Brain white matter hyperintensities in Kawasaki disease: a case-control study

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Abstract

Cerebrobascular involvement of Kawasaki disease (KD) is poorly studied. White matter hyperintensities (WMH) indicate cerebral small vessel disease and increases risk for stroke. We investigated if childhood KD is associated with WMHs later in adulthood. In this case-control study, patients diagnosed with KD (cases) at our tertiary hospital between 1978 and 1995 were invited to brain magnetic resonance (MRI) between 2016 and 2017. Migraine patients (controls) with available brain MRI were matched with cases (ratio 4:1) by age (±2 years) and sex. Two blinded neuroradiologists evaluated independently the brain MRI scans. Modified Scheltens' visual rating scale was used to evaluate WMH burden. Mean age (years, [SD]) at the time of brain MRI was 33.3 [3.8] and 32.8 [4.0] for cases (n=40) and controls (n=160), respectively (*P*=.53). Mean follow-up time for cases was 29.5 years [4.3]. Cases had higher total WMH burden (*P*=.003), deep WMH burden (*P*=.003), and more periventricular WMHs (prevalence 7.5% vs. 0%, *P*=.008) than controls. Myocarditis at the acute phase of KD increased risk for periventricular WMHs (*P*<.05). None of the cases had symptomatic ischemic stroke. History of KD could be associated with increased WMH burden. More studies are needed to confirm our results.

Introduction

Kawasaki disease (KD) is a childhood vasculitis affecting small and medium sized arteries of the entire body[1] and 30% may present central nervous system symptoms[2] and signs of intracranial vasculitis[3]. Symptomatic brain infarct is rare in KD patients and limited to case reports.[4]

White matter hyperintensities (WMH) usually indicate cerebral small vessel disease.[5] High WMH burden is associated with an increased risk of death, stroke, psychiatric disorders and dementia.[6, 7] Prevalence of WMH increases with age from 5% in healthy young adults[8] to over 60% in elderly[9]. Compared to general population, migraine patients have higher risk for WMHs[10, 11, 12] with a prevalence of 11% in children[13] and 39-44% in young adults without significant difference between migraine subtypes[14].

Although previous studies suggests that KD affects also cerebral vessels[2, 3, 15, 16] this area is poorly studied and it is unknown if KD is associated with WMHs later in adulthood.[17] However, recent study found that KD might increase risk for hemorrhagic and ischemic stroke.[18]

The objective of this study was to investigate if KD is associated with WMHs in the long-term follow-up, which could indicate cerebrovascular involvement of KD and increased risk for cerebrovascular diseases.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents.

This study was approved by Ethics Committee of the Hospital District of Southwest Finland. Written informed consent was obtained from all cases in the study. Informed consent was not required for controls, because controls were included from retrospective register. All methods were performed in accordance with STROBE guidelines and Declaration of Helsinki.

Study population

Cases

KD patients who were diagnosed and treated in the catchment area of the Turku University Hospital (population of 887 000 citizens) from 1978 to 1995 were identified retrospectively by using diagnostic codes (International Classification Code-9, 446.1; International Classification Code-10, M30.3). Diagnosis were confirmed from the patient records for each patient according to American Heart Association (AHA) 2004 diagnostic criteria for complete KD.[19] Patients with a current age of ≥ 25 years and a history of KD occurring in the childhood were included in this study. Age criteria was based on protocol for this cohort described in the earlier study.[20] Patients with current age < 25 years, Marfans syndrome, Ehler-Danlos syndrome type IV, polycystic kidney disease or history of intracranial aneurysms or bleeding were excluded. Patients with a positive family history of intracranial aneurysms were also excluded.

There were 87 KD patients diagnosed between 1978 and 1995. From 87 KD patients, 27 were excluded because of age < 25 years. Based on a review of patient records, none of the 87 KD patients had been diagnosed with ischemic or hemorrhagic stroke before beginning the study enrollment year 2016. An invitation letter was sent to 60 patients who met the inclusion criteria and 40 of them were willing to participate in the study, and 20 refused. Prior to brain magnetic resonance imaging (MRI), patients were interviewed for past medical history (hypertension, diabetes mellitus, hypertension, migraine, hyperlipidemia, depression, history of stroke, neurological symptoms), medication, smoking, alcohol consumption and possible signs of heart or lung problems.

Of 40 cases, 37 had accurate information on which drug KD had been treated with and 37 patients had accurate information about echocardiographic data during the acute phase of KD. From 37 patients 22 were treated with intravenous immunoglobulin and 15 patients with aspirin only.

This was a population-based study, since all the patients were collected from our catchment area.

Controls

All patients who had undergone brain MRI for any reason (n= 39 993) between 2003 and 2020 in our tertiary hospital were reviewed to include migraine patients (controls). Of these patients, 1062 had migraine diagnosis (International Classification Code-10, G43.0-G43.3) in patient records. Of 1062 migraine patients, 68 were excluded because of intracranial tumor, history of acute brain infarction, sinus

thrombosis or subarachnoid- /intracerebral hemorrhage. None of the controls had as history of KD, other vasculitis or brain diseases. From 994 migraine patients, controls were matched (4 controls to 1 case) randomly by age (±2 years at the time of the brain MRI) and sex with cases. Patient records were reviewed for hypertension, hypercholesterolemia, type 1- and type 2-diabetes, smoking and migraine subtype. Smoking was categorized as never smoker vs. current- or ex-smoker.

Brain MRI Data Acquisition

For cases, MRI scans were conducted on a Philips Ingenia 3T scanner (Philips Medical Systems, Best, the Netherlands). Axial 3D T2-weighted sequence with TR (Repetition Time) of 2500 ms (milliseconds), TE (Time Echo) of 250 ms, matrix of 352 x 352 and slice thickness of 1 mm (millimeters) was obtained. We also obtained a coronal 2D FLAIR (Fluid Attenuation Inversion Recovery) sequence with TR of 4800, TI (Time Inversion) of 1650 ms, TE of 285 ms, matrix of 352 x 352 and slice thickness of 3 mm, sagittal 3DT1 sequence with TR of 81 ms, TE of 3.7 ms, matrix of 320 x 320 and slice thickness of 1 mm was obtained as well as susceptibility-weighted sequence with TR of 20 ms, TE of 27 ms, matrix of 512 x 512 and slice thickness of 2 mm. These sequences were obtained to find and exclude any brain pathology. MR angiography using a axial Time-Of-Flight (TOF) sequence with TR of 23 ms, TE of 3.5 ms, matrix of 640 x 640 and slice thickness of 1.2 mm was performed to evaluate the arteries of the brains. TOF images were interpreted as such and also 3D reconstructions in two different planes were built and interpreted.

For controls, MRI scans were conducted with any available 1.5-3T scanners at our catchment area with a routine MRI protocol that includes the following sequences; T1- and T2-weighted sequences, susceptibility-weighted sequences, and FLAIR sequences. MRI scanner type and field strength for each control is presented in **Supplemental Table S1**.

Brain Imaging and Analysis

For controls and cases, two neuroradiologist (each with more than 10 years of experience in neuroradiology), blinded to case-control status and clinical data, evaluated independently the number, the location and the size of WMHs from the fluid-attenuated inversion recovery (FLAIR)-sequences and T2-weighted images. In addition, microbleeds and lacunes of presumed vascular origin were evaluated in the same blinded fashion. Conflicting interpretations between the two radiologists were resolved by consensus of the two interpreters.

Lesions ≥2 mm were categorized as WMH. Modified Scheltens' visual rating scale was used to evaluate WMH burden,[21, 22, 23] because WMHs located in the basal ganglia or brainstem were excluded according to neuroimaging strandards for WMHs[24]. Modified Scheltens' visual rating scale provides scoring system for periventricular WMH (0-9 points) and deep white matter hyperintesities (0-24 points) (**Supplemental**

Table S2).[22, 23] WMH located less than 10 mm from the ventricles was categorized as periventricular WMH.[25] Subcortical WMHs was categorized as deep WMHs.

Lacune of presumed vascular origin was categorized as round or ovoid, subcortical, fluid-filled cavity of between 3mm and 15 mm in diameter from T1-weighted, T2-weighted and FLAIR sequenses.[24] Location of lacune was defined by vascular territory.[24] Microbleeds were evaluated from susceptibility sequences and differiantiated from sponatenous intracerebral hemorrhages with T1-weighted and T2-weighted or FLAIR sequences.[24]

Statistical Analysis

All analyses were performed using SPSS Statistics 27 (IBM Corp., Armonk, NY, USA).

Mean ages within cases and between cases and controls were compared with two-sample t-test. Percentage distribution of total, deep, and periventricular Scheltens' score were compared between cases and controls by using Chi-square test and Fisher's exact test to evaluate total, deep and periventricular WMH burden. Chi-square and Fisher's exact test were also used to test the association of categorical variables with Scheltens' score. Scheltens' score was dichotomized to 0 vs ≥1 to compare prevalence and risk factors for total WMHs, deep WMHs and periventricular WMHs within cases and controls, and between cases and controls with chi-square and Fisher's exact test. In those with positive WMH findings (Scheltens' score ≥1), Scheltens' score values were compared between cases and controls by using Mann-Whitney U-test. P-values less than 0.05 were considered as statistically significant. Missing data for each variable were excluded from the analyses.

Cohen's kappa (k) analysis was used to evaluate inter-observer agreement for the WMH prevalence at the first evaluation round. Kappa value between 0.00-0.20 was defined as slight agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement and 0.81-1.00 almost perfect agreement.[26]

Results

Demographics and mean Scheltens' scores for cases and controls are presented in Table 1 and study population in flow chart Fig. 1.

Table 1
Demographics for 40 cases and 160 controls.

Variable	Cases (n = 40)	Controls (n = 160)	p-value
Mean age at time of brain MRI, years (SD)	33.3 (3.8)	32.8 (4.0)	0.53
Sex, *n* (%)			
Men	25 (62.5)	100 (62.5)	1.0
Female	15 (37.5)	60 (37.5)	1.0
Hypertension, *n* (%)	2 (5)	15 (9.4)	0.53
Hypercholesterolemia, *n* (%)	0 (0)	11 (6.9)	0.13
Type 1 diabetes, *n* (%)	1 (2.5)	3 (1.9)	1.0
Type 2 diabetes, *n* (%)	1 (2.5)	16 (10)	0.20
Migraine with aura, *n* (%)	2 (5.0)	69 (43.1)	**< 0.001**
Migraine without aura, *n* (%)	2 (5.0)	91(56.9)	**< 0.001**
Never smoker, *n* (%)	19 (47.5)	66 (54.1)	0.58
Smoker/ex-smoker, *n* (%)	21 (52.5)	56 (45.9)	0.58
Missing data for smoking, *n*	0	38	
Brain MRI findings			
Prevalence of WMHs, *n (%)*	8 (20)	18 (11.3)	0.14
Prevalence of deep WMHs, *n* (%)	8 (20)	18 (11.3)	0.14
Prevalence of periventricular WMHs, *n* (%)	3 (7.5)	0 (0)	**0.008**
Total Scheltens' Score, median (IQR)	4.0 (4.5)	1.0 (0)	**0.003**
Scheltens' score for deep WMH, median (IQR)	3.0 (3.0)	1.0 (0)	**0.003**
Scheltens' score for periventricular WMH, median (IQR)	0 (1.5)	0 (0)	**0.007**
Lacune of presumed vascular origin, *n (%)*	3 (7.5)	3 (1.9)	0.096
Vascular territory for lacune			
Posterior cerebral artery, *n*	2 (5.0)	3 (1.9)	0.26
Middle cerebral artery, n	1 (2.5)	0 (0)	0.20

Variable	Cases (n = 40)	Controls (n = 160)	p-value
Hemorrhage/microbleeds, *n (%)*	0 (0)	0 (0)	1.0
Cerebral artery stenosis	0 (0)	N/A	

Mean age for cases (n = 40) and controls (n = 160) was 33.3 (SD, 3.8) years and 32.8 (SD, 4.0) years, p > 0.5. Of the cases and controls, 62.5% were men. KD was diagnosed at an average age of 3.9 years and mean follow-up time (from KD diagnosis to brain MRI) was 29.5 years (SD, 4.3). Of the 160 controls, 147 had undergone brain MRI because of migraine related symptoms (**Supplemental Table S3**).

Cases vs. controls

Cases had higher total WMH burden ($P = .003$), deep WMH burden ($P = .003$) and more periventricular WMHs (prevalence 7.5% vs. 0%, $P = .008$) compared to controls (Table 1). Distribution of Scheltens' score is presented separately in the Fig. 2. Lacune of presumed vascular origin was found in 3 cases (7.5%) and in 3 controls (1.9%), $P = .096$. There were no microbleeds in cases or in controls (Table 1).

Hypercholesterolemia, hypertension, type-1- or type 2-diabetes, migraine with aura, or smoking were not significantly associated with presentation of WMHs ($P > 0.05$) in cases (Table 2) or in controls (Table 3).

Table 2
Clinical characteristics and their risk factors for deep and periventricular white matter hyperintensities (WMH) in 40 cases during the acute onset of Kawasaki disease (KD) and at the brain MRI.

Variables	Total n = 40	Deep WMH n = 8	p value	Periventricular WMH n = 3	p value
Acute onset of KD, demographics					
Mean age at KD diagnosis, mean years, (SD)	3.9 (3.1)	Yes: 5.0 (3.9) No: 3.7 (2.9)	0.3	Yes: 1.8 (1.2) No: 4.1 (3.2)	0.2
Sex, n (%)					
Female	15 (37.5)	7/15 (46.7)	**0.002**	3/15 (20)	**0.046**
Men	25 (62.5)	1/25 (4.0)		0/25 (0)	
IVIG treatment, n (%)					
Yes	22 (52.5)	5/22 (22.7)	1.0	3/22 (13.6)	0.3
No	15 (37.5)	3/15 (20.0)		0/15 (0)	
Missing data, n	3 (7.5)	0/3 (0)		0 (0/3)	
Coronary artery dilatation/aneurysm, n (%)					
Yes	6 (15)	1/6 (16.7)	1.0	1/6 (16.7)	0.3
No	31 (80)	6/31 (19.4)		1/31 (3.2)	
Missing data	3 (7.5)	1/3 (33.3)		1/3 (33.3)	
Coronary artery aneurysm, n (%)					
Yes	2 (5.0)	0/2 (0)	1.0	0/2 (0)	1.0
No	35 (87.5)	7/35 (20)		2/35 (5.7)	
Missing data,	3 (7.5)	1/3 (33.3)		1/3 (33.3)	
Myocarditis, n (%)					
Yes	7 (17.5)	3/7 (42.9)	0.1	2/7 (28.6)	**0.03**
No	30 (75.0)	4/30 (13.3)		0/30 (0)	
Missing data	3 (7.5)	1/3 (33.3)		1/3 (33.3)	
Hepatitis, n (%)					

Variables	Total n = 40	Deep WMH n = 8	p value	Periventricular WMH n = 3	p value
Yes	5 (12.5)	1/5 (20.0)	1.00	0/5 (0)	1.00
No	32 (80.0)	6/32 (18.8)		2/32 (6.3)	
Missing data	3 (7.5)	1/3 (33.3)		1/3 (33.3)	
Gallbladder hydrops, n (%)					
Yes	2 (5.0)	0/2 (0)	1.00	0/2 (0)	1.00
No	35 (87.5)	7/35 (20)		2/35 (5.7)	
Missing data	3 (7.5)	1/3 (33.3)		1/3 (33.3)	
Meningitis, n (%)					
Yes	3 (7.5)	1/3 (33.3)	0.48	0/3 (0)	1.00
No	34 (85.0)	6/34 (17.7)		2/34 (5.9)	
Missing data	3 (7.5)	1/3 (33.3)		1/3 (33.3)	
Anterior uveitis, n (%)					
Yes	6 (15.0)	0/6 (0)	0.6	0/6 (0)	1.0
No	31 (77.5)	7/31 (22.6)		2/31 (6.5)	
Missing data	3 (7.5)	1/3 (33.3)		1/3 (33.3)	
Relapse requiring re-treatment, n (%)					
Yes	4 (10)	1/4 (25)	1.0	0/4 (0)	1.0
No	36 (90)	7/36 (19.4)		3/36 (8.3)	
Kawasaki Disease Shock Syndrome	0 (0)	-		-	
Follow-up demographics					
Mean age at brain MRI, years (SD)	33.3 (3.8)	Yes: 33.1 (2.9) No: 33.3 (4.1)	0.9	Yes: 30.3 (2.9) No: 33.5 (3.8)	0.1
Migraine with aura, n (%)					
Yes	2 (5)	0/2 (0)	1.0	0/2 (0)	1.0
No	38 (95)	8/38 (21.1)		3/38 (7.9)	

Variables	Total n = 40	Deep WMH n = 8	p value	Periventricular WMH n = 3	p value
Migraine without aura, n (%)					
Yes	2 (5)	0/2 (0)	1.0	0/2 (0)	1.0
No	38 (95)	8/38 (21.1)		3/38 (7.9)	
Hypertension, n (%)					
Yes	1 (2.5)	0/1 (0)	1.0	0/1 (0)	1.0
No	39 (97.5)	8/39 (20.5)		3/39 (7.7)	
Type 1 diabetes, n (%)					
Yes	1 (2.5)	0/1 (0)	1.0	0/1 (0)	1.0
No	0 (0)	8/39 (20.5)		3/39 (7.7)	
Type 2 diabetes, n (%)	0 (0)	-		-	
Hypercholesterolemia, n (%)	0 (0)	-		-	
Smoking, n (%)					
Smoker or ex-smoker	21 (52.5)	3/21 (14.3)	0.4	1/21 (4.8)	0.6
Never smoker	19 (47.5)	5/19 (26.3)		2/19 (10.5)	
Symptomatic ischemic stroke, n (%)	0 (0)	-		-	-
Neurological symptoms, n (%)	0 (0)	-		-	-
Depression, n (%)					
Yes	3 (7.5)	1/3 (33.3)	0.5	1/3 (33.3)	0.2
No	37 (92.5)	7/37 (18.9)		2/37 (5.4)	

Table 3
Clinical characteristics and their risk factors for deep white matter hyperintensities (WMH) in 160 controls. There were no periventricular WMHs in controls.

Variables	**Total n = 160**	**Deep WMH n = 18**	**p value**
Mean age at brain MRI, years (SD)	33.3 (3.8)	Yes: 34.4 (3.5) No: 32.6 (4.1)	0.3
Sex			
Female	60 (37.5)	5/60 (8.3)	0.5
Men	100 (62.5)	13/100 (13.0)	
Migraine, n (%)			
With aura	69 (43.1)	10/69 (14.5)	0.3
Without aura	91 (56.9)	8/91 (8.8)	
Hypertension, n (%)			
Yes	15 (9.4)	2/15 (13.3)	0.68
No	145 (90.6)	16/145 (11.0)	
Type 1 diabetes, n (%)			
Yes	3 (1.9)	0/3 (0)	1.0
No	157 (98.2)	18/157 (11.5)	
Type 2 diabetes, n (%)		-	
Yes	16 (10)	4/16 (25.0)	0.086
No	144 (90)	14/144 (9.7)	
Hypercholesterolemia, n (%)		-	
Yes	11 (6.9)	1/11 (9.1)	1.0
No	149 (93.1)	17/149 (11.4)	
Smoking, n (%)			
Smoker or ex-smoker	56 (35.0)	8/56 (14.3)	0.4
Never smoker	66 (41.2)	9/66 (13.6)	
Missing data	38 (23.8)	1/38 (2.6)	
Symptomatic ischemic stroke, n (%)	0 (0)	-	

Cases

None of the cases had been diagnosed with ischemic stroke during the time-period between KD diagnosis and follow-up MRI. Of the 37 cases with available information on complications during the acute onset of KD, seven had myocarditis during the acute phase of KD and two of them (28%) had periventricular WMHs, while those without myocarditis (n = 30) did not have any periventricular WMHs (0%), $P = .03$. Females had more deep ($P = .002$ and periventricular WMHs compared to males. Prevalence of deep WMHs were higher in patients with myocarditis (prevalence 42.9%) than in those without myocarditis (prevalence 13.3%), but the difference was not statistically significant ($P = .1$). Prevalence of deep and periventricular WMHs were similar in those who were treated with intravenous immunoglobulin and those who were not ($P > .3$). Five patients had coronary artery aneurysm or dilatation during the acute phase of KD and one of them had deep WMH. Two patient had coronary artery aneurysm and none of them had WMH findings (Table 2).

Inter-observer agreement

Inter-observer agreement for WMHs was fair (k = 0.42, CI 95% 0.25–0.60) for the first evaluation. From 200 study subjects, there were disagreement in 26 interpret of WMHs, which was resolved by consensus in the second evaluation.

Discussion

In this long-term follow-up study of KD patients, WMH burden and prevalence of periventricular WMHs was significantly higher in patients with a history of KD compared to controls.

KD was first discovered in 1967, yet all long-term effects are still unknown.[1] KD patients might have higher risk for cardiovascular diseases and long-term effects to systemic arteries[27], but whether KD is linked to cerebrovascular diseases in a long-term is unclear[17, 18]. To our knowledge, this study was first to describe that history of KD is related to increased WMH burden in the long-term follow-up.

There are several possible mechanisms for why KD may be associated with an increased risk of WMHs. Hypoperfusion, the blood-brain barrier dysfunction and inflammation are potential underlying pathophysiological mechanism for WMHs.[28] Although KD is affecting predominantly medium-sized extracranial arteries, 1–30% might develop central nervous system symptoms (facial nerve paresis, meningeal irritation, bulging fontanelles, convulsions, somnolence, extreme irritability, headache) in acute KD.[2] Localized cerebral hypoperfusion has been reported in 29–72% of KD patients without neurological symptoms during the acute illness and lasting even several months afterwards, possibly indicating cerebral vasculitis.[15, 16] Elevated inflammatory cytokines and pleocytosis in cerebrospinal fluid during the acute phase of KD has been found in 40–60% of patients, suggesting central nervous system inflammation in KD.[29]

Interestingly, KD was particularly associated with periventricular WMHs (prevalence 7.5% in cases and 0% in controls). We also found that myocarditis during the acute phase of KD increased risk for periventricular WMHs, one explanation for this finding could be hypoperfusion as well. Myocarditis is common in KD and can cause hemodynamic instability in severe cases.[30] Periventricular WMHs are often related to advanced age and cerebral small vessel disease, and could be more susceptible to hypoperfusion.[31] Periventricular WMHs and deep WMHs has a different histopathological findings and clinical consequences, but studies suggests that periventricular and deep WMHs are probably continuum of same pathological process.[5] In KD patients, females had more periventricular and deep WMHs compared to males. One explanation could be that females may be more susceptible to WMHs due to genetic risk factors.[32]

In our study, WMH burden was significantly higher in KD patients compared to controls with migraine, despite the fact that in previous studies migraine has been shown to be associated with an increased WMH burden compared to healthy controls[10, 11, 12]. Prevalence of WMHs was 20% in KD patients, which is four times higher than reported in healthy young adults with a similar age[8]. In contrast, prevalence of WMH in cases (migraine patients) was comparable to pediatric migraine patients (11% vs 11%),[13] but lower than reported in young adults with migraine[14].

KD is treated with intravenous immunoglobulin and aspirin to prevent coronary artery aneurysms.[27] Intravenous immunoglobulin treatment may increase risk for thromboembolic complications.[33, 34] In the present study, a relatively large proportion of KD patients were diagnosed before intravenous immunoglobulin treatment was established[35], which allowed comparison of groups in terms of treatment. We did not find a significant difference in WMH prevalence or total WMH burden between KD patients treated with or without intravenous immunoglobulin. In KD, coronary artery aneurysms may predispose more severe systemic inflammation.[36] In our study, five patients had coronary artery dilatations or aneurysms and only one had periventricular and deep WMHs. Two KD patients had coronary artery aneurysm, but no WMHs. However, because of small number of patients with coronary artery aneurysms, no conclusions can be drawn on this finding.

Increased WMH burden is associated with higher risk for stroke, dementia, depression and all-cause mortality.[6, 7] Furthermore, increased WMH burden could be associated with different psychiatric disorders in children.[37] Acute ischemic stroke after KD is uncommon and limited to single case reports.[4] KD could be also associated with an increased risk of epilepsy and neurodevelopmental disorders, but pathophysiology of these phenomenon is unclear.[38] We did not perform neuropsychological evaluation on study subjects, so no conclusions can be drawn on this issue from our study.

Limitations

One of the limitation was modest number of cases in this study. However, this was a population-based study as we reviewed all KD treated and diagnosed in our hospital district area and were able to recruit 40

of 60 patients who met inclusion criteria for our study.

Migraine patients were selected as a control group, because WMHs have been extensively studied in this population and migraine patients are more homogenous population compared to headache patients in general which increases the repeatability of this study design. We acknowledge that migraine patients has increased risk for WMHs,[14] but because we were able to show that WMHs burden is higher in KD compared to migraine patients this do not affect our conclusions and really gives further confirmation to our results. Another limitation for control group was that they were selected retrospectively, which may have caused selection bias. However, one could assume that selection bias would rather have led to a higher number of WMH findings in control patients, because migraine patients are not routinely undergoing brain MRI.

Another limitation is that we had no brain MRI imaging during the acute phase KD, so it is uncertain in which point WMHs occurred in Kawasaki disease patients.

There are limitations in the interpretation of WMHs. One major limitation was that brain imaging was performed on control patients with several different MRI scanners, which may have affected WMH interpretation. However, proposed image acquisition standards for WMH imaging[24] were achieved also with controls. We evaluated WMH changes on a widely used quantitative visual rating scale,[24] one reason for this was that applying automatic segmentation tools to different scanners could have caused serious inter-scanner variability[39]. Compared to automatic segmentation tools, visual rating scales are more prone inter-rater variability, but on the other hand are more achievable method.[24] Nevertheless, we used blinded review by two fellowship-trained neuroradiologists, and discrepancies were resolved using consensus. In addition, visual rating scales are comparable to automatic segmentation tools when assessing WMH burden[40], but are inferior in grouping small differences and WMH progression[41].

Conclusion

Our study suggest that patients with a history of Kawasaki disease might have increased risk for WMHs, but it remains unclear whether WMHs occur during or after the acute phase of KD. More studies are needed to confirm our results.

Declarations

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Competing interests

This study was supported by grant no. 17018 from the Pro Humanitate Foundation. The authors declare no competing interests.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

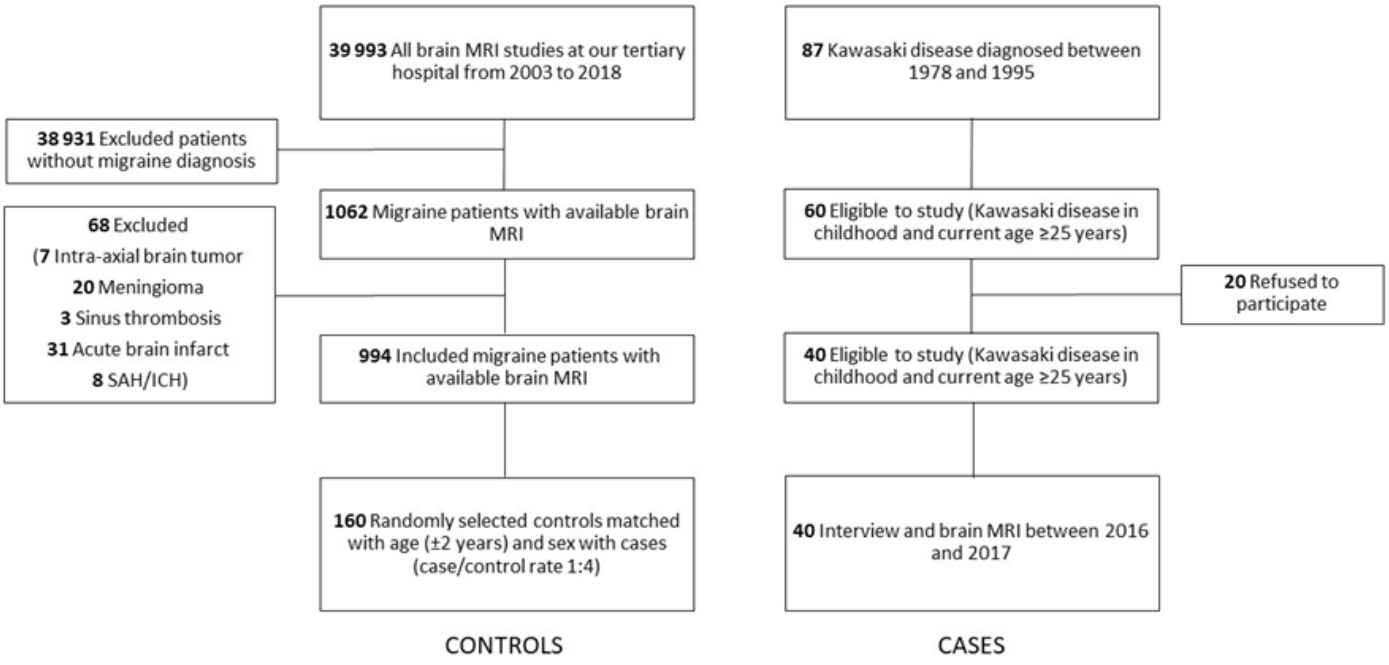

Figure 1

Flow Chart

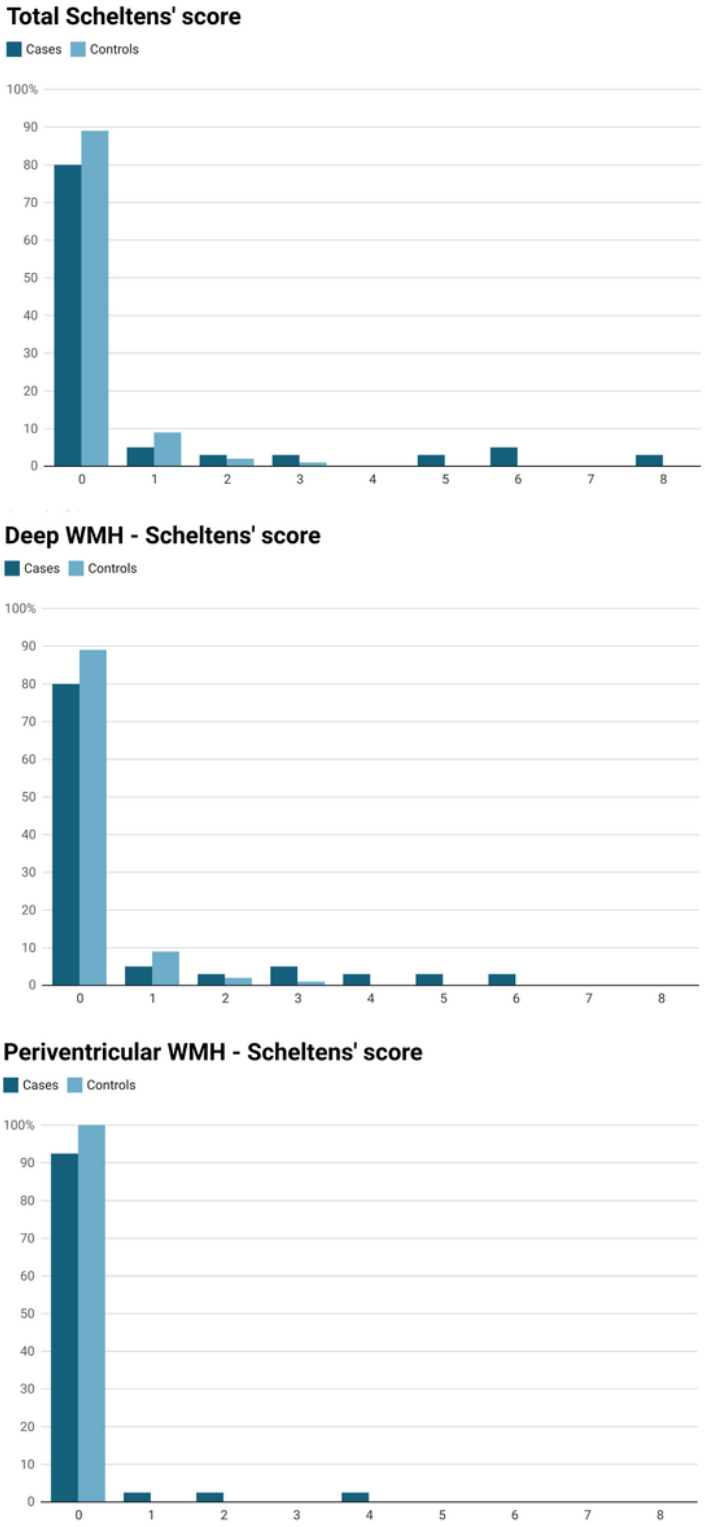

Figure 2

White matter hyperintensity scores (WMH) assesed by Scheltens' visual rating scale in 40 cases (Kawasaki disease) and 160 controls (migraine patients).

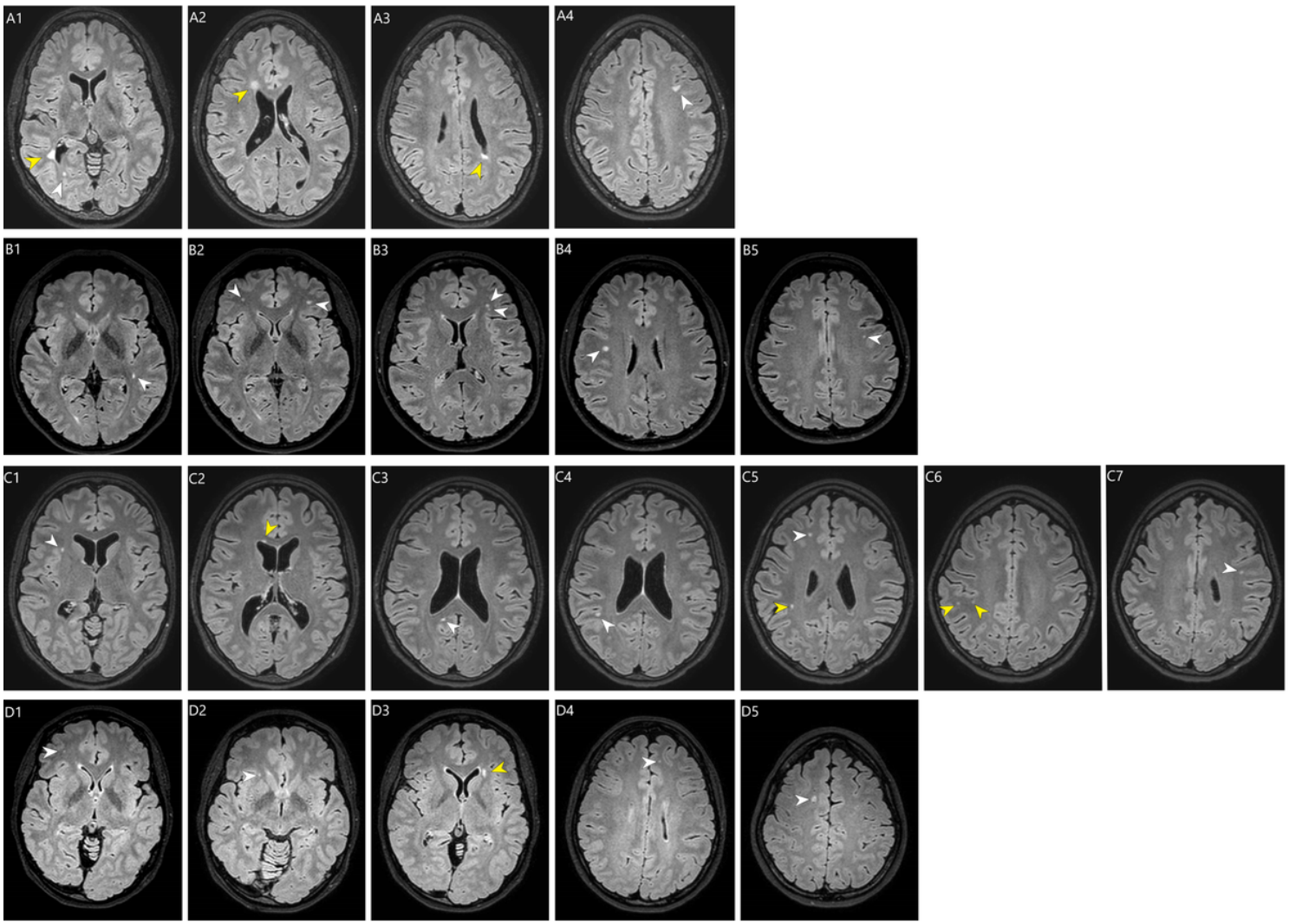

Figure 3

Brain MRI (T2-flair) of the white matter hyperintensities in four cases (Kawasaki disease).

A1-A4, a case (Kawasaki disease) with a total Scheltens' score of 8. A1: Periventricular WMH >5 mm in the right occipital horn (yellow arrow; Scheltens' score=2) and in the deep occipital lobe WMH <3 mm (white arrow; Scheltens' score= 1). A2: Periventricular WMH >5 mm in the right frontal horn (yellow arrow; Scheltens' score 2). A3: Periventricular WMH >5 mm in the left ventricle (yellow arrow; no score, because already score has been given from this area). A4: deep WMH 4-10 mm in the left frontal lobe (white arrow; Scheltens'= score 3).

B1-B4, a case (Kawasaki disease) with a total Schelten score of 6. B1: deep WMH 4-10 mm in the left temporal lobe (white arrow; Scheltens' score= 3). B2-B5: multiple deep WMH in the both frontal lobes (white arrows), in the B2 (left white arrow) and B4 (white arrow) the size of the largest WMHs are 4-10 mm (Scheltens' score= 3).

C1-C7, a case (Kawasaki disease) with a total Schelten score of 6. C1, C5 and C7: multiple deep WMH <3 mm in the frontal lobes (white arrows; Scheltens' score= 1). C2: periventricular WMH ≤5 mm in the right

frontal horn (yellow arrow; Scheltens’ score= 1). C3 deep WMH <3mm in the right occipital lobe (white arrow; Scheltens’ score= 1). C4 (white arrow), C5 (yellow arrow) and C6 (yellow arrows): deep WMHs in the right parietal lobe, in the C4 (white arrow) size of WMH is 4-10 mm (Scheltens’ score= 1).

D1-D5, a case (Kawasaki disease) with a total Schelten score of 5. D1, D2, D4 and D5: Deep WMHs in the frontal lobes (white arrows). In the D5 (white arrow) the size of the WMH is 4-10mm (Scheltens’ score= 3). D3: periventricular WMH size >5 mm next to left frontal horn (yellow arrow; Scheltens’ score= 2).

Supplementary Files

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- SupplementalTables.pdf