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ORIGINAL COMMUNICATION

Clinical presentation of Moyamoya angiopathy in Europeans: experiences from Germany with 200 patients

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Abstract

Introduction Moyamoya angiopathy (MMA) is a rare vasopathy, especially among European Caucasians. Data about demographics, clinical presentation, comorbid conditions, radiological findings as well as laboratory and cerebral spinal fluid (CSF) data are sparse.

Methods Patients with MMA treated in the Alfried Krupp Hospital, Essen, Germany, between 2010 and 2017 with focus on demographic, clinical, radiological and laboratory as well as CSF data were evaluated retrospectively. Patients with non-Caucasian family background were excluded from this study.

Results Altogether 200 European Caucasian patients with MMA were identified. There was a female predominance of 3.2:1. The mean age at first presentation was 32.9 years and the mean age of diagnosis was 36.0 years. Eleven of 194 index patients (5.7%) showed a familial presentation. In 11.6% posterior cerebral artery was additionally involved, in 4% additionally cerebral aneurysm and in 2.5% dysgenesis of corpus callosum was found. Most patients suffered from transient ischemic attacks (71.5%) and stroke (82%). Cerebral hemorrhage was found in 9.5%. Livedo racemosa was an associated symptom in 12.8% of patients and thyroid diseases were found in 23.8%.

Conclusions Compared with Asian data, cerebral hemorrhages are infrequent and female predominance is accentuated among European Caucasians. Some former unknown rare features like associated livedo racemosa, dysgenesis of corpus callosum and associated syncope have been discovered systematically for the first time in this huge European Caucasian cohort.

Keywords Moyamoya angiopathy · Europeans · Clinical presentation · Demographics · Moyamoya · Caucasians · Europe

Introduction

In Japan and Korea, Moyamoya angiopathy (MMA) is the most common cause of stroke in children and young adults. Consequently, the disease is well known in this region. By contrast, little is known about the disease in Caucasians, especially in Europeans.

MMA is an umbrella term for vasculopathies which are characterized by bilateral progressive stenosis and eventually occlusion of the distal internal carotid arteries, anterior portions of the circle of Willis and in particular the anterior and middle cerebral arteries. Traditionally, MMA is separated in Moyamoya syndrome (MMS) and Moyamoya disease (MMD) [1]. Nowadays, unilateral variants are also included in the spectrum of MMA. MMD is the term exclusively used to describe idiopathic forms of the disease, whereas the term MMS is used for angiographic vasculopathies with Moyamoya phenomenon and associated conditions, such as status post-radiation therapy, Down syndrome, neurofibromatosis type 1 (Recklinghausen's disease) and status post-meningitis [1, 2].

Etiologically, the Asian founder variant was not found in European patients [3] and the spectrum of underlying mutations seems to be wider [4].

In Asia, typical presentations of the disease include cerebral hemorrhage and transient or manifest cerebral ischemia,

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but also headache, arterial hypertension and movement disorders. Clinical data on MMA among Caucasians, especially in Central Europe, are sparse [5–7]. Most scientific studies on Caucasian MMA are more focused on neurosurgical topics [8, 9] (Fig. 1).

Disease characteristics including clinical presentation, radiological features, comorbid features and CSF and laboratory data are widely neglected in non-Asian literature. To date, presentation of MMA in Central European Caucasians has been investigated only in three systematic studies [5, 10, 11]. In addition, two older neurosurgical case series are available describing clinical experiences with MMA patients in the European population [5, 12, 13].

The significance of US studies on the presentation of MMA in Caucasians is limited by the fact that most of these studies looked at mixed ethnicities. Another limitation to US studies is that some studies did not differentiate between MMD and MMS [14–16].

Thus, in the light of the available data, clinical presentation of MMA in Caucasians in Central Europe is not well described. In particular, it is unclear whether disease presentation among European Caucasians differs from that observed in Japan and Korea.

Materials and methods

Study design

Patients with MMA treated in the Alfried Krupp Hospital, Essen, Germany, between 2010 and 2017 were evaluated retrospectively. MMA was defined as stenosis and occlusion of the intracranial portion of internal carotid artery combined with typical Moyamoya collaterals (Moyamoya phenomenon). Patients in which intracranial arteriopathy was interpreted as arteriosclerotic were excluded from participation. Patients with a unilateral Moyamoya phenomenon and assumed idiopathic origin were included as unilateral variant of Moyamoya angiopathy (uMMA) Thus, the inclusion criteria were compatible with the guidelines of the Research Committee of the Ministry of Health and Welfare, Japan.

Patients with Asian or ethnic family background other than European Caucasian (for example, Romani family background) were excluded from the study. Despite the term "Caucasian" being controversial, only those patients who called themselves "Central European Caucasian", and lived in Germany, Austria or in the Netherlands were included.

Demographic, clinical and paraclinical analysis

The following patient characteristics were included in the analysis: ethnicity, gender, family history, retrospectively determined start of symptoms, age at the time of first diagnosis, progression, unilateral or bilateral MMD, MMS or

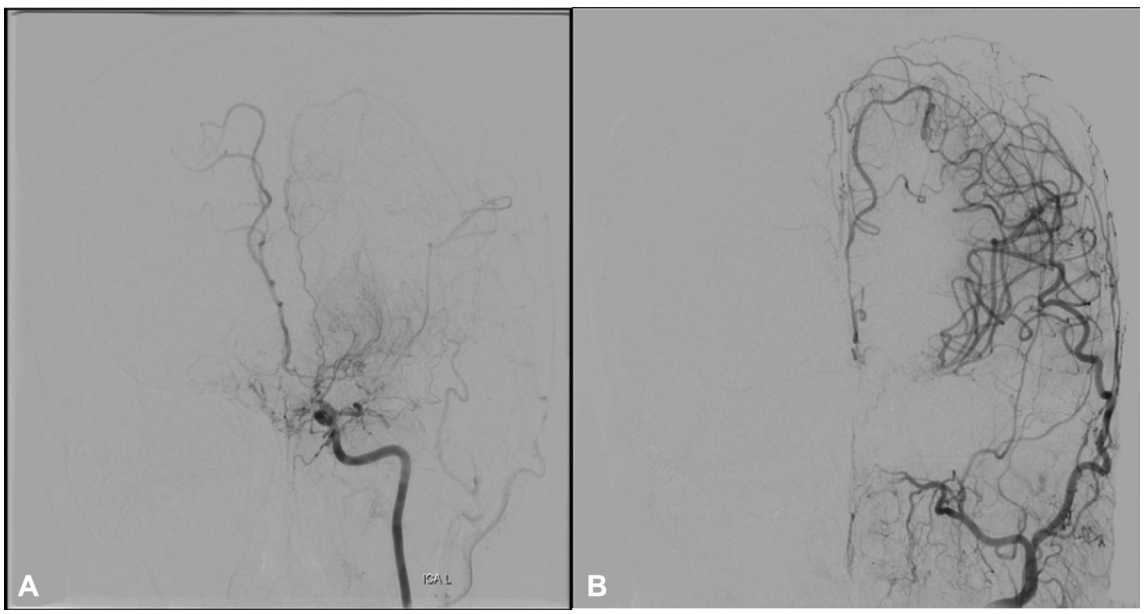

Fig. 1 Angiography of a patient before bypass surgery injected in internal carotid artery (**a**), and after bypass surgery injected in external carotid artery (**b**)

uMMA, clinical manifestation, involvement of the posterior cerebral artery (PCA), vertebrobasilar involvement, and extracranial arteriosclerosis.

In addition, comorbid diagnoses were considered. Laboratory data were analyzed.

The study was approved by the local ethics committees of the University of Duisburg-Essen and all patients gave written informed consent.

Results

Demographic data

Two-hundred Caucasian patients consecutively treated at the Alfried Krupp hospital, Essen, Germany were included in this study. Fifteen patients were excluded due to non-Caucasian family origin. Hundred and thirty-six of 200 patients (68%) were diagnosed as having MMD, 47 (23.5%) as uMMA and in 17 participants (8.5%) as MMS. There was a female predominance with 152 (76%) women and 48 men (24%) This predominance was evident in all subgroups (MMD: 74.3% versus 25.7%, uMMA: 78.7% versus 21.3% and for MMS 82.4% versus 17.6%).

The age at symptom onset was 32.9 years in the mean (median 32, range 1–74, standard deviation 14.04 years) for 197 patients with available data. The age of definitive diagnosis was 36 years (mean; median 35, range 3–71, standard deviation 14.09). Symptoms began in adulthood (> 18 years) in most of our patients (87.3% $n = 172$). Only 12.7% ($n = 25$) of 197 analyzed patients reported childhood symptom onset. Out of 194 index patients, 11 (5.7%) had a familiar clustering, especially a vertical pattern of inheritance was found with two or more affected family members. For detailed analysis, see Table 1.

Vascular and cerebral features

Twenty-three (11.6%) of 199 patients with available data showed involvement of at least one posterior cerebral artery in addition to typical Moyamoya phenomenon. Vertebrobasilar arteries were involved in 14 (7%) out of 199 analyzed patients. In 8 out of all 200 patients (4%), a cerebral aneurysm had been diagnosed. In five patients (2.5%), MRI depicted a dysgenesis of the corpus callosum (Fig. 2).

For detailed analysis see Table 1.

Clinical features

The great majority of patients experienced ischemic cerebral symptoms: 71.5% (143 out of 200) were diagnosed with at least one transient ischemic attack, 82% (164 out of 200) with at least one stroke in retrospective analysis. Nineteen of 200 patients with MMA (9.5%) suffered from cerebral or subarachnoid hemorrhage. Other often registered symptoms were headaches (50%, $n = 100$ out of 200) and seizures (30.5%, 61 out of 200). Infrequently found symptoms were syncope in 6.5% (13 out of 200), cognitive deficits in 3% (6 out of 200) and retinal ischemia in 1.5% (3 out of 200) of all patients. For detailed analysis see Table 1.

Associated clinical features

Fifty percent of all patients suffered from arterial hypertension. Livedo racemosa was found in 12.8% of all 188 analyzed patients. In 15.5% of all 200 patients, comorbid psychiatric diseases were registered. Additional data are listed in Table 2.

Associated laboratory features

Additional data and data about subgroups are listed in detail in Table 2.

Discussion

In 2008, we published our first study on systematical workup of European Caucasian MMD, based on a rather small cohort of 21 patients. Despite being the first study concerning neurological symptoms, two prior studies investigated neurosurgical treatment options and postoperative outcomes [13, 17]. In a cohort study from Berlin, Germany, 153 patients with bilateral and unilateral Moyamoya disease have been described [10, 11].

Our study elucidates the general clinical presentation of MMA in European Caucasians in the so far biggest cohort.

Demographic data

The mean age at the start of symptoms could be replicated in this larger cohort compared with the former studies (here: mean 32.9 years, Kraemer 2008: 34 years, Acker 2015: 34 years). Our study demonstrated a later age of onset compared with Asian studies. This verified the former clinical assumption of a later development of the angiopathy in Caucasians [18]. However, it is necessary to consider that our center is specialized in adult onset Moyamoya and that misdiagnosis is common in Europe.

The female predominance (here: 3.2:1) in our study was comparable with those of the Berlin group (2.9:1). Thus, the female predominance found and replicated in European Caucasians is higher than those in Asian populations.

In contrast to the patient population in this study [19], familial clustering was not found in the European prior cohorts. Here we report 5.7% of 194 index patients. As

Table 1 Demographic, neuroradiological and clinical features

	MMA	MMD	uMMA	MMS
All patients, *n* (%)	200	136 (68.0%)	47 (23.5%)	17 (8.5%)
Male, *n* (%)	48 (24.0%)	35 (25.7%)	10 (21.3%)	3 (17.6%)
Female, *n* (%)	152 (76.0%)	101 (74.3%)	37 (78.7%)	14 (82.4%)
Age of onset in years, *n* in mean (± SD)	32.9[a] (± 14.04)	33.0[b] (± 14.04)	33.6[c] (± 13.23)	26.6 (± 14.66)
Age of onset in years, median (range)	32 (1–71)	33 (3–64)	32 (15–71)	27 (1–48)
Age of diagnosis in years, mean (± SD)	36.0[a] (± 14.09)	36.3[b] (± 14.27)	35.0[c] (± 13.04)	32.4 (± 14.72)
Age of diagnosis in years, median (range)	35 (3–71)	38 (3–67)	33 (16–71)	32 (3–58)
Number of children at onset, *n* (%)	25[a] (12.7%)	17[b] (12.7%)	4[c] (8.7%)	4 (23.5%)
Number of adults at onset, *n* (%)	172[a] (87.3%)	117[b] (87.3%)	42[c] (91.3%)	13 (76.5%)
Familial cases, *n* (%)	11 out of 194 (5.7%)	8 out of 131 (6.1%)	2 out of 47 (4.3%)	1 out of 16 (6.3%)
Vascular and cerebral features				
P1 stenosis, *n* (%)	23[d] (11.6%)	22[e] (16.3%)	1 (2.1%)	0 (0.0%)
Vertebrobasilar impairment, *n* (%)	14[d] (7.0%)	10[e] (7.4%)	1 (2.1%)	3 (17.6%)
Extracranial impairment, *n* (%)	35[d] (17.6%)	28[e] (20.7%)	4 (8.5%)	3 (17.6%)
Intracranial aneurysms, *n* (%)	8 (4.0%)	6 (4.4%)	1 (2.1%)	1 (5.9%)
Corpus callosum dysgenesis, *n* (%)	5 (2.5%)	0 (0.0%)	1 (2.1%)	4 (23.5%)
Symptoms				
TIA/Limb shaking TIA, *n* (%)	143 (71.5%)	99 (72.8%)	34 (72.3%)	10 (58.8%)
Stroke, *n* (%)	164 (82%)	122 (89.7%)	27 (57.4%)	15 (88.2%)
Hemorrhage, *n* (%)	19 (9.5%)	13 (9.6%)	6 (12.8%)	1 (5.9%)
Headache, *n* (%)	100 (50%)	64 (47.1%)	30 (63.8%)	7 (41.2%)
Epilepsy, *n* (%)	61 (30.%)	49 (36.1%)	9 (19.1%)	3 (17.6%)
Syncope, *n* (%)	13 (6.5%)	9 (6.6%)	3 (6.4%)	1 (5.9%)
Cognitive deficits, *n* (%)	6 (3.0%)	2 (1.5%)	0 (0.0%)	4 (23.5%)
Retinal stroke, *n* (%)	3 (1.5%)	3 (2.2%)	0 (0%)	0 (0%)

Due to missing data, the cohort was smaller than indicated in line one

[a] $n = 197$

[b] $n = 134$

[c] $n = 46$

[d] $n = 199$

[e] $n = 135$

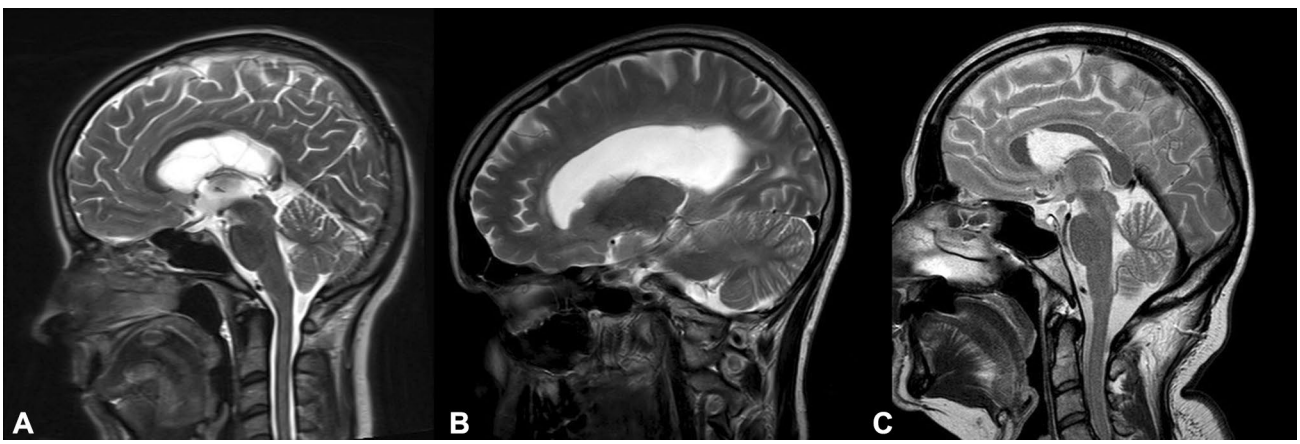

Fig. 2 MRI of the brain with abnormalities of corpus callosum in three different patients

Table 2 Associated clinical and laboratory features

	#	MMA	#	MMD	#	uMMA	#	MMS
Associated clinical features								
Cardiac illness in medical history, *n* (%)	200	12 (6.0%)	136	10 (7.3%)	47	1 (2.1%)	17	1 (5.9%)
Arterial hypertension, *n* (%)	199	100 (50.2%)	135	74 (54.4%)	47	20 (42.5%)	17	6 (35.3%)
Adiposity, *n* (%)	197	54 (27.4%)	133	33 (24.8%)	46	16 (34.8%)	17	5 (29.4%)
Smoking, *n* (%)	195	76 (39.0%)	132	59 (44.7%)	46	13 (28.3%)	17	4 (23.5%)
Diabetes mellitus, *n* (%)	198	21 (10.6%)	134	15 (11.2%)	47	4 (8.5%)	17	2 (11.8%)
Livedo racemosa, *n* (%)	188	24 (12.8%)	127	18 (14.2%)	45	6 (12.8%)	16	0 (0.0%)
Psychiatric comorbidity, *n* (%)	200	31 (15.5%)	24	24 (17.6%)	47	5 (10.6%)	17	2 (11.8%)
Associated laboratory features								
Lp (a) elevated, *n* (%)	110	24 (21.8%)	80	19 (23.8%)	24	4 (16.0%)	6	1 (16.0%)
Thyreoid abnormalities, *n* (%)	147	35 (23.8%)	94	20 (21.3%)	31	7 (22.6%)	12	8 (60.0%)
Hypercholesteremia, *n* (%)	200	29 (14.5%)	136	20 (14.7%)	47	8 (17.0%)	17	1 (5.9%)
Heterozygous factor V, *n* (%)	200	5 (2.5%)	136	5 (3.7%)	47	0 (0.0%)	17	0 (0.0%)
CSF abnormalities								
Oligoclonal banding, *n* (%)	148	6 (4.1%)	90	3 (3.0%)	42	1 (2.4%)	12	2 (16.0%)
Elevated cell count, *n* (%)	148	3 (2.0%)	90	1 (1.0%)	42	2 (4.8%)	12	0 (0.0%)
Elevated protein, *n* (%)	148	4 (2.7%)	90	2 (2.0%)	42	2 (4.8%)	12	0 (0.0%)
Antibodies								
ANA, *n* (%)	161	17 (10.6%)	109	11 (10.1%)	40	4 (10%)	12	2 (16.0%)
ENA, *n* (%)	161	2 (1.2%)	109	1 (0.9%)	40	1 (2.5%)	12	0 (0.0%)
Cardiolipin, *n* (%)	161	3 (1.9%)	109	1 (0.9%)	40	2 (5.0%)	12	0 (0.0%)

Represents the number of patients that were analyzed

recently discussed, heterogeneous genetic reasons seem to be more common in Caucasians as originally thought [4, 19].

Vascular and cerebral features

The percentage of uMMA in the whole cohort was high with 23.5% compared to the data from the Berlin group (17% in MMD and 11.5% in MMS), data from the US with 17.8% [20] and Asian data with 10.6%.

Prospective studies with Asian patients reported posterior cerebral artery involvement in up to 37.1% of the cases [21]. In this European patient cohort, a percentage share of up to 16.3% for the MMD subgroup was found. This was lower than described in the Berlin cohort with 32% [10]. The percentage of 4% of patients with cerebral aneurysms is comparable to the Berlin cohort with 3% [10, 22]. It has been recently demonstrated in Caucasians that microaneurysms can be reversible after bypass surgery [23]. If aneurysms larger than 6 mm persist after bypass surgery, treatment options should be discussed.

Interestingly, in this cohort of 200 European patients, 5 patients showed corpus callosum agenesis. Three of them had MMS with associated neurofibromatosis type 1 [24], but one patient had an idiopathic unilateral variant of MMA without signs of neurofibromatosis. This feature has been reported in MMA in two of these patients for the first time just recently [24]. Dysplastic corpus callosum in MMA has been reported once in a single patient with an ACTA 2 mutation [25]. However, reports about association of corpus callosum abnormalities in PHACE (Posterior fossa brain malformations, Hemangioma, Arterial lesions, Cardiac abnormalities, and Eye abnormalities) and microcephalic osteodysplastic primordial dwarfism (MODP) syndromes, which are associated diseases with MMA, point to a pathophysiological rather than a coincidental link [26].

Clinical features and associated clinical features

In line with data from the Berlin cohort [10, 11], an ischemic event was the presenting feature in the great majority of patients: 82% of patients suffered from strokes and 71.5% from transient ischemic attacks. Cerebral hemorrhages were found in 9.5% of all patients. This corresponds to the Berlin data with 8.5% in MMD and 8.2% in MMS, respectively.

Although syncope is an often neglected symptom in literature concerning MMA, they were found in 6.5% of our patients. Despite the high incidence of neurocardiogenic syncope in the normal population, intolerance to orthostatic maneuvers in MMA [27] argues for a special risk in MMA and the need for instructing patients to avoid triggers and to learn physical prophylaxis exercises.

Another remarkable insight from this study is the high incidence (50%) of arterial hypertension in our cohort. This is much higher than expected in the normal German population in that age (maximal 17% [28]). Pressure passive cerebral circulation can be assumed as the main mechanism as no patient had renal artery stenosis [29]. Careful but consequent treatment of arterial hypertension is important.

Another uncovered symptom earlier not realized to be widely associated with MMA is the involvement of the skin with livedo racemosa. Livedo racemosa has to be differentiated from livedo reticularis, as it is generalized and persists in warmth [30]. This skin symptom has rarely been described in MMA earlier [31–33]. This finding could reflect a global vasomotor dysfunction arguing that MMA represents a more generalized disease than former thought. Moreover, it is associated with a wide range of autoimmune diseases, which were all excluded in our cohort, but also with migraine-like headaches that have been described to be common in Caucasian MMA [7].

Associated laboratory, CSF and antibody features

In the current literature, thyroid disease is reported to be frequently associated with Asian MMA. Also, in Caucasians thyroid diseases associated with MMA have been described [11, 34]. The high percentage of 23.8% in our cohort confirms these former studies.

In conclusion, this detailed systematic study illuminates the demographic and clinical presentation of MMA in European Caucasians. It has strengths and limitations. Referring bias to our center specialized in adult onset MMA may have influenced the data concerning demographics. Moreover, comparison of frequency distributions with normal German population was not possible due to missing data about education and social status. Another limitation of this study is the retrospective design which could influence the observed frequencies, for example, an underestimation of cognitive symptoms (due to no systematic testing) could be hypothesized.

On the other hand, it builds on the largest consecutive cohort of European MMA patients ever published at a single center. Moreover, inclusion criteria were strict with established diagnostic workup including CSF and angiography to exclude differential diagnoses. In contrast to preselected neurosurgical studies from the US and Europe [10, 11, 20], this cohort is from a neurological center independent from bypass indication. Therefore, this cohort could be seen as representative for Caucasian MMA patients living in central Europe [5–7, 19]. This study allows characterizing European MMA in depth. In summary (1) cerebral hemorrhages are infrequent compared with Asian data (2) female predominance is accentuated in contrast to Asian epidemiology (3) some former unknown rare features like associated livedo racemosa, dysgenesis of corpus callosum and associated syncope have been discovered systematically for the first time in this huge cohort.

Together with the Berlin studies [10, 11], this study enlarges the number of reported Caucasian patients treated in Germany up to approximately 400 individuals.

Nevertheless, a European network registry is warranted to analyze if these two German-predominant cohorts are representative for all European Caucasian patients and if genetic differences within Europe affect disease presentation. In the future, diagnostic and treatment regimens concerning this rare disease should be built on real-world data from such huge European cohorts [35].

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Compliance with ethical standards

Conflicts of interest Markus Kraemer received research grants from Novartis and Merck Serono and travel/accommodation/meeting expenses or lecture honoraria from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Teva and Shire Germany. Jan Claudius Schwitalla has no conflict of interest. Frank Diesner has no conflict of interest. Hans-Peter Hartung received, with approval of the Rector of Heinrich-Heine-University and the CEO of University of Düsseldorf Hospital honoraria for consulting, serving on steering committees and speaking from Biogen, CSL Behring, Geneuro, Genzyme, LFB, Medimmune, Merck, Novartis, Octapharma, Opexa, Receptos/Celgene, Roche, Sanofi, and Teva. Orhan Aktas received, with approval of the Rector of Heinrich-Heine-University, grants from the German Research Foundation (DFG), the German Ministry for Education and Research (BMBF) as part of the German Competence Network Multiple Sclerosis (KKNMS; for NEMOS NationNMO-PAT FKZ 01GI1602B), the Eugène Devic European Network (EU-FP7), honoraria and travel/accommodation/meeting expenses from Almirall, Bayer, Biogen, Medimmune, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Teva. Peter Berlit has no conflict of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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