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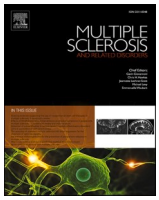

Longitudinal change of serum NfL as disease activity biomarker candidate in MOGAD: A descriptive cohort study

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ABSTRACT

Background: Myelin oligodendrocyte glycoprotein antibody (MOG-IgG)-associated disease (MOGAD) is an autoinflammatory disease of the central nervous system. MOGAD often follows a relapsing course that can lead to severe disability, but monophasic disease is possible as well. Currently, there is an unmet clinical need for disease activity biomarkers in MOGAD. Serum neurofilament light chain (sNfL) is a sensitive biomarker for neuroaxonal damage. However, data on longitudinal change of sNfL as disease activity biomarker for MOGAD are scarce.
Objective: To describe the longitudinal course of sNfL in adult patients with MOGAD in an active as well as a stable disease state in relation to clinical parameters and serum MOG-IgG titers.
Methods: We conducted a retrospective, exploratory, monocentric cohort study of adult patients with MOGAD. Cohort 1 consisted of five patients in whom NfL was tested as part of their routine clinical workup, all of which had active disease (maximum 6 months since last attack, median 3 months). Cohort 2 comprised 13 patients, which were tested for NfL in the context of a longitudinal study at predefined time intervals, mostly during remission (median 10 months since last attack). sNfL was measured using single molecule array (Simoa) technology at least at two time points (median 3) within a median observation time of 5 months in cohort 1, and at baseline and after a median duration of 12 months in cohort 2. MOG-IgG titers were measured by a fixed cell-based assay.
Results: Change in sNfL correlated positively with change in MOG-IgG titers (rho=0.59, $p = 0.027$). The variability of sNfL (difference between highest and lowest level) during the observation period was higher in patients who had an attack within six months before baseline (median 37 [interquartile range [IQR] 10–64] pg/ml vs. 2.3 [IQR 1–5] pg/ml, $p = 0.006$). sNfL increased in patients with an attack during the observation period. Patients with baseline sNfL measurement within two weeks after attack symptom onset displayed relatively low initial sNfL with an increase afterwards.
Conclusions: Longitudinal sNfL change correlates with MOG-IgG titer change and may be a promising biomarker candidate for disease activity in MOGAD. Increasing sNfL levels might be utilized to adjudicate suspected attacks. In acute attacks, sNfL increase may occur with a delay after symptom onset.

1. Introduction

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a demyelinating autoimmune disorder of the central nervous system that often follows a relapsing course (Banwell et al., 2023; Jarius et al., 2018, 2016a). However, a proportion of patients have

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monophasic disease (Satukijchai et al., 2022) or a decreasing relapse rate in the long-term disease course (Akaishi et al., 2022). This translates into considerable uncertainty regarding both when to initiate and when to terminate immunotherapy (Whittam et al., 2020b). Moreover, recognition of attacks in MOGAD is complicated by a variety of possible clinical manifestations. Furthermore, there may be a temporal delay between the appearance of clinical symptoms and MRI abnormalities (Cacciaguerra et al., 2024; Sechi et al., 2021). Therefore, biomarkers for disease activity are an unmet clinical need in MOGAD.

Quantitative body fluid biomarkers are generally well-suited for monitoring disease activity because they reflect dynamic processes and can be measured repeatedly. Promising body fluid biomarker candidates for MOGAD are serum myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG) titers and serum neurofilament light chain (sNfL) concentrations. During many attacks, MOG-IgG titers are higher than in remission (Gastaldi et al., 2022; Jarius et al., 2016b). Furthermore, high MOG-IgG titers during remission have been shown to be associated with an increased relapse risk (Gastaldi et al., 2022). sNfL is a sensitive biomarker for neuroaxonal damage (Khalil et al., 2018), and is elevated during attacks in MOGAD (Hyun et al., 2022). Recently, a correlation of serum MOG-IgG titers and sNfL has been reported in a series of eight children with relapsing MOGAD (Horellou et al., 2023). Because of the long half-life of sNfL (Azizi et al., 2021), longitudinal sNfL changes may provide relevant information in the context of a relapsing disease. However, the value of the longitudinal course of sNfL as a biomarker in MOGAD has not been established to date.

Here, we analyzed the longitudinal dynamics of sNfL concentrations in two cohorts of adult patients with MOGAD and assessed the association of longitudinal sNfL dynamics with MOG-IgG titers and clinical findings.

2. Patients and methods

2.1. Patients and study design

We investigated two non-overlapping cohorts of adult patients with a diagnosis of MOGAD according to the criteria proposed by Banwell et al. (Banwell et al., 2023) and by Jarius et al. (Jarius et al., 2018). All patients participated in observational studies (EA1/041/14 (Keller et al., 2015), EA1/362/20 (Sperber et al., 2022)) at the Department of Neurology, Charité – Universitätsmedizin Berlin, Germany, and the Experimental and Clinical Research Center, Berlin, Germany.

Cohort 1 consisted of five patients in whom at least two sNfL tests were conducted during clinical routine visits (minimum 2, median 3, maximum 6; total = 17, corresponding to 12 longitudinal sNfL episodes) at Charité - Universitätsmedizin Berlin, Germany, within a median observation period of 5 (range 4–12) months. All patients had "active" disease (≤6 months since last attack), of which one patient had subacute disease (≤90 days) and two patients had an attack (onset ≤21 days) at baseline. Demographic and clinical data were recorded at study visits or retrieved from medical records. Longitudinal MOG-IgG values were available for all patients. The first sNfL measurement per patient was designated baseline.

Cohort 2 comprised 13 patients of whom serum samples were obtained at baseline and after a median of 12 (interquartile range [IQR] 12–14 months) follow-up at study visits at the Experimental and Clinical Research Center, Berlin, Germany. They were previously reported in an investigation focusing on sGFAP and sNfL in neuromyelitis optica spectrum disorders (Schindler et al., 2021). Seven patients were in stable remission (>6 months since last attack) and six had "active" disease (≤6 months), of which none had subacute disease (≤90 days) and one had an attack at baseline. Clinical data were captured at baseline, 12 months, and (n = 11) 24 months follow-up. Longitudinal MOG-IgG were available from 9/13 patients.

2.2. sNfL measurement

In cohort 1, sNfL was measured during clinical routine visits by commercial laboratory (Simoa Nf-light kit®, SR-S immunoassay analyzer, Simoa®, Quanterix Corp, Boston, USA). In cohort 2, all sNfL concentrations were determined in parallel by single molecule array assay (Simoa) as previously described (Schindler et al., 2021). All serum samples were stored at −80 °C until testing.

Change in sNfL was calculated as the difference between the last and first available concentration. To account for short-term changes and assess the longitudinal variability, we additionally calculated the maximum sNfL difference (maximum – minimum recorded concentration). Moreover, we describe episodes of sNfL change (difference between each two subsequently measured concentrations). We dichotomized all episodes as sNfL increase/decrease and refrained from statistical analyses of sNfL episodes due to unequal intervals and unequal number of episodes per patient.

2.3. MOG-IgG testing

MOG-IgG titers were determined using a fixed cell-based assay (fCBA; Euroimmun, Lübeck, Germany), according to the manufacturer's protocol. MOG-IgG were considered positive at a titer >=1:10 and high positive >=1:100. Change in MOG-IgG titers was calculated as the difference between the denominators of the last and first titer. Because MOG-IgG was not assessed on the same day as baseline sNfL in patient_1_01 and patient_1_05, the closest test (+10 days and −28 days, respectively) was used as baseline. No patient underwent plasma exchange (PLEX) at baseline. During the observation period, in cohort 1 patient_1_01 underwent PLEX 17–26 days and immunoadsorption (IA) eight months after baseline. In cohort 2, patient_2_01 and patient_2_03 had IA four months and patient_2_05 had PLEX eight months after baseline.

2.4. Statistical analyses

Statistical analyses were conducted using R (Wickham H and E, 2019). Standardized mean differences (SMD) were calculated without assumption of equal variances using package "TOSTER" (Lakens, 2017) for continuous and "tableone" (Pollard et al., 2018) for categorical variables. Median and IQR are reported when $n > 5$, and maximum-minimum-range (range) when $n<=5$. Spearman's rank correlation coefficients (rho) were calculated. Group differences were assessed by Wilcoxon rank sum-test for continuous and by chi-squared test for categorical variables. Intra-individual association of sNfL and MOG-IgG was assessed by a linear mixed effects model (dependent variable: sNfL; fixed effects: MOG-IgG titer, age, disease duration, interval, cohort; random effect: individual; packages "lme4" (Bates et al., 2015), "lmerTest" (Kuznetsova et al., 2017)). Due to the explorative nature of this study, we refrained from correction for multiple testing, interpret p-values cautiously, and refer to effect sizes (rho, SMD). Commonly, SMD>=0.5 or rho>=0.3 are considered moderate and SMD>=0.8 or rho>=0.5 are considered large effects (Cohen, 1988).

3. Results

3.1. Baseline demographic and clinical characteristics

Demographic and clinical characteristics are summarized in Table 1. Median time since last attack was shorter in cohort 1 (3 [range 0–6] months;) than in cohort 2 (10 [IQR 5–26] months; SMD=0.77, $p = 0.03$). In cohort 1, three of five patients had an attack within 90 days to baseline, but only one patient in cohort 2 (SMD=0.82, $p = 0.35$). Median disease duration was shorter in cohort 1 (4 [range 0–182] months) than in cohort 2 (55 [IQR 24–135] months; SMD=0.40, $p = 0.08$). Most patients were on immunotherapy at baseline, with oral prednisolone being

Table 1
Baseline demographic and clinical characteristics.

		Cohort 1		Cohort 2	SMD
N		5		13	–
N, longitudinal MOG-IgG		5		9	–
Age, years	*Median (Range)*	46 (28 – 71)	*Median (IQR)*	48 (33 – 55)	0.24
Sex	*Female / Male (%Female)*	2 / 3 (40%)	*Female / Male (% Female)*	10 / 3 (77%)	0.81
Disease duration, months	*Median (Range)*	4 (0 – 182)	*Median (IQR)*	55 (24 – 135)	0.40
Months since last attack	*Median (Range)*	3 (0 – 6)	*Median (IQR)*	10 (5 – 26)	0.77
Number of previous attacks	*Median (Range)*	1 (1 – 3)	*Median (IQR)*	4 (2 – 5)	1.1
Immunotherapy	*Yes / No (%Yes) Drug (N)*	4 / 1 (80%) Oral prednisolone (3) Rituximab (2)	*Yes / No (%Yes), Drug (N)*	10 / 3 (77%) Azathioprine (1) Methotrexat (1) Oral prednisolone (3) Rituximab (7)	0.77
EDSS	*Median (Range)*	2 (1 – 3.5)	*Median (IQR)*	2.5 (2.0 – 3.5)	0.46
First MOG-IgG titer	*Clear / low positive (% clear positive)*	5 / 0 (100%)	*Clear / low positive (% clear positive)*	7 / 6 (54%)	1.3
	Median (Range) months after disease onset	1 (0 – 179)	*Median (IQR) months after disease onset*	50 (11 – 134)	0.39
MOG-IgG at baseline, titer	*Median (Range)*	1:32 (negative – 1:100)	*Median (IQR)*	Negative (negative – 1:32)	0.21
sNfL, pg/ml	*Median (Range)*	14.9 (8.3 – 85.5)	*Median (IQR)*	23.1 (14.8 – 43.8)	0.07

Baseline was defined as the time of first sNfL testing in both cohorts.
Immunotherapy: patients receiving more than one drug were counted for each (cohort 2: one patient with rituximab, methotrexate, and prednisolone; cohort 1: one patient with rituximab and prednisolone).
EDSS: In cohort 1, EDSS was available at baseline only for one patient (1_04); for three patients EDSS was available +/- 2 months from baseline, for 1 patient (1_01) EDSS was available only around 9 months after baseline. Excluding patient 1_01 median EDSS = 1.75 (range 1 – 3.5).
First MOG-IgG titer: The first available serum MOG-IgG titer, as assessed by a live or fixed cell-based assay.
MOG-IgG at baseline: In cohort 1, the MOG-IgG at the time point closest to first sNfL testing was used in 2 patients (1_01 and 1_05) where no titer was available at the same day as first sNfL.
Abbreviations: EDSS = extended disability status scale, IQR = interquartile range, MOG-IgG = serum anti-myelin oligodendrocyte glycoprotein immunoglobulin G, SMD = standardized mean difference, sNfL = serum neurofilament light chain.

the most frequently used drug in cohort 1 and rituximab in cohort 2 (Table 1).

3.2. Association of the longitudinal dynamics of sNfL and mog-igg

Analyzing cohort 1 and 2 together, baseline sNfL and MOG-IgG titers did not correlate on group level (rho=0.01, $p = 0.96$). However, higher sNfL was associated with higher MOG-IgG titers when investigating all available measurements in a mixed effects model (β=0.055, 95%-confidence interval 0.016–0.090, $p = 0.011$). Likewise, change in sNfL (last - first measurement) and change in MOG-IgG titer correlated positively (rho=0.59, $p = 0.027$) in both cohorts analyzed together. Next, we investigated both cohorts separately. In cohort 1, we refrained from statistical analyses due to small sample size. In cohort 2, change in sNfL correlated positively with change in MOG-IgG titer (rho=0.68, $p = 0.045$). Individual sNfL and MOG-IgG courses are depicted in Fig. 1 (cohort 1) and Fig. 2 (cohort 2).

A total of 25 sNfL episodes (difference between two subsequent measurements) were recorded. This included ten episodes of sNfL increase in nine patients. MOG-IgG titers increased in three and were stable in five of these ten episodes (not available: two). One sNfL episode with "stable" MOG-IgG (patient_1_01) comprised a titer increase (1:100 to 1:320) followed by decrease to the starting value. Fifteen episodes of sNfL decrease were recorded in 11 patients. MOG-IgG titers decreased in six and were stable in six of these 15 episodes (not available: two). One episode (patient_1_01) spanned a biphasic MOG-IgG course with a decrease followed by an increase (1:100 to 1:32 to 1:320).

Vice versa, a total of nine episodes of MOG-IgG titer change with parallel (+/−1 month) sNfL measurements were recorded in seven patients. Except for the biphasic MOG-IgG course in patient_1_01, each change in titers was accompanied by a concordant change in sNfL (Figs. 1 and 2).

3.3. Association between longitudinal dynamics of sNfL and prior disease activity

Eleven patients had an attack within six months before baseline ("active"), and seven patients did not ("stable"). The difference between highest and lowest sNfL was higher in the "active" (37 [IQR 10–64]pg/ml) than the "stable" subgroup (2.3 [IQR 1–5]pg/ml; SMD=1.3, $p = 0.006$; Fig. 3A). Median sNfL change between first and last available measurement was non-significantly higher in "active" (−7 [IQR −49–2] pg/ml) than in "stable" patients (0.4 [IQR −4–1] pg/ml; SMD=0.20, $p = 0.44$). A higher number of attacks before baseline correlated non-significantly with a smaller decrease between first and last sNfL (rho=0.41, $p = 0.09$) and correlated with a lower difference between highest and lowest sNfL (rho=−0.78, $p = 0.0001$; Fig. 3B). Maximum sNfL was higher in the "active" subgroup (54 [IQR 29 – 85]pg/ml vs. 18 [12–29]pg/ml; SMD=0.88, $p = 0.04$), and correlated with the number of previous attacks (rho=−0.62, $p = 0.006$), while minimum sNfL did not (23 [IQR 11–25]pg/ml vs. 15 [11–24]pg/ml, SMD=0.23, $p = 0.75$); rho=−0.02, $p = 0.93$).

Seven patients had a disease duration of less than six months at baseline and eleven patients had a disease duration of more than six months. The median difference between first and last sNfL was higher in the patients with a disease duration <6 months (−37 [IQR −64- −8] pg/ml vs. 0.9 [IQR −2–2] pg/ml; SMD=−1.3, $p = 0.008$). Likewise, they showed a higher median difference between highest and lowest sNfL (49 [IQR 26–64] pg/ml vs. 2.3 [IQR 1–7] pg/ml; SMD=0.86, $p = 0.006$).

3.4. Longitudinal dynamics of sNfL in patients with an attack at baseline

Two patients had an acute attack within 14 days before baseline (patient_1_01, patient_1_03). Patient_1_01 had the first disease manifestation with LETM and encephalitis, patient_1_03 had a relapse with brainstem encephalitis. MRI within days before baseline showed new

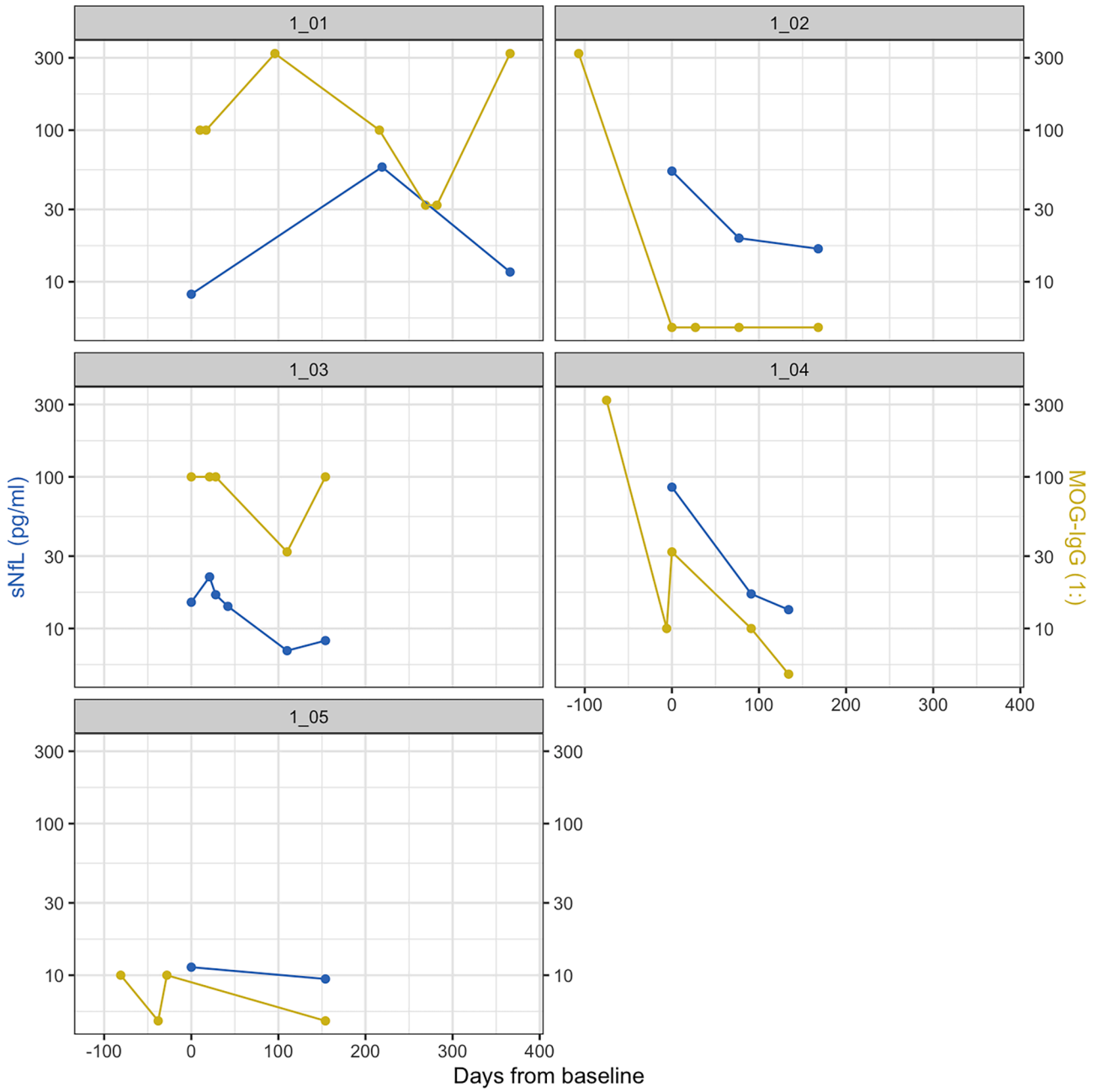

Fig. 1. Longitudinal sNfL and serum MOG-IgG in patients with MOGAD in cohort 1.
Each panel indicates one patient. MOG-IgG titers before baseline are additionally shown where available (patients 1_02, 1_04, 1_05) to illustrate the sequence of sNfL vs. MOG-IgG change. The assay-specific cut-off for positive MOG-IgG is >= 1:10. Negative MOG-IgG are visualized as 1:5 on the log-scale. Abbreviations: MOG-IgG = serum anti-myelin oligodendrocyte glycoprotein immunoglobulin G, sNfL = serum neurofilament light chain.

T2-lesions but no Gd-enhancement in both cases. In both patients, sNfL strongly increased after baseline (patient_1_01: 8.3pg/ml to 57.1pg/ml, +688%, at seven months; patient_1_03: 14.6pg/ml to 21.9pg/ml, +47.0%, at 21 days) and decreased afterwards (Fig. 1).

3.5. Association of longitudinal dynamics of sNfL and attacks during the observation period

Each patient with an attack during the observation period ($n = 5$) showed an sNfL increase, except one patient with strongly elevated baseline sNfL, measured during an attack. However, the sNfL increase was small (4% and 6%) in two patients, who had exclusively episodes of optic neuritis (one and two). Vice versa, four of nine patients with at least one episode of sNfL increase had an attack during the study (44%), but only one of nine patients without an episode of sNfL increase (11%; odds ratio=5.8, SMD=0.71, $p = 0.29$).

In addition, patient_2_05 reported insidious symptom worsening during the study that was not regarded an attack at the study center, but the patient received IVMP and PLEX four months before the second sNfL measurement at an external hospital and was treated with immunoadsorption and IVIG shortly after the follow-up visit. EDSS score increased from 6.0 to 7.5 between baseline and follow-up (ambulation functional system "walking 100 m with unilateral assistance" to "wheelchair bound"). sNfL showed a strong increase (28.0 to 157.0pg/ml, +561%).

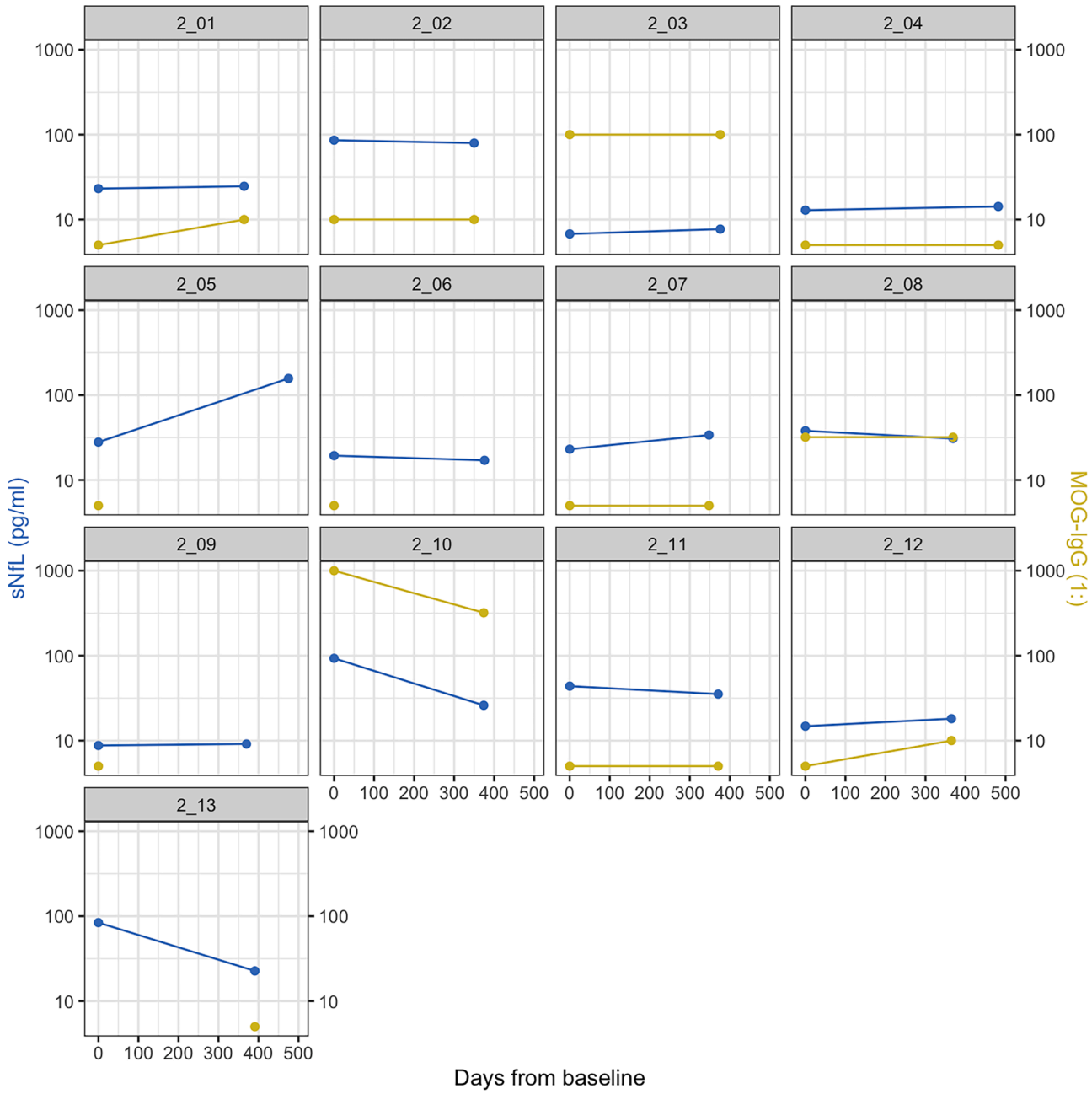

Fig. 2. Longitudinal sNfL and serum MOG-IgG in patients with MOGAD in cohort 2.
Each panel indicates one patient. The assay specific cut-off for positive MOG-IgG is >= 1:10. Negative MOG-IgG are visualized as 1:5 on the log-scale. Abbreviations: MOG-IgG = serum anti-myelin oligodendrocyte glycoprotein immunoglobulin G, sNfL = serum neurofilament light chain.

3.6. Association of longitudinal dynamics of sNfL and attacks after the observation period

In cohort 1, no systematic information on attacks after the last sNfL measurement was available. Patient_1_03 contacted the treating neurologist one month after follow-up and reported newly developed retroorbital pain with eye movement. Symptoms resolved after few days with an increased dose of oral prednisolone (4 mg/d to 10 mg/d). No MRI was acquired. The episode was preceded by a moderate increase of sNfL (7.1 to 8.3pg/ml, +17%) between two and one months earlier.

In cohort 2, four of eleven patients with 24 months follow-up experienced an attack within one year after the follow-up visit. Three of these patients also had at least one attack between first and last sNfL measurement. sNfL increased between first and last measurement in three of four patients. The patient (patient_2_10) without sNfL increase had an acute attack and strongly elevated sNfL at baseline. Of eleven patients with 24 months follow-up, six patients had an sNfL increase and five did not. Three of the six patients with sNfL increase (50%) had an attack after follow-up, but only one of five patients without sNfL increase (20%; odds ratio=3.5, SMD=0.55, $p = 0.69$).

3.7. Change in maintenance immunotherapy

In cohort 1, maintenance immunotherapy was started after baseline in three patients. Patient_1_01 received three doses of rituximab between one and seven months after baseline, accompanied by a strong sNfL increase between baseline and seven months (Fig. 1). After an attack of optic neuritis one month after the second sNfL measurement, rituximab was discontinued, and tocilizumab initiated. The period of strong sNfL decrease in this patient (7–12 months after baseline)

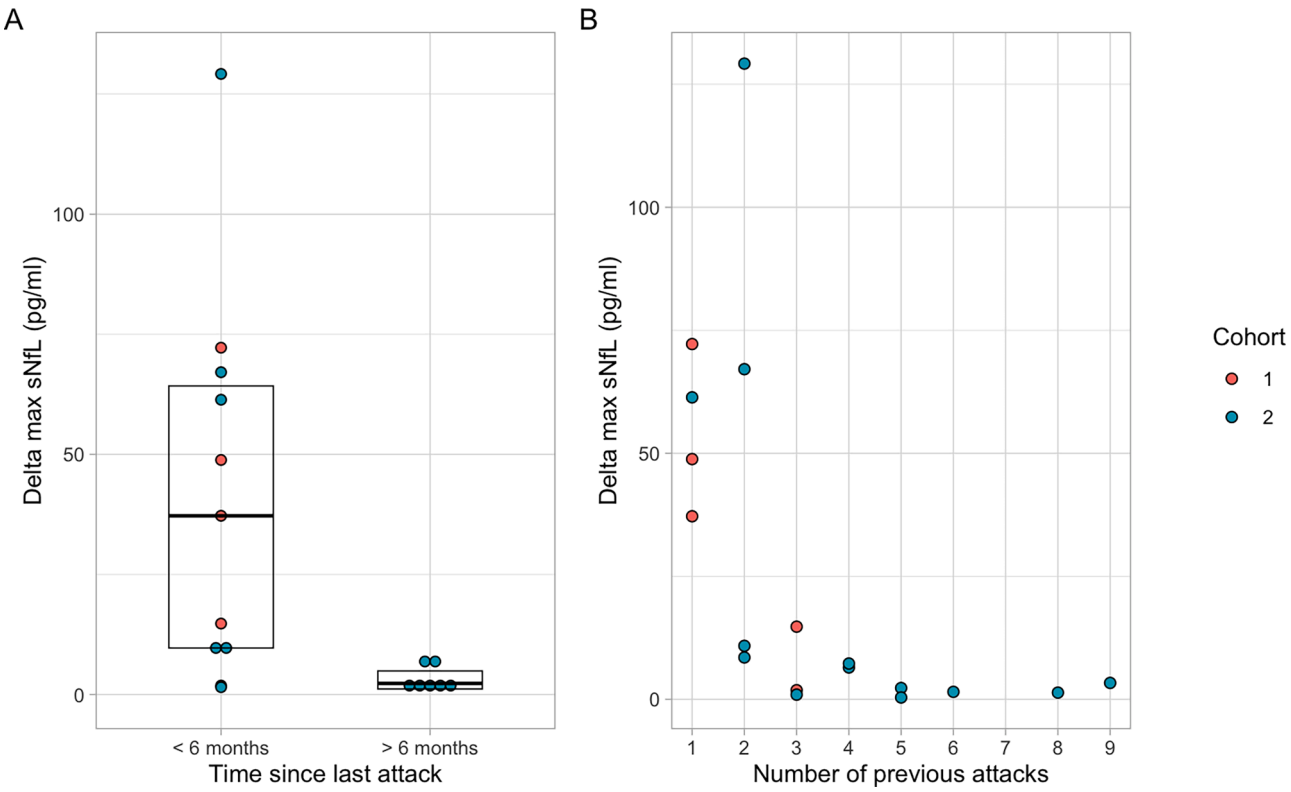

Fig. 3. Dependence of the maximum change in sNfL on time since last attack (A) and number of previous attacks (B) at baseline.
All patients from cohort 1 ($n = 5$) and cohort 2 ($n = 13$) are included. Maximum sNfL difference indicates maximum minus minimum recorded sNfL per patients. Disease state was regarded active when time between last attack to baseline was <6 months. Fig. 3A: SMD = 1.3, $p = 0.006$ (Wilcoxon rank-sum test). Fig. 3B: rho = −0.78, $p = 0.0001$ (Spearman rank correlation). Abbreviations: SMD = standardized mean difference, sNfL = serum neurofilament light chain.

comprises one cycle each of IVMP and immunoadsorption as well as the initiation of tocilizumab. Patient_1_03 was started on rituximab one day after the third sNfL measurement. sNfL continued to decrease afterwards. Patient_1_04 was started on monthly IVIG three weeks after baseline, concordant with a strong decrease of sNfL (Fig. 1).

In cohort 2, maintenance immunotherapy was initiated or switched during the study in two patients. Patient_2_07 was started on rituximab three months after baseline. sNfL increased moderately. Patient_2_10 was switched from rituximab to mycophenolate mofetil (MMF) after an attack, five months after baseline. sNfL decreased strongly (Fig. 2).

4. Discussion

The main findings of this explorative study of longitudinal sNfL changes in patients with MOGAD in relation to MOG-IgG titer changes and to clinical events are: (1) Changes in sNfL correlate with changes in MOG-IgG titers. (2) Strong changes in sNfL occur mainly in temporal relation to attacks and may appear predominantly early after disease onset. (3) Increase of sNfL may support clinically suspected attacks, while the absence of strong changes in sNfL over one year does not rule out the occurrence of attacks in-between, especially attacks of optic neuritis. In acute attacks, sNfL increase might follow the onset of symptoms with a delay.

A correlation between sNfL and MOG-IgG titers was recently shown in pediatric patients (Horellou et al., 2023). Furthermore, both sNfL (Hyun et al., 2022; Luo et al., 2022) and MOG-IgG titers (Gastaldi et al., 2022; Jarius et al., 2016b) are often higher during attacks. Our study extends these findings by demonstrating a correlation between changes in sNfL and MOG-IgG titers. This supports the notion, that changes in sNfL reflect disease-specific processes in MOGAD and, therefore, may represent a suitable disease activity biomarker candidate.

The association between changes in sNfL and MOG-IgG titers was mostly driven by changes in association with attacks. However, even MOG-IgG titer changes remote from attacks were accompanied by subtle concordant sNfL changes. This could hypothetically imply unrecognized disease activity in these patients and warrants further investigation.

MOG-IgG titers are a promising biomarker candidate for disease activity in MOGAD (Gastaldi et al., 2022; ZhangBao et al., 2023). Nonetheless, it appears reasonable to explore sNfL as an additional biomarker. Titers, in contrast to concentrations, have a discrete scale and, therefore, subtle changes might stay unnoticed. Furthermore, comparability of MOG-IgG titers is limited by assay heterogeneity and, to some degree, inter-rater variability. Moreover, MOG-IgG titers reflect a peripheral inflammatory process while sNfL indicates end-organ damage.

Strong changes in sNfL were mainly detected after attacks, implying prolonged sNfL normalization over months, as previously reported (Azizi et al., 2021; Hyun et al., 2022). This is supported by the association between higher baseline sNfL and shorter time since last attack, which we have previously shown in an overlapping cohort (Schindler et al., 2021). However, in some patients an increase of sNfL was detected within the months following an attack. Hypothetically, the subacute disease state might be a surrogate for higher disease activity. In support of this notion, clustering of attacks in MOGAD has been suggested, especially during early disease (Akaishi et al., 2022; Chen et al., 2023). These findings are in line with a previous study demonstrating most pronounced sNfL changes in the early disease phase (Mariotto et al., 2021). Likewise, in our study, stronger sNfL changes were observed in patients with a recent disease onset. However, a valid distinction between time since last attack and since first manifestation as the main determinate of sNfL change was not possible, because only few patients with a short time since the last attack had longstanding disease. A possible influence of disease duration on the longitudinal variability of sNfL might be mediated by the number of previous attacks. However,

attenuated increase rather than incomplete normalization of sNfL appears to cause the milder change of sNfL in patients with a higher number of previous attacks.

Attack-related sNfL changes and prolonged sNfL normalization after one-time CNS damage (Azizi et al., 2021) combine to an advantage of longitudinal sNfL change over one single measurement as a biomarker for disease activity. While in steady state sNfL concentrations indicate ongoing neuroaxonal damage, one elevated sNfL concentration cannot differentiate between "past neuroaxonal damage" and "increased rate of neuroaxonal damage". Furthermore, the overlap between sNfL in attack and remission (Kim et al., 2020; Luo et al., 2022) might favor the additional analysis of sNfL changes. Ideally, future larger studies should incorporate both adjusted sNfL concentrations (Benkert et al., 2022) and longitudinal sNfL changes.

Previous studies found no predictive value of sNfL for future attacks (Horellou et al., 2023). While our cohort was too small to systematically address this aspect, the occurrence of new symptoms in two patients (patient_2_07, patient_1_03) after an sNfL increase and the numerically higher proportion of future attacks in patients with sNfL increase suggest, that further investigations are warranted. Furthermore, sNfL increase might be useful to corroborate clinically suspected attacks. This is illustrated by the increasing sNfL in patients with an attack during the study and in association with disability worsening in patient_2_05. In contrast, the clinical usability of stable sNfL to exclude a suspected attack might be limited, especially for optic neuritis with a low volume of damaged neuroaxonal tissue. Generally, the extent of sNfL increase is associated with attack severity (Horellou et al., 2023; Mariotto et al., 2021). Nevertheless, the direction of the subtle sNfL change in patients with optic neuritis during the study was increasing in all cases.

Analyses of immunotherapy effects on sNfL in MOGAD are complicated by the frequent start shortly after an attack, within a period of sNfL decrease. In this investigation, all patients starting rituximab ($n = 3$) had at least one episode of sNfL increase within nine months thereafter. In contrast, no sNfL increase was recorded after initiation of another immunotherapy ($n = 3$; MMF, IVIG, tocilizumab), preceded by rituximab treatment in two of three cases. These findings should be interpreted with caution, due to the low number and inconsistent sampling intervals. However, in the light of recent findings suggestive for limited efficacy of rituximab in MOGAD (Durozard et al., 2020; Spagni et al., 2023; Whittam et al., 2020a) further investigations of sNfL dynamics in relation to treatment changes may be of interest.

The comparably low sNfL in two patients shortly after acute symptom onset, each followed by sNfL increase, suggests a potential delay of neuroaxonal damage after symptom onset. Initial MRI did not show Gd-enhancement though new T2 lesions were already evident in both cases. A delay of both sNfL increase (Mariotto et al., 2021) and appearance of MRI abnormalities (Cacciaguerra et al., 2024; Sechi et al., 2021) has previously been reported in MOGAD. The improved recovery with early acute treatment (Rode et al., 2022; Stiebel-Kalish et al., 2019) might reflect these findings. A possible delay of neuroaxonal injury after symptom onset could imply a therapeutic window of opportunity in acute MOGAD. Taken together, future longitudinal studies including fluid and imaging biomarkers should investigate the sequence of demyelination and neuroaxonal damage in the early acute phase in MOGAD.

This study is limited by the small number of participants. This is a consequence of the low incidence of MOGAD that should be addressed by multi-center approaches in the future. Furthermore, use of real-world data lead to inconsistent sampling intervals that limits comparability. As a consequence of these limitations, we refrained from advanced statistical analyses and consider this study hypothesis-generating. As an additional limitation, the follow-up interval of one year in cohort 2 might be too long to detect potential small, transient sNfL changes due to optic neuritis.

Altogether, sNfL changes in MOGAD might reflect disease-related end-organ damage and may be utilized as biomarker for disease activity. The changes of sNfL during early acute attacks as well as in the context of optic neuritis warrant further investigation.

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CRediT authorship contribution statement

Patrick Schindler: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Judith Bellmann-Strobl:** Writing – review & editing, Supervision, Investigation. **Jens Kuhle:** Writing – review & editing, Resources, Methodology, Investigation. **Brigitte Wildemann:** Writing – review & editing, Investigation. **Sven Jarius:** Writing – review & editing, Investigation. **Friedemann Paul:** Writing – review & editing, Supervision, Resources, Investigation. **Klemens Ruprecht:** Writing – review & editing, Supervision, Resources, Investigation, Conceptualization.

Declaration of competing interest

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