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Research paper

Using jitter analysis with concentric needle electrodes to assess disease status and treatment responses in myasthenia gravis

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ABSTRACT

Objective: This study assesses the utility of jitter analysis with concentric needles to evaluate disease severity in myasthenia gravis (MG), correlate changes in jitter with clinical status as well as identify reasons for any discordance.
Methods: We performed a retrospective chart review of 82 MG patients and extracted data on demographics, MG subtype, antibody status, clinical scales, electrophysiology, and interventions at baseline and follow-up.
Results: Baseline MGII scores correlated with jitter ($r = 0.25$, $p = 0.024$) and abnormal pairs ($r = 0.24$, $p = 0.03$). After 28 months, MGII scores correlated with jitter ($r = 0.31$, $p = 0.006$), abnormal pairs ($r = 0.29$, $p = 0.009$), and pairs with blocks ($r = 0.35$, $p = 0.001$). Changes in MGII scores correlated with changes in jitter ($r = 0.35$, $p = 0.002$), abnormal pairs ($r = 0.27$, $p = 0.014$), and pairs with blocks ($r = 0.36$, $p = 0.001$).
Conclusions: Concentric needle jitter analysis may have the potential to evaluate baseline and sequential disease severity in MG.
Significance: This study highlights the potential for improved MG patient care through precise assessment and management using concentric needle jitter analysis to improve the accuracy of MG diagnosis and monitoring of disease activity.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disorder causing impaired neuromuscular transmission and leading to fatigable and fluctuating weakness (Lindstrom et al. 1976). Repetitive nerve stimulation (RNS), single fibre electromyography (SFEMG) and autoantibody testing, such as anti-acetylcholine antibodies (anti-ACHR antibodies) and anti-muscle specific kinase antibodies (anti-MUSK antibodies), play an important role in the diagnosis. SFEMG is known to have the highest sensitivity for the diagnosis of MG and has a higher negative predictive value in identifying patients who do not have MG (Guan et al., 2015; Padua et al., 2014; Rakocevic et al., 2017).

In previous studies, abnormal SFEMG findings such as higher mean jitter value, the percentage of pairs with increased jitter values, and the percentage of pairs with impulse blocking correlated significantly with disease severity (Konishi et al. 1981; Abraham et al., 2017a).

It was suggested that these parameters might serve as a prognostic tool in the management of MG (Baruca et al., 2016). However, there is scarce literature regarding the utility of serial SFEMG studies using concentric needle electrodes, especially with regard to (a) correlation with changes in disease status, (b) the ability to guide treatment decisions, and (c) the presence of discordance between clinical status and SFEMG observations. An improved understanding of these gaps may provide evidence to aid longitudinal follow-up in a real-world setting.

Our aim was to determine whether (a) the jitter analysis findings performed with concentric needles in MG correlated with clinical severity at the initial and follow-up visits, (b) changes in the jitter analysis findings during follow-up correlated with changes in disease status, and if (c) there was any discordance between changes in clinical status and jitter analysis findings.

2. Methods

We performed a retrospective chart review of consecutive subjects newly diagnosed with MG attending the Prosserman Family

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Neuromuscular Clinic at the Toronto General Hospital from January 2015 to February 2023. Patients were included only if they had jitter analysis using a concentric needle electrode performed at baseline and during a subsequent follow-up visit. The diagnosis of MG was based on the presentation of fatigable weakness involving ocular, bulbar or limb muscles supported with abnormal electrophysiological tests (SFEMG) or positive serology (anti-AChR or anti-MUSK antibodies).

The study was approved by the UHN ethics research board (REB). A waiver of consent was obtained for this retrospective study.

We extracted the demographic findings, age at symptom onset, duration of symptoms, the subtype of MG, antibody status, thymic pathology, clinical assessment scales such as the myasthenia gravis impairment index (MGII), single simple question (SSQ), and patient acceptable symptoms state (PASS) from the patient charts. The therapeutic interventions and clinical assessment scales at the follow-up visits were also noted. Reflex testing for anti-MuSK antibody was performed when testing for anti-AChR antibody was negative.

The jitter analysis data included mean jitter (μs), percentage (%) of pairs with abnormal jitter, and % of pairs with blocking. All values were obtained from the same muscle (frontalis or orbicularis oculi) on follow-up. MGII and jitter analysis were performed by trained neurologists under the supervision of a senior author (VB). The same individual did not conduct both assessments during the initial visit and follow-up, limiting confirmation bias. In our study, voluntary jitter analysis was employed capturing muscle activity during slight activation. A concentric needle electrode (30 gauge, 25 mm length) with a filter setup of 1 kHz high-pass and 10 kHz low-pass was employed. The subjects were instructed not to take pyridostigmine on the day of testing. The frontalis muscle was tested in subjects with both generalised and ocular MG. In patients with suspected ocular MG, a second muscle, the orbicularis oculi, was tested if the study from the frontalis was normal. As per the institutional protocol, the study was stopped after 3 abnormal pairs or after recording 20 normal potential pairs (Abraham et al., 2017b). Studies were considered abnormal if (1) the mean jitter exceeded the upper limit of normal for the muscle, (2) more than 10 % of pairs had abnormal jitter and (3) percentage of pairs with any blocking were present. Published reference values for mean jitter in the muscle [frontalis 28 μs, orbicularis oculi 31 μs] and jitter of individual pairs [frontalis 38 μs, orbicularis oculi 45 μs] using concentric needles were used (Stålberg et al., 2016).

We used the myasthenia gravis impairment index (MGII) to assess disease status. MGII has 22 patient-reported and 6 physician-assessed items ranging from a normal of 0 to a maximum severity of 84 (Barnett et al., 2016). The MGII incorporates both ocular (subscore range 0–23) and generalised impairments (subscore range 0–61). MGII has advantages of less floor effect, being simpler, less time-consuming, and centred on the patient's symptoms compared to myasthenia gravis–specific activities of daily living (MG-ADL), Myasthenia Gravis Composite (MGC), and the Quantitative Myasthenia Gravis Scale (QMGS) (De Meel et al., 2020). It has greater sensitivity in assessing ocular disease severity and also assesses fatigability. Strong correlations of the MGII with other patient-reported outcomes, such as the patient acceptable symptom state (PASS) and the single simple question (SSQ), have also been demonstrated (Abraham et al., 2018; Menon et al., 2020). The minimal important difference (MID) for the total MGII score in an individual patient is 5.5 (Barnett et al., 2017). "Improvement" and "worsening" in this study were defined by a change in MGII of $\geq$6, and changes in MGII < 6 were classified as "same (unchanged)".

In addition to determining absolute values of mean jitter, percentage of pairs with abnormal jitter and percentage of pairs with blocking, we also classified changes at follow-up compared to baseline as "improved" or "worsened" based on a percentage change (reduction/increase) in the mean jitter value of 15 % (Katzberg et al., 2014).

2.1. Statistical analysis

We used the Statistical Package for Social Sciences (SPSS version 21.0) for statistical analyses. Data were presented as a number (percentage) for categorical variables and mean ± SD for continuous variables. Pearson's and Spearman's correlations (for parametric and non-parametric data, respectively) were used to analyze the association between jitter analysis and clinical severity scores. For correlations, values <0.4 were considered as weak, 0.4–0.6 as moderate and >0.6 as strong. Individual associations between categorical variables were analyzed using the Chi-square test. Analysis of variance (ANOVA) and the Kruskal-Wallis test were used to assess the differences between the groups. The Dunn correction for multiple post hoc comparisons was performed. Statistical significance was set at $P < 0.05$.

3. Results

Of 1120 MG patients evaluated in our clinic from January 2015 to February 2023, a total of 82 with SFEMG during their first visit had repeat studies. The mean age of the population was 62.6 (14.08) years, and the median duration of symptoms was 40 (IQR 12–108) months. Of the 82 patients, 49 (59.8 %) were females, and 33 (40.2 %) were males. 53 (64.6 %) patients had generalized MG and 20 (24.4 %) had ocular MG. In this cohort, 9 (11 %) had thymoma-associated MG. Thymectomy was done in 38 (46.3 %) of patients. 42 (51.2 %) patients had positive anti-AChR antibody titres and 6 % has MuSK antibodies. All patients with anti-MuSK antibodies (5) in our cohort had generalised MG. At baseline, the mean MGII was 18.5 (13.1), and the median MGII was 17 (IQR 7.25–26). The mean SSQ was 61.4 % (28.0). At the first visit, the PASS question was answered by 44 patients; 12 answered PASS yes, and 32 answered no.

As shown in Table 1, distinct clinical and electrophysiological profiles were observed among the MG subtypes. Ocular MG patients had the lowest mean MGII (11.2 ± 7.1). Patients with generalized MG had mean jitter (77.63 ± 55.1 μs), mean abnormal jitter pairs 46.47 % (33.14) and pairs with blocking 33.72 % (33.47). The MuSK MG subgroup had the highest mean jitter (104.9 ± 54.1 μs), as well as the number of recordings with abnormal jitter and blocking.

As shown in Table 2, patients with seronegative MG had significantly lower mean jitter (58.94 ± 35.56 μs) and also a lower percentage of recordings with abnormal jitter and blocking compared to antibody-positive (both anti-AChR and anti-MuSK) MG (96.14 ± 73.1 μs).

Table 2 demonstrates that there were no significant differences in mean MGII between patients who underwent prior thymectomy and those who did not. Additionally, no significant associations were observed between thymectomy status and mean jitter, percentage of recordings with abnormal jitter, or percentage of recordings with blocking.

The correlation between the disease severity scale (MGII) and jitter analysis variables at the first visit are presented in Table 3. There were statistically significant but weak correlations between the MGII and jitter analysis variables apart from the mean percentage of pairs with blocking.

Table 1
Comparison of clinical factors and concentric needle SFEMG parameters.

MG subtype	Ocular MG (n = 20)	Generalised MG (n = 48)	MuSK Ab MG (n = 5)	Thymoma MG (n = 9)	P value	Significant pairwise comparisons
Variable						
MGII score (mean, SD)	11.2 (7.07)	21.06 (13.69)	23 (11.54)	19.44 (16.27)	**0.009***	Ocular vs Generalised MG 0.001*
Mean jitter (μs) (mean, SD)	75.67 (74.85)	75.12 (55.18)	104.9(54.07)	81.32 (62.40)	**0.039***	Ocular vs generalised MG 0.033* Ocular vs MuSK MG 0.009*
% of recordings with abnormal jitter (mean, SD)	32.85 (27.47)	43.37 (32.11)	82.81(18.95)	47.89 (27.62)	**0.04***	Generalised vs MuSK MG 0.017* Ocular vs MuSK MG 0.009*
% of recordings with any block (mean, SD)	27.15 (29.73)	30.25 (31.08)	76.61(31.58)	43.88 (29.11)	**0.018***	Generalised vs MuSK MG 0.017* Thymoma associated MG vs ocular MG 0.031*

Ocular MG refers to subjects with isolated ocular involvement, Generalised MG includes subjects with generalised involvement who are both anti-AChR antibody positive and seronegative, and negative for both anti-MuSK antibodies and thymoma, MuSK Ab MG to subjects with features of generalised MG who were anti-MuSK Ab positive, and Thymoma MG to patients who had MG and an associated thymoma.
The first p-value is for overall trend, and the subsequent p-values are calculated only if this first p-value for trend is significant. The additional p-values are specific pairwise comparisons between groups, in order to locate exactly where the differences are (as opposed for the first p-value which is for overall trend only).

Table 2
Comparison of antibody and prior thymectomy status and concentric needle SFEMG parameters.

Variable	Antibody positive MG (n = 47, 42 with anti-AchR and 5 with anti-MuSK)	Antibody negative MG (n = 35)	P value (for antibody positive vs negative MG)	Prior thymectomy done (n = 38)	No thymectomy done (n = 44)	P value (for prior thymectomy vs no thymectomy)
MGII (mean, SD)	17.17 (11.87)	20.23 (14.35)	0.92	20 (14.26)	17.39 (12.02)	0.057
Mean jitter (μs), (mean, SD)	96.14 (73.10)	58.94 (35.56)	0.01*	78.25 (63.35)	78.21 (59.10)	0.74
% of recordings with abnormal jitter (mean, SD)	53.76 (34.41)	33.48 (24.41)	0.034*	44.94 (31.05)	43.16 (31.84)	0.91
% of recordings with any blocking (mean, SD)	41.78 (36.21)	25.58 (25.81)	0.09	33.52 (32.37)	34.39 (32.93)	0.91

Antibody positive MG includes the subjects with anti-AChR/anti-MuSK antibodies with either ocular/generalised/thymoma associated MG.

Table 3
Correlations between disease severity (MGII) and concentric needle SFEMG parameters.

Variable	Correlation coefficient	P value
First visit		
MGII vs mean jitter	0.25	**0.024***
MGII vs % of pairs with abnormal jitter	0.24	**0.03***
MGII vs % of pairs with any blocking	0.1	**0.39**
Follow-up visit		
MGII vs mean jitter	0.31	**0.006***
MGII vs % of pairs with abnormal jitter	0.29	**0.009***
MGII vs % of pairs with any blocking	0.35	**0.001***
Comparison of changes between first and follow-up visits		
Change in MGII vs change in mean jitter	0.35	**0.002***
Change in MGII vs change in % of pairs with abnormal jitter	0.27	**0.014***
Change in MGII vs change in % of pairs with any blocking	0.36	**0.001***

The median duration between the two jitter studies was 28 months (IQR 13.5–48). Medications used in the interval included pyridostigmine 64 (78 %), prednisone 34 (41.5 %), mycophenolate mofetil 15 (19.7 %), azathioprine 14 (17.1 %), immunoglobulin 10 (13.2 %) and plasma exchange 3 (3.6 %). There were statistically significant correlations between the MGII and all the jitter variables at the follow-up visit, as depicted in Table 3, although the correlations were weak.

At the time of the follow-up visit, 47 patients had improved, 10 remained unchanged, and 25 worsened. The change in clinical status showed a statistically significant association with the change in the jitter analysis variables, as depicted in Fig. 1 and Table 4 ($p < 0.0001^*$). The comparisons of changes in jitter analysis variables (improved, same, and worsened) between the clinically improved, same and worsened subgroups were also statistically significant ($p < 0.0001^*$).

Repetitive nerve stimulation (RNS) from the frontalis muscle was performed in all the subjects. RNS showed a decremental response in 25.6 % subjects. A decremental response in the RNS was associated with a higher MGII score (25.8 (11.4)) vs 16.3 (13), p value 0.008*) in those who had a normal RNS. Subjects who had a decremental response in the RNS had higher mean jitter values (143.13 (79.42) μs vs 55.47 (29.27) μs, p value < 0.001*) in our cohort.

Of note, 7 patients showed discordance between the clinical status at follow-up and jitter analysis findings. These included 5 patients who reported clinical worsening but had improvement in jitter and 2 patients who reported clinical improvement but had worsening of jitter. The 5 patients with clinical worsening had other comorbid illnesses such as respiratory illness, bipolar disorder, obstructive sleep apnea, peripheral vertigo, and migraines which may have contributed to non-specific worsening of symptoms. There was no objective worsening weakness of the ocular, bulbar or limb muscles on the clinical examination in any of these patients. All of these patients improved/remained stable during their subsequent follow-up assessments without any treatment interventions for MG. Of interest, one patient had features of deconditioning related to chronic use of corticosteroids and had improvement in clinical status after a reduction in the dose of

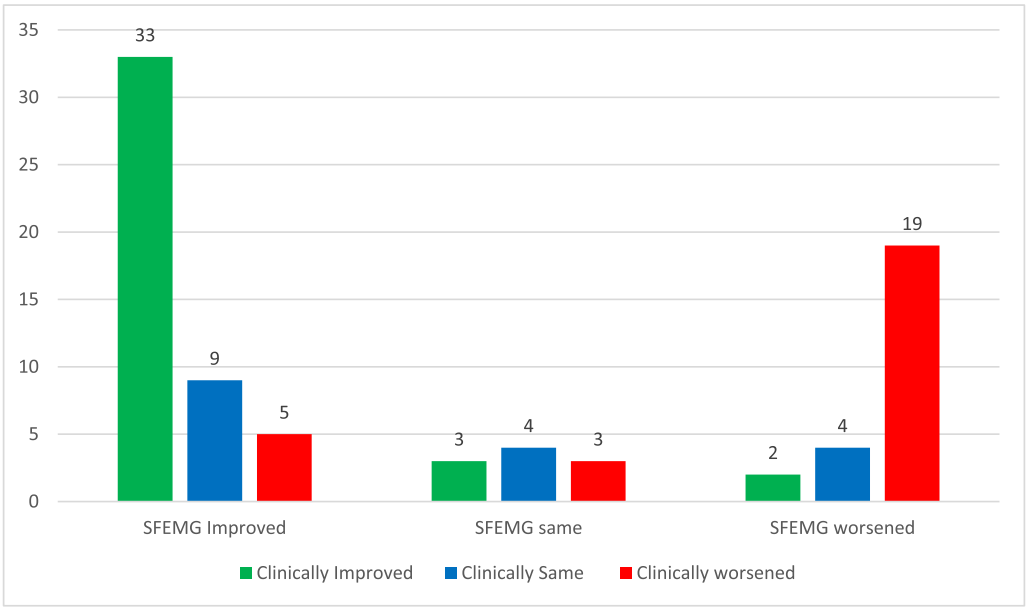

Fig. 1. Comparison of changes in clinical status with changes in concentric needle SFEMG. The Y-axis shows the number of patients who clinically improved, remained the same or worsened.

Table 4
Comparison of mean changes in disease severity (MGII) and concentric needle SFEMG parameters. between the first and follow-up visits.

Clinical status	Improved	Stable	Worse	P values
Change in MGII	−10.11 (7.61)	1.11 (4.67)	9.96 (11.10)	**< 0.001***
Change in mean jitter	−44.59 (70.51)	−22.47 (46.23)	32.62 (51.72)	**< 0.001***
Change in % of pairs with abnormal jitter	−30.85 (34.65)	−12.9 (16.41)	10.84 (36.51)	**0.013***
Change in % of pairs with any blocking	−31.43 (33.71)	−16.29 (19.37)	16.11 (40.88)	**< 0.001***

prednisone. Two patients had worsening jitter analysis variables but an improved clinical status. The worsening in jitter analysis variables was attributed to the previous administration of botulinum toxin in one patient. In the other patient (anti-MuSK-MG), clinical improvement was reported at the time of assessment despite the worsening noted in jitter analysis variables. However, the patient had clinical worsening at a subsequent visit three months later and required escalation of therapy.

The mean changes in clinical severity scores and jitter analysis variables are provided in Table 4. Statistically significant differences in the mean changes in the jitter values, number of recordings with abnormal jitter and blocking between the groups (improvement, unchanged and worsened) were observed. The changes in jitter analysis variables paralleled changes in MGII as shown in Fig. 1.

There was no significant association between the mean jitter at baseline with the clinical status (improved, same, worsened) at the time of the last follow-up (p value 0.52). However, there was a significant association between the mean jitter value obtained during the follow-up SFEMG study with the clinical status (p value 0.001*).

4. Discussion

In this study, we showed that abnormalities in jitter analysis using concentric needle electrodes correlated with disease severity in MG as measured by the MGII at baseline and follow-up visits. The changes in jitter analysis variables also correlated with changes in disease severity scales. Although statistically significant, the correlations were weak. The changes in clinical status (improved, same, worsened) were also significantly associated with the changes in the jitter analysis (improved, same, worsened).

Our findings are consistent with other studies (Konishi et al. 1981; Abraham et al., 2017a), indicating that jitter analysis in patients with MG is associated with disease severity. The findings suggest a broader role for repeat SFEMG in MG patients, especially before major changes in therapeutic strategies. Our study's identification of a notable association between changes in jitter analysis and clinical status aligns with findings in other studies (Sanders and Massey, 2017). Sanders et al. demonstrated that changes in all SFEMG parameters in the extensor digitorum and frontalis muscles predicted changes in clinical severity in MG (Sanders and Howard, 1986). In another study, there was a strong correlation between overall clinical improvement and a decrement of at least 10 % in mean jitter in one muscle, indicating that serial measurements of jitter can be useful in following the course of the disease and in assessing the effects of treatment. Meriggioli and Rowin (2003) published the observation that patients who demonstrated a positive response to immunosuppressive therapy also exhibited a decrease in mean consecutive difference (MCD) values suggesting that SFEMG may have potential value as an early treatment response marker (Meriggioli and Rowin, 2003). In another retrospective study of patients treated with cyclosporine, the MCD fell more than 10 % from the pre-treatment value in all patients (Ciafaloni et al., 2000).

Of particular interest in the current study was the discordance between the clinical response and SFEMG in 7 patients. The results in this subset of patients suggest that changes in SFEMG can be used to guide treatment decisions. In patients with improved SFEMG but worsening symptoms, comorbidities and adverse effects of medication need to be considered. In the contrasting set-

ting of worsening SFEMG parameters in a patient who is clinically stable, impending clinical deterioration needs to be considered as well as other factors, such as the use of botox.

Although statistically significant, the correlation coefficients in this study were weak. This could reflect the small cohort of patients. Other factors that could contribute to this include variable severity of MG involvement, selectivity of muscle involvement and the clinical severity score used. There were also a number of patients who had clinical-electrophysiological discordance or remained stable both clinically and electrophysiologically. A similar strength of correlation was reported in a previous study which compared the clinical severity of MG with jitter values (Abraham et al., 2017a).

While the study suggests an association between jitter analysis and MG severity, other limitations should be acknowledged, specifically the retrospective nature of the study. Being a referral center, a higher proportion of patients with severe MG were included. In our study, the concentric needle SFEMG studies at the first visit were performed for confirmation of the diagnosis of MG, and the follow-up studies as an objective assessment before changes in therapeutic strategies were made. Jitter values and other parameters may be erroneously increased when fewer than 20 pairs are sampled. Moreover, the variable follow-up period between the studies, partly attributable to the Covid pandemic, also limits the interpretation of our findings.

Hence, future studies with shorter and clearly defined follow-up intervals are likely to provide greater insights into the correlation between changes in jitter analysis and treatment response, especially if done in the early stages of MG. This could potentially justify repeat studies as a guide for adjusting treatment strategies and refine the clinical application of jitter analysis in MG management. One must also acknowledge that the routine use of jitter analysis during longitudinal follow-up visits may not always be practical in real-world settings due to factors such as time constraints and patient preferences.

5. Conclusions

Jitter analysis has the potential to provide insight into the treatment response and guide therapeutic changes in MG, particularly in patients with persistent and refractory symptoms. Prospective studies are needed to confirm these observations and explore their utility in studying the benefits of various novel therapies.

5.1. Significance

The current study highlights the potential of jitter analysis using concentric needles as a valuable diagnostic and monitoring tool for MG. Jitter studies provide an objective means of diagnosing MG and assessing disease severity over time, potentially reducing long-term complications and enhancing patient care. Additionally, the discordance between clinical measures and jitter analysis findings offers insights into the complexity of MG assessment and the need for tools that are more specific. This sequential assessment approach, coupled with the understanding of discordance, could potentially improve the management of MG.

Conflict of interest

Prof Vera Bril has received grants from Argenx, UCB, AZ-Alexion, Octapharma, Pharnext, Johnson & Johnson, Viela, Roche, Takeda, Ionis, Immunovant, Winsantor.

She is consultant at: Grifols, UCB, CSL, Takeda, Octapharma, Alexion, Akcea, Ionis, Alnylam, ArgenX, Sanofi, Momenta (J&J), Pfizer, Japan Tobacco, Roche, Janssen, Immunovant, Novo-Nordisk, Winsantor.

She received payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from: CSL, ArgenX, Alnylam, Akcea.

She receives support for attending meetings and/or travel from: ArgenX, CSL,UCB.

She Participated on a Data Safety Monitoring Board or Advisory Board: ArgenX, CSL, UCB, Alexion, Alnylam, Takeda, Ionis, Akcea.

She has relationships with (committee or advocacy group, paid or unpaid): GBS/CIDP Patient group, MG Canada (patient group), Amyloidosis Patient group. None of these are related to this work.

Dr Hans Katzberg is a Consultant at Grifols, CSL Behring, Octapharma, Takaeda, Akcea, Alexion, Terumo, UCB, Roche, Argenx, Dyne, Merz, Dianthus. He receives clinical trial/research support: CSL Behring, Takaeda, Roche, Argenx DSMB participation: Alexion, UCB, Abcuro. None of these are related to this work.

Dr. Carolina Barnett-Tapia has served as member of advisory board for Alexion, argenx, Sanofi and Cartesian, and has been a consultant for Janssen and Takeda. She has research received grants from Grifols, Octapharma, US Department of Defence, MGNet and Muscular Dystrophy Canada. None of these are related to this work.

The authors Vinaya Bhandari, and Ajith Sivadasan have no conflict of interest to declare.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

CRediT authorship contribution statement

Vinaya Bhandari: Writing – review & editing. **Ajith Sivadasan:** Writing – review & editing. **Carolina Barnett-Tapia:** Supervision. **Hans Katzberg:** Writing – review & editing. **Vera Bril:** Writing – review & editing, Supervision.

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