher grade of retinal arteriosclerosis, and smaller diameter of retinal artery compared with isolated hypertension patients. The changes of retinal arteriosclerosis include thinning and straightening of the retinal artery, which is like copper wire or silver wire. The sclerotic artery can compress the vein at the intersection with the vein, which is called AVN. In severe cases, retinal vessel spasm, stenosis, obstruction, and hemorrhages can occur. In our study, retinal arteriosclerosis grades, CRAE and AVR seemed to be more sensitive compared with the rest of lesions. AVN barely failed to attain statistical significance($P = 0.066$). And retinal arteries, instead of veins, showed differences between the two groups. Based on these findings, it's indicative that a higher level of serum HCY may aggravate retinal vessel abnormalities. Researchers have found H-type hypertension could cause more severe cerebrovascular damage compared with isolated hypertension[13, 14]. Similarly, H-type hypertension may cause more serious damage to the retinal vessels. This is similar with what we observed in the present study.

We further analyzed the risk factors of retinopathy. The ratio of H-type hypertension was significantly higher in retinopathy group. Age, history of diabetes and courses of hypertension also showed significant differences in two types of outcomes. Further analysis demonstrated that although the related risk factors were adjusted, H-type hypertension was still a risk factor of retinopathy. Sottilotta et al found that elevated plasma homocysteine could be an independent risk factor of retinal vascular occlusive disease which is closely related to coronary, cerebral, and peripheral atherosclerotic vascular disease[15]. A previous study also the evaluate the availability of HCY as a biomarker for diabetic retinopathy screening, and the result was that HCY could be a strong candidate[4]. Retinopathy described above was closely related to the damage of the retinal vessels. The pathological changes of the retinal vessels are regarded as the window to observe systemic vascular problems. Hypertension can cause sclerosis of small arteries. Tyagi et al found that HCY is one of the circulating plasma factors that may play a critical role in the development of hypertension[16, 17]. There may be an interaction between HCY and hypertension. The mechanism of damage of HCY to small arteries is not completely clear, but the endothelium damage of small vessels by HCY may be an important one of the reasons.

The impact of HCY on small arteries has attracted more and more attention[18–20]. Retinal vessels are the unique small vessels that can be directly observed throughout the body. We directly measured the diameters to evaluate the changes of retinal vessels. And we found that artery was more likely decreased

in H-type hypertension, yet the changes of venules were not obvious. The patients in this study all suffered from hypertension, and the difference of retinal abnormalities were caused by HCY. However, whether HCY damages retinal vessels through the superposition effect of hypertension or directly damages retinal vessels remains controversial[4, 12]. Serum HCY is a sulfur-containing amino acid, which is an important intermediate product produced during the metabolism of methionine and cysteine. It has three metabolic pathways. Abnormalities in any of these three metabolic pathways can lead to increased HCY. One of the metabolic pathways is that HCY is catalyzed by vitamin B6 dependent cystathionine β synthetase. HCY is converted to cysteine and eventually metabolizes in the body to produce H_2S in the process. Accumulating evidence indicated that H_2S is a physiological vasorelaxant and reduced production of H_2S in the vascular tissue leads to hypertension[11, 21, 22]. Besides, HHCY may cause direct toxicity and vascular endothelial injury, which may induce hypertension or aggravating the damage of hypertension to vessels[23–25]. Collectively, HCY also activates certain metalloproteinases which can cause degradation of collagen and elastin leading to vascular hypertrophy[26, 27]. Moreover, the accumulation of HCY leads to increased cellular oxidative stress in which mitochondrial thioredoxin and peroxiredoxin are decreased and NADH oxidase activity is increased[21]. In a word, the mechanism of HCY induced arteriosclerosis mainly includes endothelial cell injury, oxidative stress and vascular remodeling. In conclusion, H-type hypertension patients have more severe vascular injury than isolated hypertension patients.

Our study has several potential limitations. There may be manual errors in measuring the diameter of blood vessels even though we tried to avoid that by taking the average value of repeated measurement. It would be better if we could use a newer and more accurate method to analyze the retinal vessel abnormalities. Secondly, when we analyzed, the small sample limited the statistical power of the model. In the future, we need to increase the sample size and conduct cohort studies to better explain these associations and meet the needs of clinical applications.

Conclusion

We demonstrated that H-type hypertension patients had worse retinopathy compared with hypertension patients, and HCY aggravated lesions of retinal vessels. The exact mechanism of H-type hypertension on retinal vessels remains to be elucidated.

Abbreviations

HCY: homocysteine; HHCY: hyperhomocysteinemia; SBP: systolic blood pressure; DBP: diastolic blood pressure; SD: standard deviation; IQR: interquartile range; LDL: low-density lipoprotein; HDL: high-density lipoprotein; CRVE: central retinal vein equivalent; CRAE: central retinal artery equivalent; AVR: arteriole-to-venule ratio.

a Continuity correction were used.

Declarations

Acknowledgements

We are grateful to all study participants for their cooperation.

Authors’ contributions

KKH participated in the design, data statistical analysis, and drafting the manuscript. WWY, SH and ZXZ helped with the data collection and analysis. YWJ helped to read and evaluated the retinal fundus photographs. MZ was involved in the design, review and editing of the manuscript.

Founding

This project was supported by the National Natural Science Foundation of China (81671284), General Program of Jiangsu Commission of Health (H2019051), Foundation of Health Planning Commission for Youths (QN201714) and Application Foundation Program of Changzhou Science and Technology (CJ20180071).

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The institutional review board of our hospital approved this study and informed consent was obtained from all participants. Written informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1] Department of Neurology, Changzhou No.2 People's Hospital Affiliated to Nanjing Medical University. No.29, Xinglong Lane, Tianning District, Changzhou 213004, Jiangsu, China. [2]Ophthalmology Department of Changzhou No.2 People's Hospital Affiliated to Nanjing Medical University, No.29, Xinglong Lane, Tianning District, Changzhou 213004, Jiangsu, China.

References

1. Phan K, Mitchell P, Liew G, Plant AJ, Wang SB, Au C, et al. Association between Retinal Arteriolar and Venule Calibre with Prevalent Heart Failure: A Cross-Sectional Study. PloS one. 2015;10 12:e0144850. doi:10.1371/journal.pone.0144850.
2. Nam KW, Kwon HM, Jeong HY, Park JH, Kwon H, Jeong SM. Serum homocysteine level is related to cerebral small vessel disease in a healthy population. Neurology. 2019;92(4):e317-e25. doi:10.1212/wnl.0000000000006816.
3. Piao X, Wu G, Yang P, Shen J, De A, Wu J, et al. Association between Homocysteine and Cerebral Small Vessel Disease: A Meta-Analysis. Journal of stroke cerebrovascular diseases: the official journal of National Stroke Association. 2018;27 9:2423–30. doi:10.1016/j.jstrokecerebrovasdis.2018.04.035.
4. Tawfik A, Mohamed R, Elsherbiny NM, DeAngelis MM, Bartoli M, Al-Shabrawey M. Homocysteine: A Potential Biomarker for Diabetic Retinopathy. Journal of clinical medicine. 2019;8 1; doi:10.3390/jcm8010121.
5. Doubal FN, MacGillivray TJ, Patton N, Dhillon B, Dennis MS, Wardlaw JM. Fractal analysis of retinal vessels suggests that a distinct vasculopathy causes lacunar stroke. Neurology. 2010;74 14:1102–7. doi:10.1212/WNL.0b013e3181d7d8b4.
6. TY W, MD K, BE RK, SM K. M, LD H. Computer-assisted measurement of retinal vessel diameters in the Beaver Dam Eye Study: methodology, correlation between eyes, and effect of refractive errors. Ophthalmology. 2004;111 6:1183–90.
7. Doubal FN, de Haan R, MacGillivray TJ, Cohn-Hokke PE, Dhillon B, Dennis MS, et al. Retinal arteriolar geometry is associated with cerebral white matter hyperintensities on magnetic resonance imaging. International journal of stroke: official journal of the International Stroke Society. 2010;5 6:434–9. doi:10.1111/j.1747-4949.2010.00483.x.
8. Hu DY, Xu XP. [Prevention of stroke relies on valid control "H" type hypertension]. Zhonghua nei ke za zhi. 2008;47 12:976–7.
9. Fu L, Li YN, Luo D, Deng S, Wu B, Hu YQ. Evidence on the causal link between homocysteine and hypertension from a meta-analysis of 40 173 individuals implementing Mendelian randomization. Journal of clinical hypertension (Greenwich Conn). 2019;21 12:1879–94. doi:10.1111/jch.13737.

10. Yang G, Wu L, Jiang B, Yang W, Qi J, Cao K, et al. H2S as a physiologic vasorelaxant: hypertension in mice with deletion of cystathionine gamma-lyase. Science. 2008;322:5901:587–90. doi:10.1126/science.1162667.
11. Gaifullina AS, Lazniewska J, Gerasimova EV, Burkhanova GF, Rzhepetskyy Y, Tomin A, et al. A potential role for T-type calcium channels in homocysteinemia-induced peripheral neuropathy. Pain. 2019;160 12:2798–810. doi:10.1097/j.pain.0000000000001669.
12. Elsherbiny NM, Sharma I, Kira D, Alhusban S, Samra YA, Jadeja R, et al. Homocysteine Induces Inflammation in Retina and Brain. Biomolecules. 2020;10 3; doi:10.3390/biom10030393.
13. Moretti R, Caruso P. The Controversial Role of Homocysteine in Neurology: From Labs to Clinical Practice. Int J Mol Sci. 2019;20 1; doi:10.3390/ijms20010231.
14. Pang H, Fu Q, Cao Q, Hao L, Zong Z. Sex differences in risk factors for stroke in patients with hypertension and hyperhomocysteinemia. Scientific reports. 2019;9 1:14313; doi:10.1038/s41598-019-50856-z.
15. Sottilotta G, Oriana V, Latella C, Luise F, Piromalli A, Ramirez F, et al. Role of hyperhomocystinemia in retinal vascular occlusive disease. Clinical applied thrombosis/hemostasis: official journal of the International Academy of Clinical Applied Thrombosis/Hemostasis. 2007;13(1):104–7. doi:10.1177/1076029606296423.
16. Lai WK, Kan MY. Homocysteine-Induced Endothelial Dysfunction. Annals of nutrition & metabolism. 2015;67 1:1–12; doi: 10.1159/000437098.
17. Tyagi N, Moshal KS, Ovechkin AV, Rodriguez W, Steed M, Henderson B, et al. Mitochondrial mechanism of oxidative stress and systemic hypertension in hyperhomocysteinemia. Journal of cellular biochemistry. 2005;96(4):665–71. doi:10.1002/jcb.20578.
18. Kloppenborg RP, Geerlings MI, Visseren FL, Mali WP, Vermeulen M, van der Graaf Y, et al. Homocysteine and progression of generalized small-vessel disease: the SMART-MR Study. Neurology. 2014;82 9:777–83. doi:10.1212/wnl.0000000000000168.
19. Park SY, An SA, Lee HB, Kim Y, Kim NK, Kim SH, et al. Different impact of hyperhomocysteinemia on cerebral small vessel ischemia and cervico-cerebral atherosclerosis in non-stroke individuals. Thrombosis research. 2013;131(1):e12-6. doi:10.1016/j.thromres.2012.11.011.
20. Ye Z, Wang C, Zhang Q, Li Y, Zhang J, Ma X, et al. Prevalence of Homocysteine-Related Hypertension in Patients With Chronic Kidney Disease. Journal of clinical hypertension (Greenwich Conn). 2017;19(2):151–60. doi:10.1111/jch.12881.
21. Pushpakumar S, Kundu S, Sen U. Endothelial dysfunction: the link between homocysteine and hydrogen sulfide. Curr Med Chem. 2014;21 32:3662–72. doi:10.2174/09298673216661407061423335.
22. Ostrakhovitch EA, Tabibzadeh S. Homocysteine and age-associated disorders. Ageing Res Rev. 2019;49:144–64. doi:10.1016/j.arr.2018.10.010.
23. 10.3109/10641963.2015.1116547

Chen Z, Wang F, Zheng Y, Zeng Q, Liu H. H-type hypertension is an important risk factor of carotid atherosclerotic plaques. Clinical and experimental hypertension (New York, NY: 1993). 2016;38 5:424-8; doi: 10.3109/10641963.2015.1116547.

24. Small HY, Migliarino S, Czesnikiewicz-Guzik M, Guzik TJ. Hypertension. Focus on autoimmunity and oxidative stress. Free Radic Biol Med. 2018;125:104–15. doi:10.1016/j.freeradbiomed.2018.05.085.
25. Li T, Liu X, Diao S, Kong Y, Duan X, Yang S, et al. H-Type Hypertension Is a Risk Factor for Cerebral Small-Vessel Disease. BioMed research international. 2020;2020:6498903. doi:10.1155/2020/6498903.
26. Sen U, Mishra PK, Tyagi N, Tyagi SC. Homocysteine to hydrogen sulfide or hypertension. Cell Biochem Biophys. 2010;57(2–3):49–58. doi:10.1007/s12013-010-9079-y.
27. Tyagi N, Gillespie W, Vacek JC, Sen U, Tyagi SC, Lominadze D. Activation of GABA-A receptor ameliorates homocysteine-induced MMP-9 activation by ERK pathway. Journal of cellular physiology. 2009;220(1):257–66. doi:10.1002/jcp.21757.

Figures

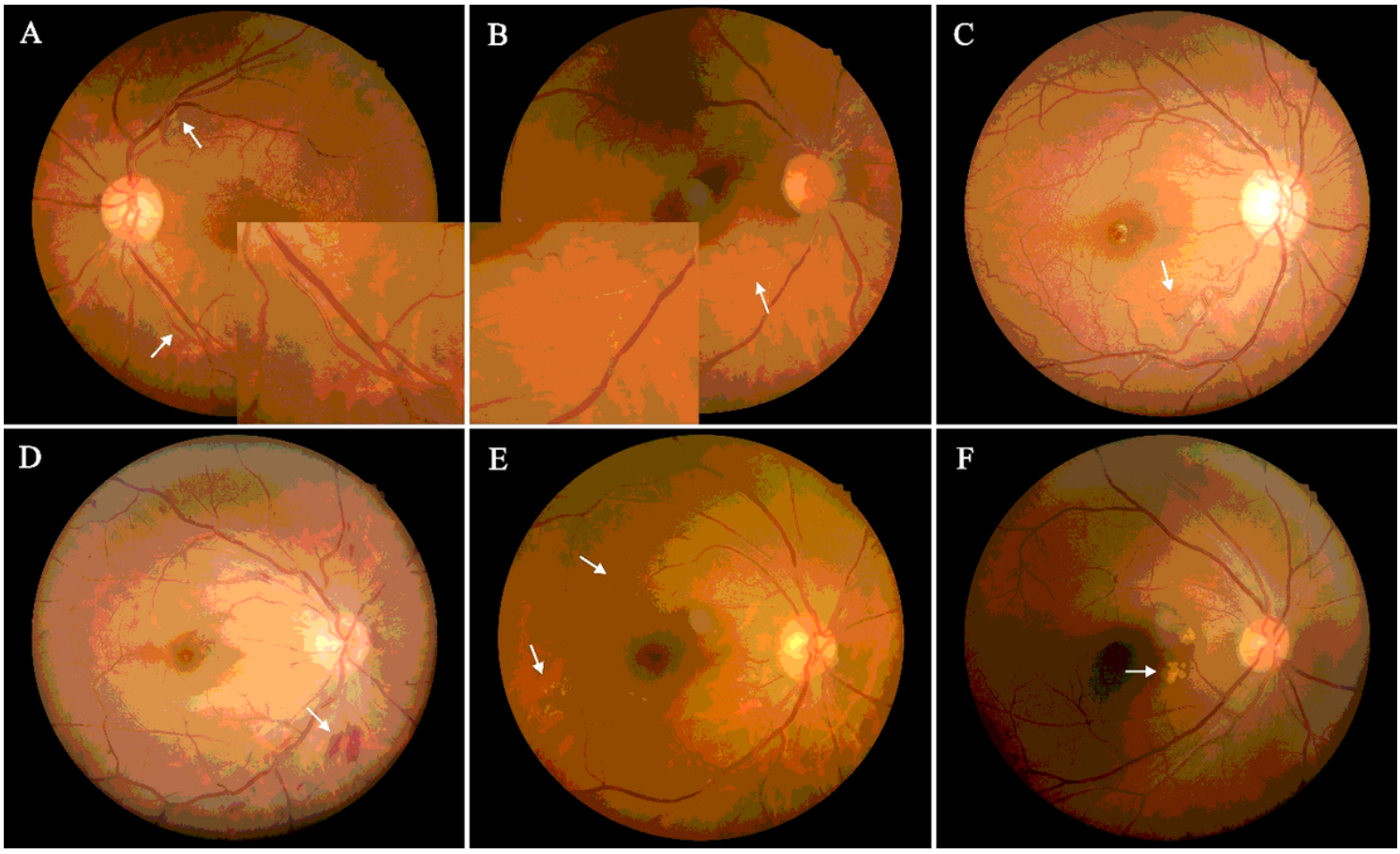

Figure 1

Retinal fundus photographs of patients. A, Arteriovenous nicking (upper arrow), normal retinal artery(magnified at the lower arrow); B, Retinal arteriosclerosis(magnified at the arrow), The retinal artery

becomes thinner, the reflection is enhanced, and the blood column becomes lighter in color; C, Retinal artery is widely wavy(arrow point). D, Hemorrhage of the retina (arrow point); E, Microangioma (upper arrow), hard exudation (lower arrow); F, Soft exudate (arrow point).