Journal of Neurology (2019) 266:1230–1235
https://doi.org/10.1007/s00415-019-09253-9

ORIGINAL COMMUNICATION

Juxtacortical lesions are associated with seizures in cerebral small vessel disease

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Received: 8 January 2019 / Revised: 15 February 2019 / Accepted: 16 February 2019 / Published online: 26 February 2019

Abstract

Background and objective Small vessel cerebrovascular disease (SVCD) can manifest with epileptic seizures and transient ischemic attacks (TIA). This study was designed to test if the extent and spatial distribution of SVCD differs in patients with focal impaired awareness seizures (FIAS) from patients with TIA.

Methods This is a retrospective single-center case–control study of elderly patients at a high cardiovascular risk. 118 patients with FIAS (cases) were compared to a matched control group of 118 patients with TIA. The extent and spatial distribution of white matter hyperintensities (WMH) characteristic for SVCD and medial temporal lobe atrophy were analyzed on magnetic resonance imaging (MRI) obtained at admission. The Fazekas, Wahlund, and Scheltens scales were used for grading. Juxtacortical small lesions were analyzed separately.

Results FIAS patients were observed to have more extensive WMH ($p < 0.001$) and more pronounced medial temporal lobe atrophy ($p < 0.001$) than TIA patients. WMH in FIAS patients were predominantly localized in supratentorial white matter compared to TIA patients ($p < 0.001$). Juxtacortical hyperintensities were far more common in FIAS patients than in TIA patients (80.5% vs. 22.0%; $p < 0.001$). Multivariate analysis revealed juxtacortical small lesions as strong independent predictor (OR, 95% CI 12.8, 6.7–24.3) and medial temporal lobe atrophy as further independent predictor of FIAS (3.1, 1.3–7.1).

Conclusions Juxtacortical small lesions and to a smaller extent medial temporal lobe atrophy are associated with epileptic seizures in elderly patients at a high cardiovascular risk. This observation may provide a structural explanation for epilepsy in SVCD. Juxtacortical small lesions in SVCD should be considered a structural cause for epilepsy and promote anticonvulsive therapy after a first seizure.

Keywords Cerebral small vessel diseases · Seizures · Transient ischemic attack · Magnetic resonance imaging

Introduction

Episodes with transient focal neurologic deficits are common in elderly patients with small vessel cerebrovascular disease (SVCD) [1]. The main differential diagnoses include transient ischemic attacks (TIA) and epileptic seizures. The clinical diagnosis may be difficult, in particular in the case of focal epileptic seizures. In contrast to other clinical manifestations of SVCD, such as cognitive decline, gait apraxia, urinary incontinence, and affective disorders, epileptic seizures have received less attention, although they occur in 24% of patients with SVCD [1–4]. Magnetic resonance imaging manifestations of SVCD include white matter hyperintensities (WMH), lacunes, brain atrophy, juxtacortical small lesions, and more recently described cortical microinfarcts [3, 5, 6]. The mechanisms by which SVCD may cause seizures are as yet unclear. The localization and spatial distribution of SVCD has been shown to predispose to certain clinical manifestations (e.g., SVCD in frontal white matter to cognitive decline and gait apraxia) [1]. We hypothesized that the extent and spatial distribution of SVCD differs in patients with seizures from patients with transient ischemic attack (TIA). In this retrospective study, we tested this hypothesis by analyzing the clinical characteristics and MRI manifestations of SVCD of elderly patients with episodes of transient focal neurologic deficits who were either diagnosed with a focal impaired awareness seizure (FIAS, cases) or with a TIA (controls).

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Methods

This is a retrospective case–control study of patients who were admitted to the Department of Neurology, University Hospital of Ulm, Germany over 12 months because of transient focal neurologic deficits. Inclusion criteria were an age of 60 years or older and the presence of at least one cardiovascular risk factor, respectively, cardiovascular event (arterial hypertension, diabetes mellitus, hypercholesterolemia, smoking, atrial fibrillation, coronary artery disease, previous myocardial infarction, peripheral artery disease, or previous stroke) and MRI imaging within 24 h after hospital admission. Patients with a focal impaired awareness seizure (FIAS, cases) were identified by diagnostic code. The diagnosis was reviewed using the following definition: an FIAS was defined as a transient episode of impaired awareness and either positive or negative sensorimotor symptoms or signs, which was clinically deemed to be of epileptic origin [7]. Patients, in whom the diagnostic work up revealed potential causes of seizures other than SCVD, were not included. Patients with the diagnosis of transient ischemic attack served as controls. TIA was defined as a transient episode of negative sensorimotor symptoms with preserved awareness, which was clinically deemed to be of ischemic origin [8]. Third party medical history by a caretaker was available in 80% of all patients. The control group of TIA patients was matched by age and sex. Exclusion criteria for both groups were: known epilepsy, the evidence of other potentially epileptogenic lesions on MRI (e.g., large cortical infarcts) and moderate or severe cognitive impairment (to exclude epileptic seizures associated with degenerative dementias). Patients with MRI scans confounded by motion artifacts were also excluded. The study protocol was approved by the local Ethics Committee of the University of Ulm, Germany.

Clinical and laboratory data, medical history, and EEG reports were collected by chart review. Sensorimotor symptoms and signs during seizures were classified in positive motor (e.g., myoclonus, automatisms), negative motor (e.g., paralysis, non-fluent aphasia, and speech arrest), positive sensory (e.g., paresthesia, pain, and photopsia), and negative sensory (hypesthesia and numbness).

MRI data were acquired using a clinical 1.5 T scanner (Magnetom TIM Symphony, Siemens Erlangen, Germany) equipped with a 12-channel head coil. Only MRI scans obtained within 24 h after admission of a patient were included. WMH were evaluated by a trained rater on coronal fluid attenuated inversion recovery (FLAIR) sequences or axial T2-weighted sequences if FLAIR was not available. WMH was classified according to the (modified) Fazekas scale and the Wahlund scale [9–11]. Juxtacortical small lesions were defined restrictively as lesions localized adjacent to the cortex (maximum distance from corticomedullary junction of 3 mm) [6]. Juxtacortical small lesions were graded from 0 to 3: 0 corresponded to no lesion, 1 to a single lesion, 2 to two or more lesions, and 3 to confluent lesions. Hippocampal atrophy was judged by the medial temporal lobe atrophy scale [12].

Statistical analyses were performed using the Statistical Package for Social Sciences version 24.0.0.0 (IBM SPSS Statistics, Armonk, N.Y., USA). Mann–Whitney *U* test and Pearson's Chi-squared test were used where appropriate. Regression analysis was conducted using a logistical model. Statistical significance was determined at an α level of 0.05. As this was a retrospective exploratory study, no correction of α levels of multiple testing was used.

Results

A total of 118 elderly patients with the clinical diagnosis of a first FIAS were identified. 118 age and sex-matched patients with a clinical diagnosis of TIA served as controls. The clinical and laboratory data are listed in Table 1. Slight, but significant differences for baseline data were observed for diabetes mellitus and HbA1c (more common, respectively, higher in FIAS patients), systolic blood pressure (higher in TIA patients) as well as in systemic inflammatory response (more common in FIAS patients).

As per definition, impaired awareness was present in all FIAS patients and in none of the TIA patients. In FIAS patients, positive motor symptoms or signs were present in 33.9% and sensory signs or symptoms in 5.9%, whereas TIA patients did not have positive symptoms per definition. Negative motor or sensory symptoms or signs occurred in all TIA patients (as per definition) and in 45.8% and 8.5%, respectively, of all FIAS patients.

The MRI characteristics are summarized in Table 2. Representative MRI scans are shown in Fig. 1. FIAS patients had more extensive WMH compared to TIA patients according to the Fazekas scale ($p < 0.001$). The analysis of Wahlund scores revealed that this difference was restricted to frontal, parietooccipital, and temporal white matter, whereas WMH in basal ganglia and infratentorial regions was similar in both groups. Juxtacortical small lesions were far more common in FIAS patients than in TIA patients (80.5% vs. 22.0%, $p < 0.001$). If present, juxtacortical small lesions were also significantly more extensive in FIAS than in TIA patients ($p < 0.001$). Medial temporal lobe atrophy was also more common in FIAS patients ($p < 0.001$).

In the multivariate logistic regression analysis (including PVH and DWMH scores, Wahlund scores for frontal, parietooccipital and temporal white matter, juxtacortical small lesions score, and medial temporal lobe atrophy score as independent variables), juxtacortical small lesions and

Table 1 Clinical and laboratory data of patients with FIAS and TIA

	FIAS $n=118$	TIA $n=118$	p value
Age, years, median (IQR)	82 (76–88)	79 (76–85)	0.104
Sex, female, n (%)	68 (57.6)	68 (57.6)	1.000
Symptoms and signs of FIAS, respectively, TIA			
Impaired awareness	118 (100)	0 (0)	
Positive motor	40 (33.9)	0 (0)	
Positive sensory	7 (5.9)	0 (0)	
Negative motor	54 (45.8)	96 (81.4)	**< 0.001**
Negative sensory	10 (8.5)	82 (69.5)	**< 0.001**
Medical history			
Arterial hypertension	96 (81.4)	97 (82.2)	0.866
Diabetes mellitus	41 (34.7)	26 (22.0)	**0.031**
Hypercholesterolemia	64 (54.2)	64 (54.2)	1.000
Smoking	36 (30.5)	37 (31.4)	0.923
Atrial fibrillation	27 (22.9)	30 (25.4)	0.649
Coronary artery disease	17 (14.4)	27 (22.9)	0.095
Previous myocardial infarction	9 (7.6)	10 (8.5)	0.811
Peripheral artery disease	8 (6.8)	9 (7.6)	0.802
Previous stroke	22 (18.6)	20 (16.9)	0.734
Antiplatelet or anticoagulant use	68 (57.6)	68 (57.6)	1.000
Statin use	56 (47.5)	59 (50.0)	0.192
Anticonvulsant therapy	2 (1.7)	1 (0.8)	0.999
Clinical characteristics on admission			
Systolic blood pressure, mmHg, mean (standard error)/median (IQR)	145 (135–170)	155 (145–175)	**0.024**
Diastolic blood pressure, mmHg	75 (65–85)	80 (70–90)	0.066
Heart rate, bpm	78 (67–85)	75 (70–83)	0.22
Body temperature, °C	36.4 (36.1–36.8)	36.4 (36.3–36.8)	0.82
Laboratory characteristics on admission			
Leukocyte count, G/l	7.9 (6.4–9.7)	7.2 (6.2–8.3)	**0.04**
Serum Sodium, mmol/l	137 (134–140)	138 (135–139)	0.68
C-reactive protein, mg/l	5.0 (2.0-22.4)	2.1 (1.1–6.7)	**< 0.001**
Creatinin, µmol/l	87 (72–107)	81 (70–102)	0.40
Low-density lipoprotein (LDL), mmol/l	3.2 (2.2–3.8)	3.3 (2.7-4.0)	0.47
High-density lipoprotein (HDL), mmol/l	1.3 (1.1–1.5)	1.2 (1.1–1.5)	0.63
Serum glucose, mmol/l	6.3 (5.6–7.7)	6.1 (5.4–7.2)	0.18
Hemoglobin A1c, %	5.9 (5.4–7.2)	5.6 (5.2-6.0)	**0.04**

Bold value indicates $p < 0.05$

medial temporal lobe atrophy scores were independently associated with FIAS compared to TIA (OR [95% CI] for juxtacortical small lesions score 2.82 [2.07–3.84], and for medial temporal lobe atrophy score 1.31 [1.01–1.70]). If juxtacortical small lesions and medial temporal lobe atrophy were included as categorial variables (grade 0 vs. grade 1–3), the presence of juxtacortical small lesions and medial temporal lobe atrophy was a strong predictor of FIAS (OR [95% CI] for juxtacortical small lesions 12.8 [6.7–24.3] and for medial temporal lobe atrophy 3.1 [1.3–7.1]).

EEG recordings were available in 108 FIAS patients (91.5%) and in 50 TIA patients (42.3%). EEG recordings were rated as pathological in 78 FIAS patients (66.1%) and in 16 TIA patients (32.0%, $p < 0.001$). Epileptiform discharges were observed in 17 FIAS patients (15.7%) and in none of the TIA patients ($p = 0.004$). Regional slow activity and generalized slow activity were significantly more common in FIAS patients compared to TIA patients (regional: 53.7% vs. 18.0%, $p < 0.001$; generalized: 41.7% vs. 14.0%, $p = 0.001$).

Table 2 MRI characteristics of patients with FIAS and TIA

	FIAS $n=118$	TIA $n=118$	p value
Fazekas scale			
Periventricular, n (%)			
0	2 (1.7)	9 (7.6)	
1	32 (27.1)	68 (57.6)	
2	39 (33.1)	27 (22.9)	
3	45 (38.1)	14 (11.9)	**<0.001**
Deep			
0	6 (5.1)	26 (22.0)	
1	31 (26.2)	57 (48.4)	
2	37 (31.4)	22 (18.6)	
3	44 (37.3)	13 (11.0)	**<0.001**
Modified Fazekas scale			
0	4 (3.4)	9 (7.6)	
1	34 (28.8)	68 (57.6)	
2	34 (28.8)	27 (22.9)	
3	46 (39.0)	14 (11.9)	**<0.001**
Wahlund scale			
Frontal lesions			
0	5 (4.2)	20 (16.9)	
1	30 (25.4)	58 (49.2)	
2	44 (37.3)	26 (22.0)	
3	39 (33.1)	14 (11.9)	**<0.001**
Parietooccipital lesions			
0	10 (8.5)	16 (13.6)	
1	18 (15.3)	45 (38.1)	
2	49 (41.5)	45 (38.1)	
3	41 (34.7)	12 (10.2)	**<0.001**
Temporal lesions			
0	15 (12.7)	48 (40.7)	
1	41 (34.7)	30 (25.4)	
2	52 (44.1)	37 (31.4)	
3	10 (8.5)	3 (2.5)	**<0.001**
Basal ganglia lesions			
0	38 (32.2)	49 (41.5)	
1	34 (28.8)	26 (22.0)	
2	42 (35.6)	39 (33.1)	
3	4 (3.4)	4 (3.4)	0.324
Infratentorial lesions			
0	59 (25.0)	67 (56.8)	
1	29 (12.3)	27 (22.9)	
2	26 (22.0)	20 (16.9)	
3	4 (3.4)	4 (3.4)	0.308
Juxtacortical small lesions			
Present	95 (80.5)	26 (22.0)	**<0.001**
Juxtacortical small lesions grade			
0	23 (19.5)	92 (78.0)	
1	28 (23.7)	9 (7.6)	
2	32 (27.1)	10 (8.5)	
3	35 (29.7)	7 (5.9)	**<0.001**
Mesial temporal atrophy scale			
0	12 (10.2)	41 (34.7)	
1	36 (30.5)	38 (32.2)	
2	31 (26.3)	19 (16.1)	
3	22 (18.6)	14 (11.9)	
4	17 (14.4)	6 (5.1)	**<0.001**

Bold value indicates $p < 0.05$

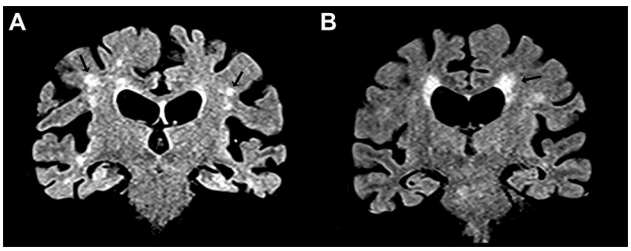

Fig. 1 Representative MRI scans (coronal FLAIR sections) of a FIAS (**a**) and a TIA patient (**b**). **a** Multiple juxtacortical small lesions (arrows), mild periventricular WMH, and more pronounced brain atrophy. **b** Periventricular WMH extending into deep white matter (arrow), no juxtacortical small lesion, and less pronounced brain atrophy

Discussion

In this retrospective study of a population of elderly patients at a high cardiovascular risk, patients with a first FIAS were observed to have more extensive SVCD than age- und sex-matched control patients with TIA. A previous study reported a higher prevalence of SVCD in patients with late-onset epilepsy compared to matched headache patients [4]. A novelty aspect of the current study was to use a study population of elderly patients at a high cardiovascular risk and thus a higher risk of SVCD. Thus, SVCD manifestations specific for epileptic seizures could be identified.

In this study, we observed that hyperintensities in white matter of cortical lobes were more common in FIAS patients than in TIA patients. Multivariate regression analysis identified juxtacortical small lesions as independent predictor of FIAS compared to TIA. Juxtacortical glioses have previously been described in a cohort of general neurologic patients and likely constitute a manifestation of SVCD [6]. Juxtacortical small lesions may explain seizures in SVCD patients.

Epileptic seizures are caused by abnormal excessive and synchronous neuronal activity of cortical neurons. Death of cortical neurons and diffuse gliotic scares are observed

after cortical microinfarcts in SVCD patients [13]. Cortical microinfarcts have recently been described in detail in histopathological and high-field MRI imaging studies [5, 9]. In the current study, cortical microinfarcts could not be assessed as these usually cannot be visualized using 1.5 T MRI [9]. Juxtacortical small lesions might serve as a surrogate marker for cortical microinfarcts, as juxtacortical white matter is supplied blood via the same penetrating arterioles as the cortex [14, 15] Affection of these arterioles in SVCD may, therefore, lead to both cortical microinfarcts and juxtacortical small lesions. While the cortex is supplied by single source arterioles, juxtacortical white matter is additionally supplied by a second source arteriole. Therefore, it can be assumed that if subcortical damage becomes visible, cortical damage is already present and more extensive than expected albeit not visible on 1.5 T MRI. This assumption is in line with the presumed high rate of several thousand cortical microinfarcts in patients with small vessel disease [16, 17]. Thus, juxtacortical small lesions may provide a surrogate marker for cortical microinfarcts that can be assessed on clinical routine 1.5–3.0 T MRI scans. This hypothesis needs to be verified in histopathological and high-resolution MRI studies.

Different mechanisms may explain seizures after cortical microinfarcts in addition to acute symptomatic seizure [18]. Cortical spreading depolarization has been reported in cortical microinfarcts but remains poorly understood [19]. Furthermore, diaschisis after neuronal death impairs cortical and subcortical circuits and integration of excitatory and inhibitory tones beyond the lesion core [20, 21]. Increased inhibitory tones after cortical microinfarcts may also explain the high rate of negative sensorimotor symptoms in FIAS patients.

Medial temporal lobe atrophy was the other independent predictor of FIAS in the multivariate analysis. Medial temporal lobe atrophy is a frequent observation in advanced SVCD [3, 22]. However, it has to be noted that SVCD and degenerative dementia like Alzheimer's disease may coexist. Patients with Alzheimer's disease may develop epileptic seizures, usually at later stages of the disease [23]. As patients with moderate to severe cognitive impairment were excluded from this study, advanced Alzheimer's disease is unlikely to account for the observed seizures in our cohort. As the odds ratio for juxtacortical small lesions was considerably higher than for medial temporal lobe atrophy (12.8 vs. 3.1), juxtacortical small lesions appear to be the key predictor of FIAS in this cohort.

There were slight differences in baseline characteristics between the two groups: diabetes mellitus was more common in FIAS patients, which could be a potential cofactor for predominant affection of cortical/juxtacortical arterioles in these patients. Systemic inflammatory response was also more common in FIAS patients, which is in line with previous studies [24].

In this study, FIAS and TIA were diagnosed clinically using established criteria [7, 8]. In specific cases, the clinical differential diagnosis between epileptic seizures and TIA may be difficult. TIA may mimic epileptic seizures, e.g., by presenting with positive motor symptoms such as myoclonus or by impaired awareness [25, 26]. On the other hand, epileptic seizures may mimic TIA, e.g., in focal atonic seizures or postictal paresis [27, 28]. To account for this difficulty in this study, epileptic seizures were distinguished from TIA by impaired awareness and either positive or negative sensorimotor symptoms (FIAS), and TIA was defined by strictly negative sensorimotor symptoms without impaired awareness. As additional ways to distinguish between FIAS and TIA, third party medical history and EEG recordings were used. Here, epileptiform discharges were observed only in FIAS patients and slow activity was more common in FIAS patients, both supporting the clinical diagnosis. Limitations of this study include the known biases inherent to retrospective design and that no high-field MRI imaging was performed.

Conclusions

In a population of elderly patients at a high cardiovascular risk, patients with a first FIAS were shown to have more extensive SVCD than patients with TIA. SVCD in FIAS patients predominantly affects supratentorial white matter. A particular manifestation of SVCD in FIAS patients is juxtacortical small lesions. This may provide a structural link between SVCD and epilepsy, which should be addressed in further studies. According to these results, juxtacortical small lesions in SVCD should be considered a structural cause for epilepsy and promote anticonvulsive therapy after a first seizure.

Author contributions SS analysis and interpretation of data and writing the manuscript. SB acquisition and analysis of data. ACL design of the study and revising the manuscript. JK design of the study and revising the manuscript. HN analysis and interpretation of data, design of the study, and revising the manuscript.

Funding None.

Compliance with ethical standards

Conflicts of interest The authors have no conflicts to declare.

Ethical approval The study protocol was approved by the local Ethics Committee of the University of Ulm, Germany.

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