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ORIGINAL COMMUNICATION

Misdiagnoses and delay of diagnoses in Moyamoya angiopathy—a large Caucasian case series

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Abstract

Background The lacking awareness of healthcare providers bears the risk of delayed or false diagnoses in rare diseases. No systematic data about misdiagnoses of Moyamoya angiopathy (MMA) are available.

Objective To evaluate the rate and pattern of missed diagnoses in MMA.

Methods Retrospective analysis of a consecutive case series from a single German referral center. Rates of missed or delayed diagnoses in Caucasian MMA patients were calculated based on discharge letters from other hospitals and systematic chart review.

Results Out of 192 Caucasian patients eventually diagnosed with MMA at our center, an initial misdiagnosis was identified in 119 patients (62%). The time between onset and diagnosis was 1 year in 24 patients, 2 years in 23 patients, 3 years in 10 patients, and > 3 years in 49 patients (mean 5.28, median 3, standard deviation 5.11, and range 4–26 years). The most common misdiagnoses were cerebral vasculitis (31%), etiologically ill-defined stroke diagnoses (30.2%), and MS (3.6%).

Conclusions This is the first systematic report which shows that patients with MMA are at high risk to be falsely diagnosed and treated. Depiction of typical vascular abnormalities in angiopathy is essential. Normal CSF cell counts, negative oligoclonal bands, and lack of infratentorial lesions as well as gadolinium-positive T1 lesions on MRI may be red flags differentiating this vasculopathy from vasculitis and MS.

Keywords Moyamoya · Misdiagnosis · Vasculitis · Multiple sclerosis

Introduction

Moyamoya angiopathy (MMA) is a rare non-inflammatory arteriopathy with stenosis or occlusion of intracranial part of internal carotid artery as well proximal parts of anterior and middle cerebral artery [1]. MMA is more common in Asia, and epidemiological data outside Asia are not clear [1–3]. Young patients present with hemodynamic or embolic transient or manifest ischemic events, with cerebral bleedings and a wide range of other cerebral symptoms including cognitive dysfunction [4, 5].

The etiology of MMA is still unknown [6, 7]. While there is a common association with autoimmune thyroid disorders and a link to HLA haplotypes, evidence for an immune mediated attack on vessels underlying the disease is not strong and immunosuppressive therapy is not effective. The current double-hit hypothesis [7], nonetheless, considers a role of immunologic triggers in the context of genetic predisposition [8]. Case reports have illustrated that MMA may mimic very common diseases like multiple sclerosis (MS) [9–11], but also other rare conditions including primary central nervous system vasculitis (PCNSV) [12] and leptomeningeal metastases [13, 14]. In MMA, it is crucial to make a correct and early diagnosis especially in the light

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of possible negative treatment consequences [15]. Patients with MMA are at a high risk of not being recognized early, before debilitating complications have set in, and of being misdiagnosed and wrongly treated. Surgical bypass interventions can minimize the high risk for recurrent ischemic and hemorrhagic complications [16, 17] (recently showed also in Caucasians [18, 19]), and antiplatelet therapy can reduce embolic strokes [20]. Misdiagnosis of MMA as a PCNSV [12, 21] or MS can result in inappropriate treatments carrying the potential risk to significantly harm the patient. However, systematic studies about the rate of misdiagnoses in MMA are lacking, particularly in regions outside Asia. Real-world evidence describing the frequency of misdiagnoses in MMA is warranted.

Materials and methods

Drawing on data from longstanding adult consecutive cohorts [3, 12, 22–24], we conducted a monocentric retrospective chart review study at the Department of Neurology of the Alfried Krupp Hospital in the metropolitan Rhine-Ruhr area in western Germany from 2010 to 2018. The chart review was performed by an ICD-10 search for ICD-10 I67.5. Included were all Caucasian patients meeting all diagnostic criteria of the Research Committee of the Japanese Ministry of Health and Welfare for Moyamoya disease and Moyamoya syndrome (umbrella term: MMA) [6, 25]. In addition, patients with unilateral arteriopathy were included if detailed assessment (see below) indicated a unilateral variant of Moyamoya angiopathy. All diagnoses were based on specialized assessments by the endauthor (MK) taking into account medical history, clinical examination, MRI, conventional angiography, serum and CSF laboratory studies and exclusion of differential diagnoses [26]. Patients with non-Caucasian ethnical background were excluded from study participation. Demographic data, age at disease onset, age at diagnosis, records cardiovascular risk factors and inflammatory markers were analyzed. Discharge letters from outside hospitals were reviewed for the previous diagnoses. Misdiagnoses were classified according to clinical, neuroradiological and laboratory data into the categories "stroke-like", "unspecific" or "others", as illustrated in Fig. 1.

The time between onset of first symptoms and correct diagnosis was assessed by retrospective chart review. Time intervals until establishment of the correct diagnosis were summarized in complete years (< 1 years, 1–2 years, 2–3 years, and so on). Statistical comparisons were made using one-way analysis of variance for multiple comparisons with Bonferroni post-hoc test. Statistical analysis and graphs were completed with Prism 6 (Graph Pad, La Holla, CA).

All relevant data are provided in this manuscript. The study was approved by the ethics committee of the University of Duisburg-Essen (registration number 13-5496-BO). Due to retrospective character of the study, and in line with the approval, no patient´s consent was necessary. There is no study registration number.

Results

Demographic data

During 2010 to 2018, 192 patients were diagnosed with MMA (ICD-10 I67.5) in our referral center for rare stroke entities and met the above-mentioned inclusion/exclusion criteria. Of these, 144 (75%) were female and 48 (25%) were male. The patients were diagnosed with bilateral Moyamoya disease ($n = 140$, 72.9%), unilateral variant of Moyamoya disease ($n = 47$, 24.5%), bilateral Moyamoya syndrome ($n = 3$, 1.6%), and unilateral variant of Moyamoya syndrome ($n = 2$, 1%). The mean age of symptom onset was 32.7 years (range 1–64; the age of disease onset was unknown in 2 patients). Mean age at diagnosis was 35.1 years (range 3–67; unknown in 3 patients). Furthermore, 25 (13%) patients were children (age < 18) at disease onset. Of these, 19 (76%) received at least one misdiagnosis. An overview of the demographic data is provided in Table 1.

Delay of diagnosis

Since this study was performed retrospectively, it was only possible to determine the latency between symptom onset and correct diagnosis based on age at first symptoms and age at correct diagnosis in 187 patients: The diagnosis was delayed 1 year or longer in 106 patients (56.7% of 187 patients). The time between onset and diagnosis was 1 year in 24 patients (22.6%), 2 years in 23 patients (21.7%), 3 years in 10 patients (9.4%), and > 3 years in 49 patients (46.2%) (mean 5.28, median 3, standard deviation 5.11, range 4–26 years). Delay of correct diagnosis did not differ between stroke-like, vasculitis, MS, or unspecific misdiagnoses (one-way ANOVA, multiple comparisons, Bonferroni correction; Fig. 2).

Misdiagnoses

119 patients (62.0%) received at least one misdiagnosis before the correct diagnosis was made (total of 126 misdiagnoses; missing data in 1 patient): 45 patients were misdiagnosed with an inflammatory, 36 patients with a stroke-like, and 45 patients with another disorder. An unspecific misdiagnosis was made in 28 cases (62.2% of patients misdiagnosed with another disorder, compare Fig. 1). An instant correct diagnosis was made in 73 patients (38%). An overview of the recruitment is provided in Fig. 1 and of the

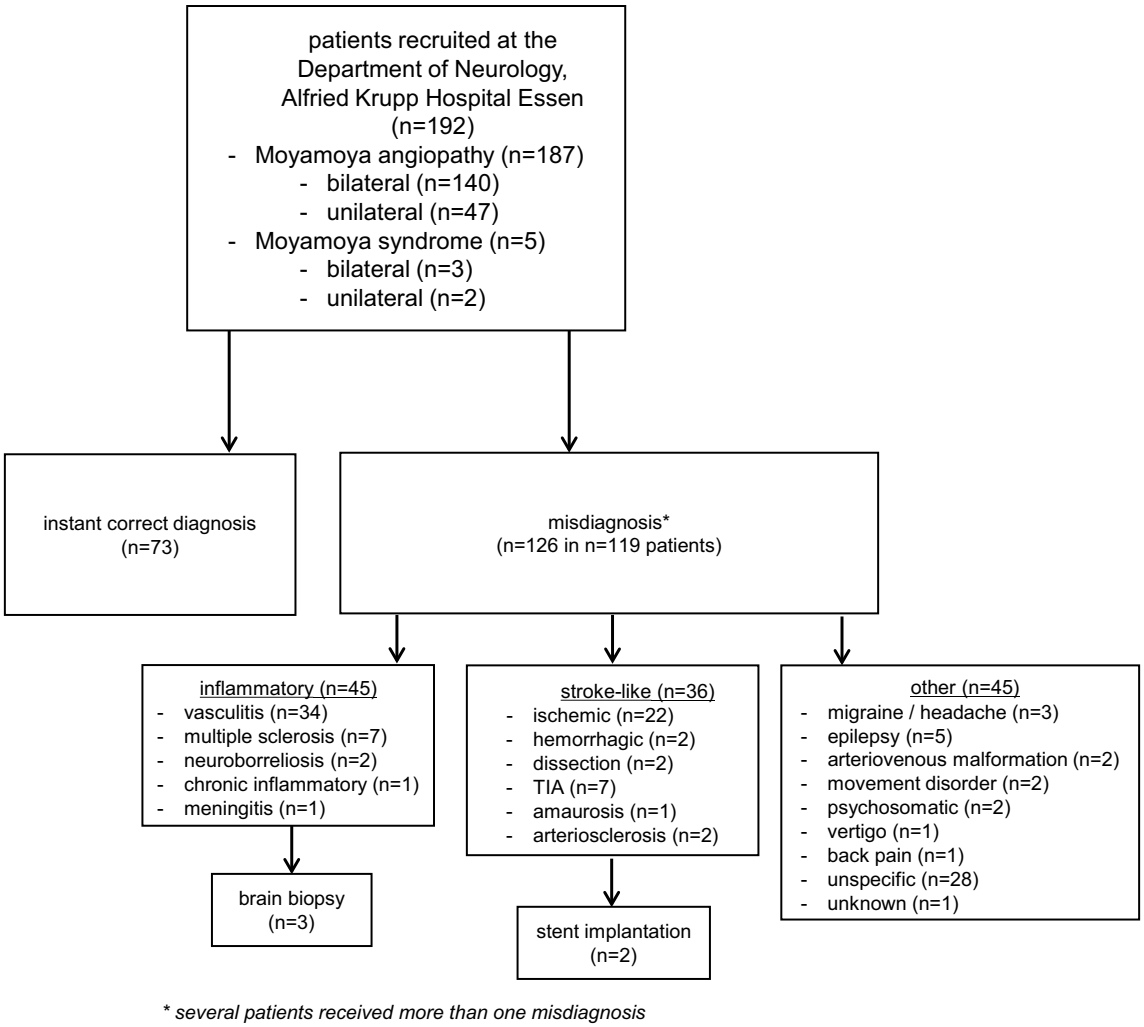

Fig. 1 Recruitment. Flowchart of the subject recruitment at the Department of Neurology, Alfried Krupp Hospital Essen. *TIA* transient ischemic attack

Table 1 Overview of the demographic data of our Moyamoya angiopathy patient cohort

Total ($n=192$)	Correct diagnosis ($n=73$)	Misdiagnosis ($n=119$)
Male	17 (23%)	31 (26%)
Female	56 (77%)	88 (74%)
Unilateral	20 (27%)	28 (24%)
Bilateral	53 (73%)	91 (76%)
Age of onset	33.5 years	31.9 years
Age of diagnosis	33.5 years	36.6 years

patients' characteristics in Table 2. CSF oligoclonal bands were negative in all patients but one, who was misdiagnosed with MS.

Misdiagnosis of MMA had an effect on diagnostic work-up and therapy. Among the patients misdiagnosed

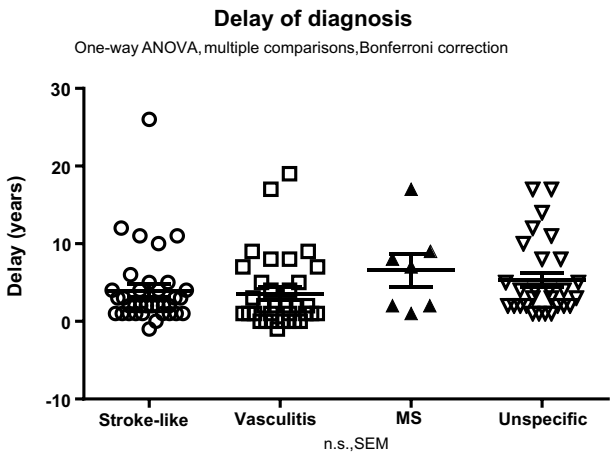

Fig. 2 Variance analysis of the delay of diagnosis. *MS* multiple sclerosis, *n.s.* not significant, *SEM* standard error of the mean

Table 2 Overview of patients' characteristics

Misdiagnosis	Mean age at correct diagnosis	Delay of diagnosis	CVRF positive			Inflammatory markers positive		
	in years	in years	aHTN	Smoking	Adiposity	OCB	ANA	ANCA
Total ($n=119$, m.d. 1)	36.62 m.d. 1	4.64 md. 2	59 (50.9%) m.d. 2	49 (43.4%) m.d. 5	30 (26.1%) m.d. 3	4 (4.5%) m.d. 29	9 (10.9%) m.d. 36	1 (1.2%) m.d. 36
Stroke-like ($n=36$)	38.31 m.d. 1	3.94 m.d. 1	24 (68.6%) m.d. 1	18 (51.4%) m.d. 1	13 (37.1%) m.d. 1	0 m.d. 11	1 (4.2%) m.d. 12	0 m.d. 12
Vasculitis ($n=34$)	36.97 md. 0	3.59 m.d. 0	16 (47.1%) m.d. 0	12 (36.4%) m.d. 1	12 (36.4%) m.d. 1	2 (5.9%) m.d. 0	4 (11.8%) m.d. 0	1 (2.9%) m.d. 0
Multiple sclerosis ($n=7$)	33.71 m.d. 0	6.57 m.d. 0	4 (57.1%) m.d. 0	3 (50%) m.d. 1	2 (28.6%) m.d. 0	1 (14.3%) m.d. 0	0 m.d. 0	0 m.d. 0
Inflammatory, other ($n=4$)	36 m.d. 0	6.75 m.d. 0	3 (75%) m.d. 0	2 (50%) m.d. 0	3 (75%) m.d. 0	0 m.d. 1	0 m.d. 2	0 m.d. 2
Unspecific ($n=28$)	34.29 m.d. 0	5.36 m.d. 0	12 (44.4%) m.d. 1	13 (48.1%) m.d. 1	3 (10.7%) m.d. 0	2 (10%) m.d. 8	4 (16.7%) m.d. 4	0 m.d. 8
Epilepsy ($n=5$)	36.8 m.d. 0	7.8 m.d. 0	1 (20%) m.d. 0	1 (20%) m.d. 0	2 (40%) m.d. 0	0 m.d. 2	0 m.d. 4	0 m.d. 4
Headache ($n=3$)	30.67 m.d. 0	10 m.d. 1	2 (66.7%) m.d. 0	1 (33.3%) m.d. 0	0 m.d. 0	0 m.d. 1	0 m.d. 2	0 m.d. 2
Other ($n=9$)	40.88 m.d. 1	6.5 m.d. 1	4 (44.4%) m.d. 0	1 (12.5%) m.d. 1	0 m.d. 1	0 m.d. 4	0 m.d. 4	0 m.d. 4
Correct diagnosis ($n=73$)	33.54 m.d. 1	n/a	36 (49.3%) m.d. 0	24 (34.3%) m.d. 3	22 (30.6%) m.d. 1	2 (3.7%) m.d. 19	6 (11.1%) m.d. 19	0 m.d. 19

CVRF cardiovascular risk factors, *aHTN* arterial hypertension, *OCB* oligoclonal bands, *ANA* antinuclear antibodies, *ANCA* anti-neutrophil cytoplasmic antibodies, *n/a* not applicable, *m.d.* missing data

for vasculitis, three underwent brain biopsy in the diagnostic process, six received steroids and two received cyclophosphamide.

Discussion

The major new findings of our study are the very high rate of misdiagnoses and the long delay of correct diagnoses in MMA. This is the first systematic report which shows that patients with MMA are at high risk to be falsely diagnosed and treated.

Inflammatory disorders were the most common misdiagnoses in our MMA cohort. It is interesting that MMA was misdiagnosed not only as frequent diagnoses like MS, but also as other rare diagnoses like CNS vasculitis. It is noteworthy that misinterpreting the ischemic MMA lesions as indicative of MS [27] or the stenoses as vasculitis may be harmful for patients regarding the diagnostic (brain biopsy) or therapeutic (steroid/cyclophosphamide treatment in vasculitis) approach [12, 21, 28]. Treatment because of a misdiagnosis as vasculitis not only bears the risks of steroid side effects like Cushing syndrome or diabetes but also the risk for precipitating disabling strokes or hemorrhages resulting from MMA pathology (see Fig. 3) [12]. In our cohort, patients misdiagnosed as MS were treated with harmless but expensive injectable therapies (glatiramer acetate and interferon beta) for years. However, nowadays, misdiagnosis as MS could be more dangerous, since the therapeutic approach in MS considered nonresponsive to platform drugs includes aggressive treatments with potentially serious adverse effects [29–31]. In our cohort, CSF markers such as oligoclonal bands were normal in all but one patient misdiagnosed as MS. Since the 2017 revision of the McDonald diagnostic criteria for MS, oligoclonal bands now have a more important role than before [32]. Therefore, the absence of oligoclonal bands should be considered a red flag concerning the diagnosis of MS and should lead to diagnostic re-consideration. Moreover, Kelly et al. showed that atypical symptoms as headaches—which are often in MMA [23]—as well as atypical MRI features are red flags for non-demyelinating diseases [33] (Fig. 4).

Distribution of lesions on brain imaging contributes to differential diagnosis between MMA and CNS inflammatory disorders [33]. None of the seven patients misdiagnosed as MS in our series had lesions in the corpus callosum. In contrast to MS, MMA does not cause infratentorial and spinal cord lesions, because almost exclusively, the territories of the anterior and middle cerebral arteries are affected. In addition, gadolinium-enhancing T1 lesions are very infrequent in MMA. Ultimately, assessment of young patients with recurrent neurological symptoms

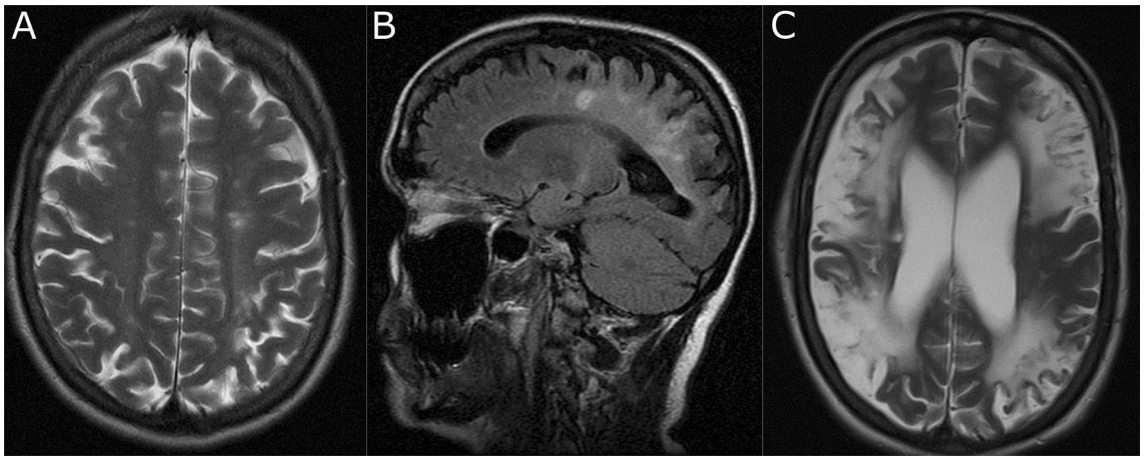

Fig. 3 MRI of a 30 year-old female patient in 2008 **a, b** misdiagnosed as MS despite negative oligoclonal banding in CSF and treated with beta interferons for years. **c** The MRI after recurrent strokes in 2014

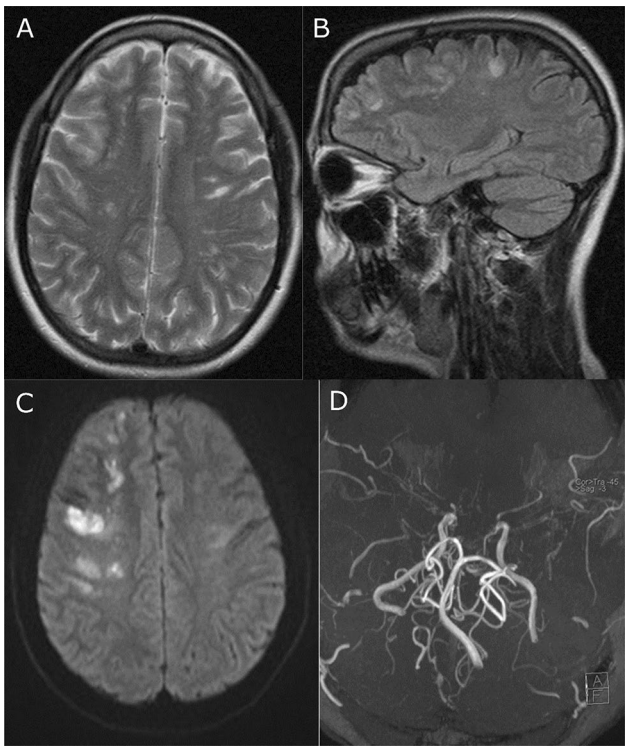

Fig. 4 MRI of a female patient begin of 20 misdiagnosed as MS in 2012 **a, b** despite negative oligoclonal banding in CSF and treated with copaxone for years. **c** Diffusion weighted images and **d** MR angiography when diagnosed as Moyamoya angiopathy in 2017

should include the vascular status and consider MMA in the differential diagnosis. The high rate of misdiagnosis of 34 patients with non-inflammatory MMA as PCNSV suggests that health care professionals are more aware of this very rare vasculitic entity than of non-inflammatory MMA. Awareness for MMA is crucial, and appropriate diagnostic steps [28] including conventional angiography should be taken. With regard to misdiagnoses of stroke-like episodes, the lack of extracranial arteriosclerosis, traditional cardiovascular risk factors, and a younger age should prompt diagnostic re-consideration. In conclusion, diagnosis of frequent neurological diseases like multiple sclerosis should be built not only on positive diagnostic criteria but also on exclusion of differential diagnosis [34], most often by judging if symptoms [33], medical history and examination as well as CSF and MRI are typical [33, 35], and not by broad differential diagnostic laboratory approaches [36].

Our study has strengths and limitations. This is the first study systematically addressing this theme. The strength points of our study are that it builds on a large consecutive cohort of MMA patients at a single center with well-established diagnostic pathway for MMA and other rare cerebrovascular disorders. The main limitation is that data were extracted retrospectively from case files.

Conclusion

In conclusion, our study is the first to systematically address the high frequency of misdiagnosis and delayed diagnosis in a large cohort of European Caucasian patients with MMA.

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Compliance with ethical standards

Conflicts of interest Authors report no conflicting interests.

Ethical approval This study was approved by local ethical committee.

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