SYLLABUS

TC34: How to Write a Paper?

Thursday, November 17, 2011 09:00 - 12:30 Hall L

Marrakesh, Morocco, November 12-17, 2011

XXth WORLD CONGRESS OF NEUROLOGY

XXth WCN 2011 MARRAKESH World Congress of Neurology

WFN

SMN SOCIETE MAROCAINE DE NEUROLOGIE

WCN Education Program

Thursday, 17 November, 2011

09:00-12:30

HOW TO WRITE A PAPER?

Chairperson: **Mark Hallett**, *USA*

HOW TO WRITE A PAPER
Robert Lisak, *USA*
Mark Hallett, *USA*

10:30-11:00 *Coffee Break*

HOW TO WRITE A PAPER

Mark Hallett, M.D.
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What to write about?

Who deserves authorship?

What should the format be?

Who is the audience?

What journal to target?

Read instructions for authors!

- Should be everything you need to know.
- Read carefully
- One detail often missed is the format of the references.
  - I suggest using an electronic reference manager, such as EndNote

PARTS OF A REGULAR ARTICLE:
PEER REVIEWED ORIGINAL OBSERVATION

- a. Title
- b. Abstract: structured or non-structured
- c. Introduction, hypothesis,aims, descriptive
- d. Methods/Materials including statistics
- e. Results: dangers of *post hoc* analysis
- f. Discussion
- g. References including formatting
- h. Tables
- i. Figures
- j. Supplementary material
- k. Potential conflicts of interest/disclosures
- i. Forms required
- m. Adequate editing
- n. Registration of clinical trials, funding for any type of study being reported
- o. Acknowledgements

a. Title/Title page

- This tells the editor, reviewer and ultimately the reader what the manuscript is about, what is the subject and/or main finding(s)
- Title for a review paper or case reports are somewhat different; less single point for a review, main finding for a case report
- Pay attention to length as well as for running title
- List authors and affiliations as per journal instructions
- Role of each author may be asked for on title page or elsewhere, follow journal guidelines
- Key words are often asked for on title page, follow instructions as to number and whether words in the title can or cannot be used as key words

b. Abstract

- Is an abstract required/needed: Full papers and reviews versus case reports and letters
- Structured vs non-structured; follow the guidelines for that journal
- Follow the length restrictions in instructions to authors
- This is where you get the attention of the editor, the reviewers and the readers. Can determine who the editor picks as reviewers, whether he/she or others involved (deputy editors, associate editors) triage the Ms or not.
- This is where the reader, especially if not in that subspecialty/field often decides if he/she is going to read the paper
- I suggest writing the Abstract last

c.Introduction

- What lead you to do the study?
  - What is the clinical or scientific issue
  - Briefly, what have others and you found- be careful not to simply reduplicate the Discussion
- What was the primary aim of the study or the hyopthesis (depending on the type of paper you are writing)
- If descriptive how is this different than prior publications in the field?
- Be careful of "this is the first time xyz has been described", it often is not. Some journals don't like this type of wording at all so at least try "to our knowledge…."

d. Methods and Materials

- Allows the reviewer and reader to judge the validity of how you did the study
- Allows the reviewer and the reader to repeat the study to validate/repeat it
- Be certain that you have suppliers, experimental conditions, doses of medications, schedule of medications, etc correct
- Check that the numbers of subjects, samples, etc against numbers in Results, Figures and Tables
- Read the Results and review Figures and Tables carefully and ensure that Methods/Materials
- Statistical methods go here in detail

e. Results

- Present the Results in a logical sequence
- Refer to Figures and Tables and be certain they are the correct Figures and Tables for the Results you are describing
- Avoid repetition and jargon
- Read it and be certain that it is not "too dense" to follow (can happen with too many numbers in a row)
- Make certain that there a Methods and Materials that match the Results; is there mention of the M/M that match the result you are describing
- Consider writing Results first, even before Introduction or Methods and Materials

f. Discussion

- This is where you summarize what you found
- How it relates to what you set out to find
- What is the importance of what you found
- What are the limitations to your finding
- How does it relate to other reports in the literature, differences from other studies
- What future studies are indicated in the future
- Avoid speculation that is excessive and especially if you have no data that relates to your speculation
- Try to avoid repeating the Introduction, watch the length

g. References and Citations

- Read the instructions to authors and if you can look at a few articles from the same journal
- Remember it is important to use the correct referencing system and to cite articles in the text (seldom cited in Results or Abstracts)
- If this is a submission to a different journal after Ms was rejected remember to check and see if the new journal uses a different referencing system and citation style
- Use End Note or similar system; easy to change for the next journal
- Avoid over referencing give the amount of data you are presenting; Instructions to authors sometimes have guidelines/limits

g. Figures

- Are all of the Figures necessary and are they related and illustrative of findings/data in Results
- Avoid repeating in Figures what you put in Tables
- Make certain of the quality of the figures particularly images, microscopic (cell cultures, histology, EM, etc), gels, reproduction of electrophysiologic recordings
- Do not show names of patients or dates of images
- If a patient is pictured cover features that are not necessary to make your point and be certain you have consent
- Figure legends should make it unnecessary to constantly refer back to Methods/Results; make certain Figure numbers are correct re when indicated in Results

h. Tables

- Make certain each Table is necessary and does not repeat what is in another Table
- If the same data is in a Figure be very certain that you really need to show the same data in a Table
- Table legends should be clear, informative and to the point
- Avoid excessive number of Tables
- Make certain Table numbers are correct and match with citation in the Results

i. Supplemental Material

- This is material that is important to have available to the interested reader but is not necessary to have to read the paper and understand and support the Results and the main messages of the paper
- Sometimes the data may be useful for others even if the data is not directly related to your paper; list of genes, activated genes, proteins that are detected in screens are good examples
- Sometimes the editor will suggest some of your data going into supplemental data
- Make certain the journal accepts supplemental data

k. Potential Conflicts of Interest/Disclosures

- Read the instructions; will often be very specific
- For some journals disclosures are not limited to commercial sources of support
- Be complete, over report rather than under report if you are not certain or contact editor
- These are critical in clinical trials, reports of therapy and any time there are descriptions of the use of any medication or devices
- All named authors need to list potential conflicts of interests
- Patents and pending patents need to be disclosed
- Source of funding for the particular study usually is listed separately

l. Forms

- Some journals require some of the information covered in the earlier slides go on special forms. Read the instructions to authors

m. Adequate editing

- Have at least one other author look at the final version before you send it
- Check for Figures, Tables, correct referencing and citations of references in the text
- Use "Spell Check" to check for any errors
- Some Spell Checks also have grammar checks as well
- Set the spelling and grammar checks for the appropriate language; some programs distinguish between US and UK/Commonwealth spelling
- If English (or whatever language is the language of the journal) and it is not your native language and you have not published a great deal in that language, get help

n. Registration of Clinical Trials/Source of Funding

- Need for registration will vary with country (countries) where study was performed but also country or the journal (when identifiable)
- Journal may require this information; check
- Source of funding, commercial or otherwise is often listed separately

o. Acknowledgements

- **Here you thank individuals who helped who are not an authors**
  - **Gifts of reagents**
  - **Helpful discussions**
  - **Review of the data and/or manuscript**

- Submitting the paper to the journal
- How is a paper reviewed?
- Outcome
  - Revision
  - Rejection!
  - Acceptance!
- Reading manuscripts
- Citations; impact factors

A Potential Role for B-Cell Activating Factor in the Pathogenesis of Autoimmune Myasthenia Gravis

Samia Ragheb, PhD; Robert Lisak, MD; Richard Lewis, MD; Gregory Van Stavern, MD; Felicitas Gonzales, BS; Kirk Simon, BS

Objective: To compare serum B-cell activating factor (BAFF) levels in patients with myasthenia gravis (MG) with those in control subjects without MG.

Design: Case-control study.

Subjects: Forty-three patients with MG were compared with control subjects without MG. These included 48 healthy subjects, 25 patients with multiple sclerosis, and 3 patients with amyotrophic lateral sclerosis.

Results: In all subjects studied, there was no correlation between the serum BAFF level and the concentration of total IgG, IgA, or IgM. The BAFF levels in patients with multiple sclerosis or amyotrophic lateral sclerosis were not significantly different from those in healthy subjects. However, BAFF levels in patients with MG were significantly higher than those of all the control subjects. There was no correlation or dependence between the serum BAFF level and the extent or severity of disease. There was a trend for BAFF levels to be higher in patients who were seropositive for acetylcholine receptor–specific antibodies.

Conclusions: We report that BAFF levels are increased in patients with autoimmune MG. Our data suggest that BAFF is likely to play a role in the pathogenesis of MG by promoting the survival and maturation of autoreactive B cells.

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AUTOIMMUNE MYASTHENIA gravis (MG) is a B cell–mediated disease in which the target autoantigen is the acetylcholine receptor (AChR) at the neuromuscular junction.[1] Most patients with generalized symptoms have circulating anti-AChR antibodies. Some patients who are seronegative for anti-AChR antibodies have circulating antibodies to muscle-specific kinase (MuSK).[2,3] The AChR-directed antibodies can bind to the various subunits of the AChR; however, most are specific for the α subunit.[4] There is no correlation between the serum antibody titer and disease severity in MG.[5] The inductive signals that lead to the breakdown of immune tolerance to the AChR remain unknown.

Although the percentage of B cells in the blood of patients with MG is the same as that of healthy subjects, the frequency of B cells that express CD71 is significantly higher in patients with MG,[6] particularly in seropositive patients. Because CD71, a transferrin receptor, is essential for the transport of iron into proliferating cells, the increased expression of CD71 suggests that the percentage of proliferating B cells is higher in patients with MG compared with healthy controls.

In some patients, the myasthenic thymus is implicated in initiating, or contributing to, the disease process.[7,8] The presence of germinal centers in the thymic perivascular space indicates that B-cell activation and proliferation are occurring within the thymus. Patients with MG with thymic follicular hyperplasia tend to have higher serum titers of AChR-specific antibodies.[5] The germinal center environment also provides the necessary signals for AChR-specific B-cell survival.[9] Germinal centers within the thymus have strong overexpression of CD23,[10] a multifunctional molecule. One of its roles is to promote the survival and differentiation of germinal center B cells through a mechanism that involves upregulation of Bcl-2.[11] Thymic germinal center B cells do overexpress Bcl-2.[12,13] In the MG thymus with follicular hyperplasia, the overexpression of CD23 and Bcl-2 provides strong evidence that the germinal center environment is promoting the survival and differentiation of AChR-specific B cells.

Within germinal centers, B cells are in close proximity to and are influenced by soluble signals from dendritic cells. Dendritic cells and other myeloid cells (monocytes/macrophages) produce and secrete B-cell activating factor (BAFF).[14-16] B-cell activating factor–transgenic animals exhibit hypergammaglobulinemia, lymphoproliferation, and B-cell hyperplasia, and they develop autoimmune disease. Conversely, in BAFF-deficient animals, there are defects in peripheral B-cell maturation and decreased levels of circulating immunoglobulins.[17] Therefore, BAFF is a potent survival factor for B cells and is necessary for peripheral B-cell differentiation. B-cell activating factor regulates Bcl-2 family members in a manner consistent with pro survival.[18,19] B-cell activating factor is an important molecule within the germinal center. Its role in promoting the survival and maturation of AChR-specific B cells has not been studied. In this study, we measured BAFF levels in the serum of patients with autoimmune MG. The BAFF levels were compared with those in control subjects without MG. These included healthy subjects, patients with multiple sclerosis (MS), and patients with amyotrophic lateral sclerosis (ALS). We report that BAFF levels were increased in patients with MG.

METHODS

SUBJECTS

Patients with MG included 29 women and 14 men with an age range of 20 to 72 years. Clinical diagnosis of MG was confirmed by electrophysiology, pharmacologic testing with edrophonium chloride, and/or serum anti-AChR and anti-MuSK antibody titers. The extent of disease and severity of symptoms were graded according to the Myasthenia Gravis Foundation of America clinical classification scale.[20] Patients with MG included those who were receiving no therapy or receiving pyridostigmine bromide only. Patients who were receiving any immunomodulatory therapy or had undergone thymectomy were excluded. Informed consent was obtained from all subjects. Patients with MG were compared with race-, sex-, and age-matched control subjects without MG. These included 48 healthy subjects, 3 patients with ALS, and 25 patients with MS. Patients with MS included 23 patients with relapsing-remitting disease, 1 patient with primary progressive disease, and 1 patient with secondary progressive disease. Patients with MS were untreated at the time of study. Serum samples from all subjects were stored at −70°C until the time of study.

BAFF ENZYME-LINKED IMMUNOSORBENT ASSAY

Serum BAFF levels were measured by an enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota), which was calibrated using soluble human recombinant BAFF as a standard. Briefly, a monoclonal antibody specific for BAFF was precoated onto a microplate. The BAFF standards and serum samples were then added in duplicate and incubated for 2 hours. After washing, an enzyme-linked polyclonal antibody that was specific for BAFF was added, and the plate was incubated for an additional 2 hours. After washing, a substrate solution was added for 30 minutes. Color developed in proportion to the amount of bound BAFF. Absorbance was measured at 450 nm. The standard curve included BAFF concentrations in the range of 62.5 pg/mL to 4000 pg/mL. The minimal detectable dose of BAFF (ie, sensitivity) was at 3.4 pg/mL. The goodness of fit for a representative standard curve was $r^2=0.9955$. The intraassay coefficient of variation was 4.9%; the interassay coefficient of variation was 8.0%. Using this assay, BAFF levels in healthy human serum are reported to be between 671 and 2447 pg/mL, with a mean (SD) of 1169 (283) pg/mL.

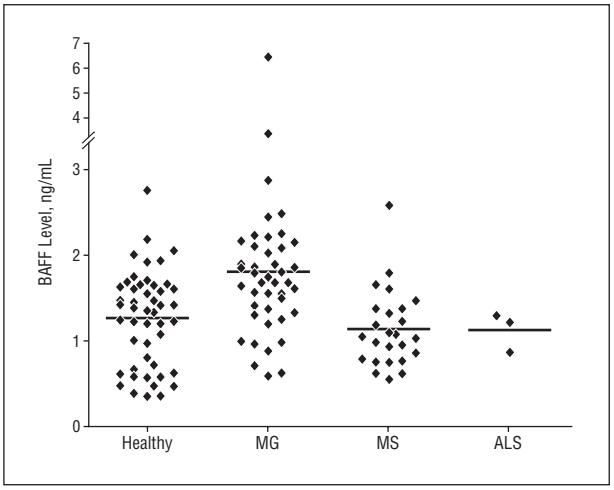

Figure 1. Serum B-cell activating factor (BAFF) levels. The BAFF levels were measured by enzyme-linked immunosorbent assay. Data are shown for 48 healthy subjects, 43 patients with myasthenia gravis (MG), 25 patients with multiple sclerosis (MS), and 3 patients with amyotrophic lateral sclerosis (ALS). Each point represents an individual. The line denotes the mean.

SERUM IMMUNOGLOBULIN MEASUREMENTS

Serum IgG, IgA, and IgM were measured by a radial immunodiffusion assay (The Binding Site, Birmingham, England). Briefly, serum was added to a well cut into an agarose gel containing monoclonal antibodies to IgG, IgA, or IgM. The IgG, IgA, or IgM in the serum diffused radially and a precipitin ring formed. The diameter of the ring was proportional to the concentration of IgG, IgA, or IgM in the serum sample. The assay was calibrated using IgG, IgA, and IgM standards of known concentration. The concentrations of IgG standards were 2250, 13 500, and 22 500 mg/L. The concentrations of IgA standards were 545, 3270, and 5450 mg/L. The concentrations of IgM standards were 265, 1590, and 2650 mg/L.

ANTI-AChR AND ANTI-MuSK

Titers of anti-AChR antibodies were determined by commercial laboratories at different times. Titers of anti-MuSK antibodies were determined by Angela Vincent, MD, at Oxford University.

STATISTICAL ANALYSIS

Linear regression analysis, the 2-tailed nonparametric Mann-Whitney test, and the nonparametric 1-way analysis of variance (Kruskal-Wallis test) were used. $P<.05$ was considered significant.

RESULTS

The BAFF levels in patients with MG were compared with those in patients with MS, a disease with an autoimmune pathogenesis that is considered to be T cell initiated.[21] The BAFF levels in patients with MG were also

Table. Mean BAFF Levels[a]

Subjects	ng/mL	
	BAFF Level, Mean (SD) (SEM)	95% Confidence Interval
Healthy subjects	1.264 (0.56) (0.08)	1.102-1.426
Patients with MG	1.810 (0.93) (0.14)	1.525-2.095
Patients with MS	1.141 (0.45) (0.09)	0.955-1.328
Patients with ALS	1.130 (0.23) (0.13)	0.562-1.698
All control subjects[b]	1.201 (0.51) (0.06)	1.091-1.312

Abbreviations: ALS, amyotrophic lateral sclerosis; BAFF, B-cell activating factor; MG, myasthenia gravis; MS, multiple sclerosis.

[a] Patients with MG vs healthy subjects, $P<.001$; patients with MG vs patients with MS, $P<.001$; patients with MG vs patients with ALS, $P=.050$; patients with MG vs all control subjects, $P<.001$.

[b] All control subjects includes healthy subjects, patients with MS, and patients with ALS.

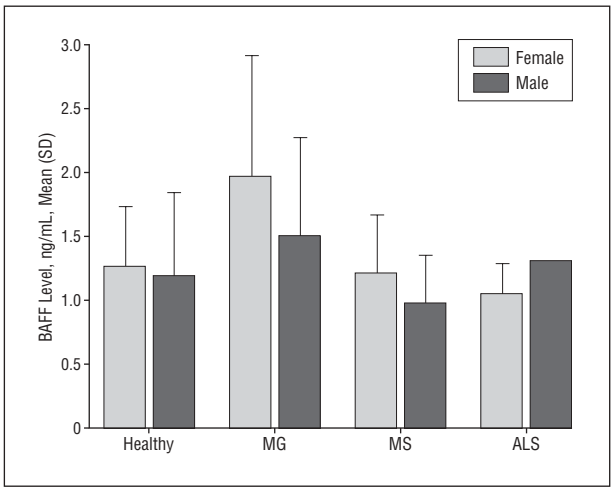

Figure 2. Effect of sex on serum B-cell activating factor (BAFF) levels. MG indicates myasthenia gravis; MS, multiple sclerosis; and ALS, amyotrophic lateral sclerosis.

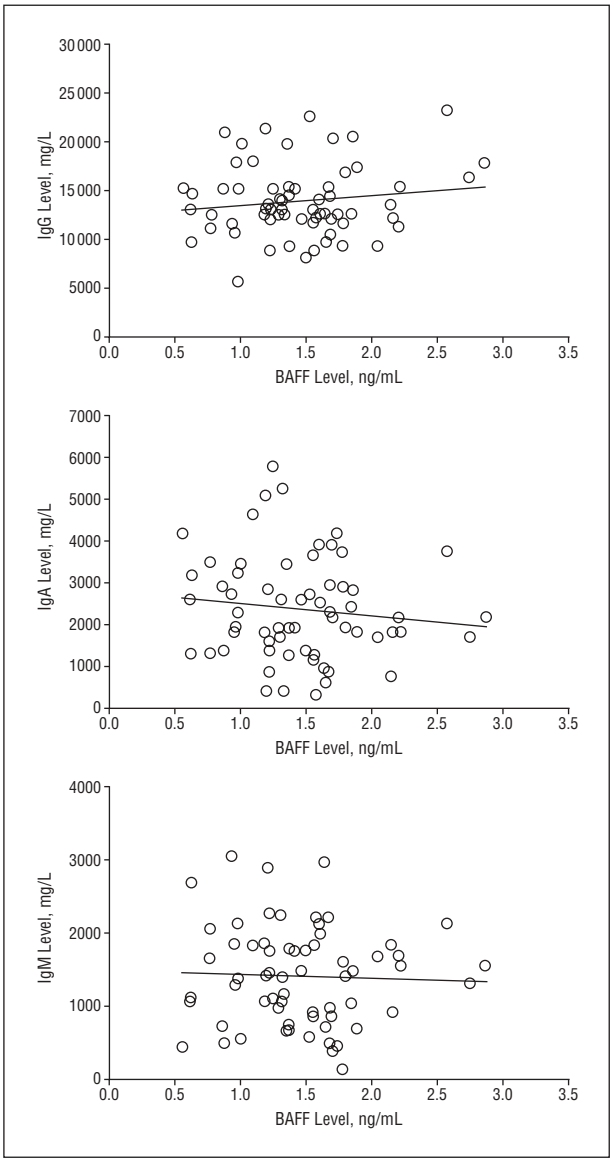

Figure 3. Correlation of B-cell activating factor (BAFF) levels with IgG, IgA, and IgM levels. The BAFF levels were measured by enzyme-linked immunosorbent assay. IgG, IgA, and IgM levels were measured by radial immunodiffusion. Each point represents an individual. The goodness of fit by linear regression analysis was IgG, $r^2=0.0190$; $P=.28$; IgA, $r^2=0.0140$; $P=.35$; and IgM, $r^2=0.0015$; $P=.76$

compared with those in patients with ALS, a neurodegenerative disorder whose pathogenesis is unknown but is not considered to be immune mediated.[22] **Figure 1** shows the serum BAFF levels in patients with MG, MS, and ALS in comparison with those in healthy subjects.

As the **Table** shows, BAFF levels in patients with MS or patients with ALS were not significantly different from those in healthy subjects. However, BAFF levels in patients with autoimmune MG were significantly higher than those in healthy subjects ($P<.001$) and higher than those in patients with MS ($P<.001$) and ALS ($P=.050$). When patients with MG were compared with all the control subjects (healthy subjects, patients with MS, and patients with ALS together), BAFF levels in the serum of patients with MG were significantly higher ($P<.001$). The mean (SD) (SEM) for patients with MG was 1.810 (0.93) (0.14) ng/mL with a 95% confidence interval of 1.525 to 2.095 ng/mL. The mean (SD) (SEM) for all control subjects was 1.201 (0.51) (0.06) ng/mL with a 95% confidence interval of 1.091 to 1.312 ng/mL. As **Figure 2** shows, for patients with MG, BAFF levels were slightly higher in female patients compared with their male counterparts; however, the difference was not statistically significant ($P>.05$). For female patients with MG (n=29), the mean (SD) BAFF level was 1.96 (0.96) ng/mL. For male patients with MG (n=14), the mean (SD) BAFF level was 1.50 (0.78) ng/mL.

To determine whether there was a correlation between the serum BAFF level and immunoglobulin concentration, we measured IgG, IgA, and IgM levels in the serum. Of the 119 subjects included in this study, 64 sera were randomly chosen. There was no correlation between the serum BAFF levels and the serum IgG, IgA, or IgM levels in any of the subject groups. **Figure 3** shows the correlation of BAFF levels with serum immunoglobulin levels for all subject groups together. Linear regression analysis showed that the goodness of fit of BAFF levels with the serum immunoglobulin levels was IgG, $r^2=0.0190$; IgA, $r^2=0.0140$; and IgM, $r^2=0.0015$.

Patients with autoimmune MG were divided into groups by the extent and severity of their clinical signs and symptoms (**Figure 4**). For each class, the mean (SD) (SEM) BAFF level was class 1, 1.69 (0.47) (0.21) ng/mL; class 2, 1.49 (0.51) (0.14) ng/mL; class 3, 2.01 (0.62) (0.16) ng/mL; and class 4, 1.50 (0.41) (0.18) ng/mL. There was no correlation or dependence between the serum BAFF level and the extent or severity of disease (analysis of variance, $P=.14$). However, patients who were seropositive for anti-AChR antibodies tended to have higher serum BAFF levels than seronegative patients (**Figure 5**). This trend did not reach statistical significance ($P=.13$). For seronegative patients with MG, the mean (SD) (SEM) BAFF level was 1.59 (0.46) (0.11) ng/mL with a 95% confidence interval of 1.37 to 1.82 ng/mL. For seropositive patients with MG, the mean (SD) (SEM) BAFF level was 2.13 (1.22) (0.28) ng/mL with a 95% confidence interval of 1.54 to 2.72 ng/mL. Three of the seronegative patients were seropositive for anti-MuSK antibodies. There was no correlation between the serum BAFF level and anti-MuSK antibody titer (data not shown; $r^2=0.0920$; $P=.80$).

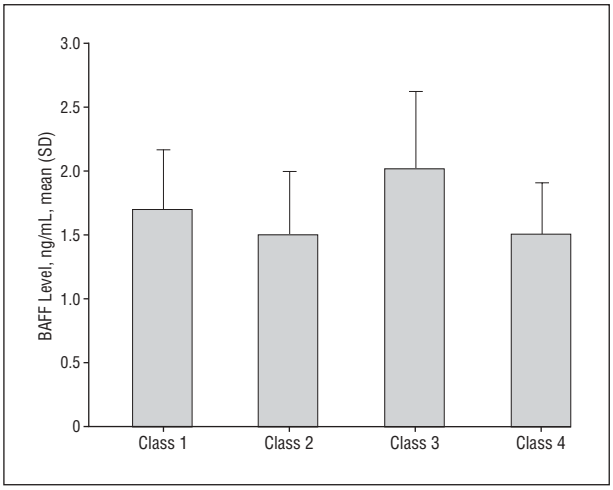

Figure 4. Effect of disease extent and severity on serum B-cell activating factor (BAFF) levels. The extent of disease and severity of symptoms were graded according to the Myasthenia Gravis Foundation of America clinical classification scale.

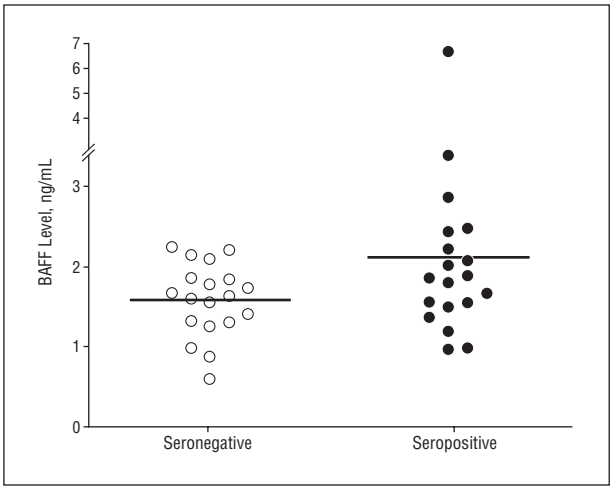

Figure 5. Effect of absence or presence of serum anti–acetylcholine receptor antibodies on serum B-cell activating factor (BAFF) levels. Each point represents an individual patient with myasthenia gravis. The line denotes the mean.

COMMENT

In human autoimmune disease, patients with systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, and celiac disease are reported to have increased serum levels of BAFF.[23-26] In this study, we demonstrate that serum BAFF levels are increased in patients with MG. We compared patients with autoimmune MG with healthy subjects, patients with MS (an immune-mediated disease with a major role for a T cell–initiated pathogenesis), and patients with ALS (a nonimmune-mediated peripheral nervous system neurodegenerative disease). Patients, regardless of diagnosis, who were receiving immunomodulatory therapy were excluded from the study. Our data show that BAFF levels in the serum of patients with MG were significantly higher than those of all the control subject groups.

Previous studies have shown that the frequency of B cells in the circulation is not increased in patients with autoimmune MG.[6] In this study, we found no difference in the serum concentrations of immunoglobulins (IgG, IgA, and IgM) between patients with MG and controls without MG (data not shown). Furthermore, there was no correlation between BAFF levels and the concentration of IgG, IgA, or IgM in the serum. Therefore, although BAFF-transgenic animals exhibit hypergammaglobulinemia, the increased BAFF levels in patients with autoimmune MG do not result in increased levels of circulating immunoglobulins.

We found no association between the serum BAFF level and the extent or severity of disease in patients with MG. This was not surprising, as previous studies have shown that there is no correlation between the serum titer of anti-AChR antibodies and disease severity.[5] There was a trend for BAFF levels to be higher in anti-AChR–seropositive patients, although the difference in BAFF levels between seropositive and seronegative patients did not reach statistical significance. We did not attempt to correlate the serum BAFF level with the titer of anti-AChR antibodies because the titers were determined by several different commercial laboratories. Based on 3 patients who were seropositive for anti-MuSK antibodies, there was no correlation between the BAFF level and the anti-MuSK antibody titer.

In autoimmune MG, dysregulation of immune signals promotes the survival, activation, and maturation of autoreactive AChR-specific B cells. Data from several laboratories demonstrate enhanced B-cell activation in patients with MG, particularly those with thymic follicular hyperplasia.[5,6,12,13,27,28] Follicular dendritic cells, and other myeloid cells, control B-cell growth, survival, and differentiation, but their role in the pathogenesis of autoimmune MG has not been thoroughly investigated. The mechanism(s) by which BAFF and its receptors regulate human B-cell function and tolerance is not known. Because autoreactive B cells are poorly competitive for survival, they are likely to have an increased depen-

dence on BAFF for survival.[29,30] In patients with thymic follicular hyperplasia, it is thought that the germinal center environment is providing signals that promote AChR-specific B-cell survival and activation. Yet these signals are not known. A recent study shows that the myasthenic thymus does express BAFF.[31] Our data on serum BAFF levels show that BAFF is likely to play a role in the pathogenesis of the disease. Furthermore, the frequency of B cells that express the BAFF receptor appears to be higher in patients with MG.[32] We propose that dysregulation of the BAFF/receptor system in MG allows autoreactive B cells to survive and mature.

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Correspondence: Samia Ragheb, PhD, Wayne State University, 3128 Elliman Bldg, 421 E Canfield Ave, Detroit, MI 48201 (sragheb@med.wayne.edu).
Author Contributions: *Study concept and design:* Ragheb and Lisak. *Acquisition of data:* Ragheb, Lisak, Lewis, Van Stavern, Gonzales, and Simon. *Analysis and interpretation of data:* Ragheb, Lisak, and Simon. *Drafting of the manuscript:* Ragheb, Lisak, Lewis, Gonzales, and Simon. *Critical revision of the manuscript for important intellectual content:* Ragheb, Lisak, and Van Stavern. *Obtained funding:* Ragheb and Lisak. *Administrative, technical, and material support:* Ragheb, Lisak, Van Stavern, Gonzales, and Simon. *Study supervision:* Ragheb and Lisak.
Financial Disclosure: None reported.
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Additional Contributions: Angela Vincent, MD, measured the levels of anti-MuSK antibodies.

REFERENCES

1. Ragheb S, Lisak RP. The immunopathogenesis of acquired (autoimmune) myasthenia gravis. In: Lisak RP, ed. *Handbook of Myasthenia Gravis and Myasthenic Syndromes.* New York, NY: Dekker; 1994:239-276.
2. Evoli A, Tonali PA, Padua L, et al. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. *Brain.* 2003;126(pt 10):2304-2311.
3. Sanders DB, El-Salem K, Massey JM, McConville J, Vincent A. Clinical aspects of MuSK antibody positive seronegative MG. *Neurology.* 2003;60(12):1978-1980.
4. Tzartos SJ, Lindstrom JM. Monoclonal antibodies used to probe acetylcholine receptor structure: localization of the main immunogenic region and detection of similarities between subunits. *Proc Natl Acad Sci U S A.* 1980;77(2):755-759.
5. Lindstrom JM, Seybold ME, Lennon VA, Whittingham S, Duane D. Antibody to acetylcholine receptor in myasthenia gravis: prevalence, clinical correlates and diagnostic value. *Neurology.* 1976;26(11):1054-1059.
6. Ragheb S, Bealmear B, Lisak R. Cell-surface expression of lymphocyte activation markers in myasthenia gravis. *Autoimmunity.* 1999;31(1):55-66.
7. Wekerle H, Ketelsen UP, Zurn AP, Fulpius BW. Intrathymic pathogenesis of myasthenia gravis: transient expression of acetylcholine receptors on thymus-derived muscle cells. *Eur J Immunol.* 1978;8(8):579-583.
8. Ragheb S, Lisak RP. The thymus and myasthenia gravis. In: Kirschner PA, ed. *Chest Surgery Clinics of North America: The Thymus.* Philadelphia, PA: Saunders; 2001:311-327.
9. Sims GP, Shiono H, Willcox N, Stott DI. Somatic hypermutation and selection of B cells in thymic germinal centers responding to acetylcholine receptor in myasthenia gravis. *J Immunol.* 2001;167(4):1935-1944.
10. Murai H, Hara H, Hatae T, Kobayashi T, Watanabe T. Expression of CD23 in the germinal center of thymus from myasthenia gravis patients. *J Neuroimmunol.* 1997;76(1-2):61-69.
11. Liu Y-J, Mason DY, Johnson GD, et al. Germinal center cells express bcl-2 protein after activation by signals which prevent their entry into apoptosis. *Eur J Immunol.* 1991;21(8):1905-1910.
12. Onodera J, Nakamura S, Nagano I, et al. Upregulation of bcl-2 in the myasthenic thymus. *Ann Neurol.* 1996;39(4):521-528.
13. Shiono H, Fujii Y, Okumura M, Takeuchi Y, Inoue M, Matsuda H. Failure to down-regulate Bcl-2 protein in thymic germinal center B cells in myasthenia gravis. *Eur J Immunol.* 1997;27(4):805-809.
14. Moore PA, Belvedere O, Orr A, et al. Blys: member of the tumor necrosis factor family and B lymphocyte stimulator. *Science.* 1999;285(5425):260-263.
15. Schneider P, MacKay F, Steiner V, et al. BAFF, a novel ligand of the tumor necrosis factor family, stimulates B cell growth. *J Exp Med.* 1999;189(11):1747-1756.
16. Nardelli B, Belvedere O, Roschke V, et al. Synthesis and release of B-lymphocyte stimulator from myeloid cells. *Blood.* 2001;97(1):198-204.
17. Mackay F, Schneider P, Rennert P, Browning J. BAFF and APRIL: a tutorial on B cell survival. *Annu Rev Immunol.* 2003;21:231-264.
18. Do RKG, Hatada E, Lee H, Tourigny MR, Hilbert D, Chen-Kiang S. Attenuation of apoptosis underlies B lymphocyte stimulator enhancement of humoral immune response. *J Exp Med.* 2000;192(7):953-964.
19. Craxton A, Draves KE, Gruppi A, Clark EA. Baff regulates B cell survival by down-regulating the BH3-only family member Bim via the ERK pathway. *J Exp Med.* 2005;202(10):1363-1374.
20. Jaretzki A, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. *Neurology.* 2000;55(1):16-23.
21. Sospedra M, Martin R. Immunology of multiple sclerosis. *Annu Rev Immunol.* 2005;23:683-747.
22. Gonzalez de Aguilar JL, Echaniz-Laguna A, Fergani A, et al. Amyotrophic lateral sclerosis: all roads lead to Rome. *J Neurochem.* 2007;101(5):1153-1160.
23. Cheema GS, Roschke V, Hilbert DM, Stohl W. Elevated serum B lymphocyte stimulator levels in patients with systemic immune-based rheumatic diseases. *Arthritis Rheum.* 2001;44(6):1313-1319.
24. Zhang J, Roschke V, Baker KP, et al. A role of B lymphocyte stimulator in systemic lupus erythematosus. *J Immunol.* 2001;166(1):6-10.
25. Groom J, Kalled SL, Cutler AH, et al. Association of BAFF/Blys overexpression and altered B cell differentiation with Sjogren's syndrome. *J Clin Invest.* 2002;109(1):59-68.
26. Fabris M, Visentini D, De Re V, et al. Elevated B cell-activating factor of the tumor necrosis factor family in coeliac disease. *Scand J Gastroenterol.* 2007;42(12):1434-1439.
27. Scadding GK, Vincent A, Newsom-Davis J, Henry K. Acetylcholine receptor antibody synthesis by thymic lymphocytes: correlation with thymic histology. *Neurology.* 1981;31(8):935-943.
28. Levinson AI, Zweiman B, Lisak RP, Dziarski A, Moskovitz AR. Thymic B-cell activation in myasthenia gravis. *Neurology.* 1984;34(4):462-468.
29. Cyster JG, Hartley SB, Goodnow CC. Competition for follicular niches excludes self-reactive cells from the recirculating B-cell repertoire. *Nature.* 1994;371(6496):389-395.
30. Thien M, Phan TG, Gardam S, et al. Excess BAFF rescues self-reactive B cells from peripheral deletion and allows them to enter forbidden follicular and marginal zone niches. *Immunity.* 2004;20(6):785-798.
31. Thangarajh M, Masterman T, Helgeland L, et al. The thymus is a source of B-cell-survival factors—APRIL and Baff—in myasthenia gravis. *J Neuroimmunol.* 2006;178(1-2):161-166.
32. Li X, Xiao B-G, Xi J-Y, Lu C-Z, Lu J-H. Decrease of $CD4^+CD25^{high}Foxp3^+$ regulatory T cells and elevation of $CD19^+$ BAFF-R^+ B cells and soluble ICAM-1 in myasthenia gravis. *Clin Immunol.* 2008;126(2):180-188.

Long-Term Follow-up of Botulinum Toxin Therapy for Focal Hand Dystonia: Outcome at 10 Years or More

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ABSTRACT

Background: Previous studies have explored the efficacy and safety of botulinum neurotoxin (BoNT) treatment for Focal hand dystonia (FHD), but none have followed a large number of patients for 10 years or more.

Methods: Retrospective study, with benefit and weakness assessed on a 0 to 4 subjective scale. Demographic, clinical and treatment characteristics were analyzed using *t* tests and Pearson correlations.

Results: Twenty FHD patients had 10 years or longer treatment. Interinjection intervals were variable. Musicians were more likely to wait longer between injections and had less complex dystonia. There was a trend for larger benefit in women and with shorter intervals. The dose increased over time. Dystonia characteristics did not predict response or side-effects, but benefit magnitude predicted longer compliance. No serious side-effects or antibody-mediated resistance occurred.

Conclusion: This is the longest reported period of BoNT treatment in the largest FHD cohort. BoNT therapy for FHD remains safe and effective after more than a decade of treatment.

Key Words: botulinum; dystonia; focal hand dystonia; safety; efficacy

Introduction

Focal hand dystonia (FHD) is a task specific focal dystonia.[1] Botulinum neurotoxin (BoNT) injection is an effective treatment,[2,3] reducing pathologic neuromuscular junction hyperactivity.[4] We previously reported the safety and effectiveness of BoNT injections for FHD in patients receiving injections for up to 6 years.[5] We continue to follow a large cohort, with 20 patients now treated for 10 years or longer.

Subjects and Methods

Patients

Patients were selected from the NIH BoNT clinic database. Diagnosis was established by initial evaluation and confirmed by ongoing observation.

BoNT Injections

Subjects returned for repeat treatment when they felt that reinjection was necessary, no more frequently than every 3 months. The initial dose and targets were based on clinical judgment,[6] with the starting dose chosen at the lower end of the range and subsequent adjustments. Injections were performed under EMG guidance, as previously described,[7] rarely supplemented by ultrasound. OnabotulinumtoxinA (Botox®, Allergan) at a concentration of 50 to 100 U/mL was used for each injection, except one single injection of RimabotulinumtoxinB (Myobloc®, Solstice Neurosciences) in one patient.

Patient Evaluations

Muscle strength was assessed using the MRC scale. The toxin distribution and dose were adjusted based on report of weakness and benefit from previous injections. Benefit was assessed on a subjective scale from 0 to 4, based on percent restoration of normal function: 0 = none, 1 = minimal (1–25% restoration of function), 2 = mild (26–50%), 3 = moderate (51–75%), 4 = excellent (76–100%). The patients self-assessed weakness following the previous injection using a similar scale, as 0 (none), 1 (<25% reduction in normal strength), 2 (26–50%), 3 (51–75%), or 4 (76–100%). The rating procedures and treatment guidelines were consistent throughout the study, and all the information was charted in a Microsoft Access database.

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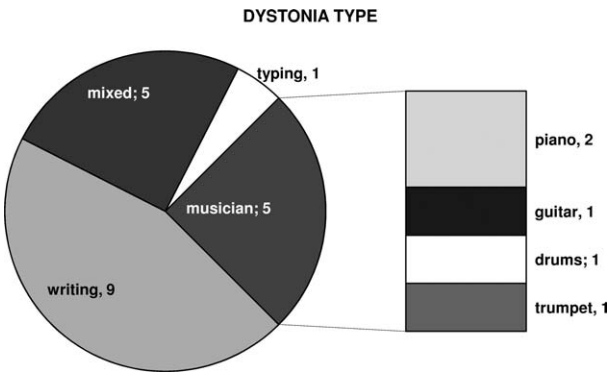

FIG. 1. Distribution of patients by FHD type.

Data Analysis

Student's *t* test and Pearson correlations were used, with $P < 0.05$ as significance threshold. All averages are presented ± standard deviation.

Results

Out of 440 patients in our database, 214 patients with FHD have been treated at least once; 20 patients continued treatment 10 years or more. Five patients had professional musician's dystonia and 15 were employed in clerical positions. Dystonia types are shown in Figure 1. Demographic and treatment characteristics are presented in Table 1.

The musicians were more likely to wait longer between injections (19.9 ± 12.4 months for musicians vs. 7.7 ± 2.3 for nonmusicians, $P < 0.002$). There was a trend for shorter interinjection intervals to be associated with higher benefit (Pearson = −0.44, $0.05 < P < 0.1$).

Most patients (11 of 20) experienced mild average benefit (grade 2). Weakness was similarly mild with 9 of 20 reporting an average grade 2 weakness, with no correlation between benefit and weakness. There was a trend towards larger benefit in women (55.9% ± 15.2% in women vs. 37.4% ± 19.5% in men, $P = 0.057$).

The patients received a higher mean dose at the end of the follow-up period compared to the initial treatment (49.9 vs. 24.9 units respectively, $P < 0.00005$). Since the first dose is typically purposefully low, we repeated the analysis excluding the first injection, with similar results (49.9 vs. 31.0 units, $P < 0.002$). The benefit was higher with the last injection compared to the initial (47.3% vs. 26%, $P = 0.039$). No significant correlation was found between dose and benefit at each visit, or between dose and weakness.

To evaluate possible outcome predictors, we performed subanalyses looking at the number of muscle groups injected, divided into: supinator or pronator, hand intrinsics, forearm flexors, forearm extensors, and proximal muscles. Eighteen of twenty patients had involvement of the forearm flexors, 16 of the extensors, 9 of the intrinsic hand muscles, 6 of the pronators or supinators, and 4 of proximal arm or shoulder muscles. Most patients had involvement of more than one muscle group, average 1.7 ± 0.8 in musicians versus 3.1 ± 0.8 in nonmusicians, $P = 0.003$. This number did not correlate with either benefit or weakness.

No patients developed immunity over the duration of follow-up. All patients tolerated the discomfort of multiple injections well; none discontinued treatment due to discomfort. There were no serious adverse effects.

Eleven of the 20 patients are still receiving injections in our clinic. Two patients discontinued treatment due to insufficient response after 5 and 26 visits, respectively. Two moved out of the area and five were lost to follow-up.

We compared this group with the patients who had less than 10 years of treatment. Among the latter, a higher proportion were professional musicians (58% vs. 25%). The patients who discontinued therapy after less than 10 years had significantly lower benefit with the last injection (32% vs. 47.2%, $P < 0.005$), and the most common reason for discontinuation was insufficient benefit (62.5%).

Discussion

This is the largest FHD cohort with the longest follow-up period reported to date. Few prior reports focused on FHD; most included only a few patients in larger dystonia populations and none followed subjects for as long as 10 years.[8–11] We previously published the 6-year outcome in our cohort[5] and Marion et al. reported 9 patients followed for 5 years or more.[12] This study extends observation to a larger cohort and longer follow-up.

Our patients were demographically typical of the FHD population, with writer's cramp the most common type. There was large variability in the frequency of treatments, likely reflecting the fact that while FHD makes particular activities difficult or impossible, it is not otherwise disabling or painful. Patients therefore often tolerate the symptoms and arrange their injections based on anticipated activities. Professional musicians often timed treatments to obtain peak effect around scheduled performances. Since BoNT effects lasted on average 3 months, the long interval between injections is not related to an extended duration of action.

There was a trend for higher benefit in patients returning for treatments at shorter intervals. It is

Table 1. Patient demographics and treatment characteristics

Variable	Value
Total number of patients	20
Gender, n (%), male/female	15 (75)/5 (25)
Age at first injection (yrs, avg. ± STD)	46.6 ± 9.45
Age at dystonia onset (yrs, avg. ± STD)	37.1 ± 9.8
Duration of follow-up (yrs, avg. ± STD)	13.6 ± 2.5
Number of visits (avg. ± STD)	19.7 ± 9.9
Average dose (BoNT A units ± STD)	46.4 ± 24.6
Interinjection interval (avg. ± STD)	11.3 ± 8.8

possible that earlier reinjection enhances residual benefit from prior treatments. As noted in earlier studies,[5,13] we found no correlation between dose and benefit. Accurate selection, localization and dose adjustments are likely more important outcome determinants.[14,15]

Our cohort required a gradual increase in dose over time. This is only partly explained by the choice of a low initial dose, since the gradual increase continued over the later years of treatment. As benefit also increased, it is possible that tolerance led to less weakness with a given dose, allowing higher doses and improved benefit. This dynamic has been seen in some previous studies,[8] but not in others.[5,16]

There is a large range of response to BoNT injections. We were unable to identify factors that predict an individual's response, other than a strong tendency for women to respond better, possibly explained by a smaller muscle mass allowing the toxin to diffuse more readily to the motor endplate in women. Previous studies proposed an inverse relation between dystonia complexity and benefit, with subjects requiring injection of more muscles benefiting less.[7,17] We did not confirm this, finding no such correlation.

The professional musicians in our cohort required injection of fewer muscles, possibly reflecting the exquisite task specificity of musician's dystonia. The need to maintain finely skilled motor control and to minimize weakness is crucial for musicians,[18–20] and the fewer muscles injected might also reflect the need to minimize weakness. We also note a smaller proportion of musicians among the patients continuing treatment more than 10 years compared to the rest of our cohort, which may be indicative of a higher threshold for satisfactory benefit.

None of the patients followed for more than 10 years developed immunity despite exposure to the first Botox (Allergan) batch, which was associated with antibodies developing in 10% of cervical dystonia treatments. The newer formulation is less immunogenic,[21] and immunoresistance tends to develop in the first 4 years of treatment.[22] We show that the risk of developing immunoresistance after more than one decade of FHD treatment is low.

Among the patients who stopped BoNT therapy while under our care, the most common reason was insufficient benefit. The average benefit at the last visit before stopping was significantly lower than the average benefit in patients continuing therapy for more than 10 years, suggesting that magnitude of benefit is an important factor determining continuation of therapy.

It is important to analyze the long-term outcome data for FHD separate from other dystonias, since the BoNT response rates differ. FHD has a lower overall response rate, with about 50% of patients receiving at least mild benefit compared to 80% for cervical dystonia and over 90% for blepharospasm.[23,24]

This study is limited in that it is retrospective and uncontrolled, which limits the strength of any conclusion. In addition, our primary outcome assessments are self-reported scales of benefit and weakness. All FHD research shares this limitation, as there are no widely accepted rating scales applicable to all FHD types.

Patients continued therapy for over 10 years in spite of only mild benefit, suggesting that even partial improvement may be worthwhile. BoNT injections maintained efficacy for over a decade, with good tolerability and no new side effects emergent with long-term treatment. ■

References

1. Sheehy MP, Marsden CD. Writers' cramp-a focal dystonia. Brain 1982;105 (Part 3):461–480.
2. Kruisdijk JJ, Koelman JH, Ongerboer de Visser BW, et al. Botulinum toxin for writer's cramp: a randomised, placebo-controlled trial and 1-year follow-up. J Neurol Neurosurg Psychiatr 2007;78: 264–270.
3. Simpson DM, Blitzer A, Brashear A, et al. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the therapeutics and technology assessment subcommittee of the American academy of neurology. Neurology 2008;70:1699–1706.
4. Grumelli C, Verderio C, Pozzi D, et al. Internalization and mechanism of action of clostridial toxins in neurons. Neurotoxicology 2005;26:761–767.
5. Karp BI, Cole RA, Cohen LG, et al. Long-term botulinum toxin treatment of focal hand dystonia. Neurology 1994;44:70–76.
6. Karp BI. Botulinum toxin treatment of occupational and focal hand dystonia. Mov Disord 2004;19 (Suppl 8):S116–S119.
7. Cohen LG, Hallett M, Geller BD, Hochberg F. Treatment of focal dystonias of the hand with botulinum toxin injections. J Neurol Neurosurg Psychiatr 1989;52:355–363.
8. Mejia NI, Vuong KD, Jankovic J. Long-term botulinum toxin efficacy, safety, and immunogenicity. Mov Disord 2005;20: 592–597.
9. Hsiung GY, Das SK, Ranawaya R, et al. Long-term efficacy of botulinum toxin A in treatment of various movement disorders over a 10-year period. Mov Disord 2002;17:1288–1293.
10. Naumann M, Albanese A, Heinen F, et al. Safety and efficacy of botulinum toxin type A following long-term use. Eur J Neurol 2006;13 (Suppl 4):35–40.
11. Chen R, Karp BI, Hallett M. Botulinum toxin type F for treatment of dystonia: long-term experience. Neurology 1998;51: 1494–1496.
12. Marion MH, Afors K, Sheehy MP. [Problems of treating writer's cramp with botulinum toxin injections: results from 10 years of experience]. Rev Neurol (Paris) 2003;159(10 Part 1):923–927.
13. Yoshimura DM, Aminoff MJ, Olney RK. Botulinum toxin therapy for limb dystonias. Neurology 1992;42(3 Part 1):627–630.
14. Comella CL, Buchman AS, Tanner CM, et al. Botulinum toxin injection for spasmodic torticollis: increased magnitude of benefit with electromyographic assistance. Neurology 1992;42:878–82.
15. Molloy FM, Shill HA, Kaelin-Lang A, Karp BI. Accuracy of muscle localization without EMG: implications for treatment of limb dystonia. Neurology 2002;58:805–807.
16. Lees AJ, Turjanski N, Rivest J, et al. Treatment of cervical dystonia hand spasms and laryngeal dystonia with botulinum toxin. J Neurol 1992;239:1–4.
17. Rivest J, Lees AJ, Marsden CD. Writer's cramp: treatment with botulinum toxin injections. Mov Disord 1991;6:55–59.
18. Jankovic J, Ashoori A. Movement disorders in musicians. Mov Disord 2008;23:1957–1965.
19. Frucht SJ. Focal task-specific dystonia of the musicians' hand—a practical approach for the clinician. J Hand Ther 2009;22: 136–142.
20. Cole R, Hallett M, Cohen LG. Double-blind trial of botulinum toxin for treatment of focal hand dystonia. Mov Disord 1995;10:466–471.
21. Jankovic J, Vuong KD, Ahsan J. Comparison of efficacy and immunogenicity of original versus current botulinum toxin in cervical dystonia. Neurology 2003;60:1186–1188.

22. Jankovic J, Schwartz K. Response and immunoresistance to botulinum toxin injections. Neurology 1995;45:1743–1746.
23. Hallett M, Benecke R, Blitzer A, Comella CL. Toxicon. 2009. 54(5):628–633.
24. Jankovic J. Botulinum toxin therapy for cervical dystonia. Neurotox Res 2006;9:145–148.

Mitochondrial Mimicry of Multiple System Atrophy of the Cerebellar Subtype

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ABSTRACT

Background: We describe a patient with clinical and radiological findings suggestive of multiple system atrophy of the cerebellar subtype (MSA-C). **Methods/Results:** Sequencing of the polymerase-γ 1 (*POLG1*) gene revealed the patient had compound heterozygous mutations of the *POLG1* gene. Muscle biopsy revealed the presence of multiple mitochondrial DNA deletions and depletion, confirming the pathogenic nature of the *POLG1* mutations. **Discussion:** This case expands the spectrum of phenotypes associated with *POLG1* mutations to include multiple system atrophy and prompts further consideration regarding whether routine screening for *POLG1* mutations is indicated in this patient population.

Key Words: mitochondrial disease; multiple system atrophy; polymerase gamma gene; parkinsonism; ataxia

Mitochondrial disorders can result from either primary defects in the mitochondrial DNA (mtDNA) or defects in nuclear encoded proteins that affect mtDNA structure or function. The maintenance of mtDNA replication is critically dependent upon mtDNA polymerase-γ,[1] encoded by the nuclear genes *POLG1* and *POLG2*. Mutations in *POLG1* have been described in patients with diverse clinical presentations that include parkinsonism and cerebellar ataxia.[2]

Here, for the first time, we describe a patient who presented with clinical and radiological findings suggestive of multiple system atrophy (MSA) of the cerebellar subtype (MSA-C), but was shown to have mutations of *POLG1*. This case highlights the importance of considering primary mitochondrial disorders in the differential diagnosis of parkinsonian syndromes.[3,4]

Case Report

Written informed consent was obtained from the patient to publish both video and brain imaging results for this case report. This 58-year-old woman had a progressive cerebellar syndrome. Her symptoms had started 9 years prior, with imbalance when getting out of a canoe or when walking up and down stairs. She also noted poor handwriting and mild incoordination of the hands. Her speech had become slurred. Her symptoms worsened toward the end of the day or when she was fatigued. In addition, the symptoms partially improved after excluding dietary gluten and she had lost 18 kg over the previous year. She had mild urinary incontinence when coughing. She has type II diabetes mellitus, treated with Pioglitazone. There is no history of epilepsy, cognitive problems, visual problems, stroke-like episodes, hearing problems, or menstrual disturbances. Her family history revealed that she had a sister who died at 2 years of age. This child, who was blind, was never able to roll, sit, or walk independently, and she also had intractable seizures. No diagnosis was ever established. The proband's brother has sensorineural hearing loss, glaucoma, and adult-onset diabetes mellitus requiring treatment with insulin.

On initial examination, 4 years after the onset of her symptoms, she had slight slowing of vertical saccades but a full range of eye movements and normal fundi. She had dysarthria, mild limb dysmetria that was worse on the left, mild slowing of foot taps bilaterally, and a mildly impaired tandem gait; tone and reflexes were normal with flexor plantar responses (see Supporting Information video). Investigations for coeliac

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Additional Supporting Information may be found in the online version of this article.

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Extreme Task Specificity in Writer's Cramp

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ABSTRACT

Background: Focal hand dystonia may be task specific, as is the case with writer's cramp. In early stages, task specificity can be so specific that it may be mistaken for a psychogenic movement disorder. **Methods:** We describe 4 patients who showed extreme task specificity in writer's cramp. They initially only had problems writing either a single letter or number. Although they were largely thought to be psychogenic, they progressed to typical writer's cramp. **Conclusions:** Early recognition of this condition may provide an opportunity for early initiation of treatment. © 2011 *Movement* Disorder Society

Key Words: dystonia; movement disorders; clinical neurology

Dystonias are characterized by excessive involuntary contractions of muscles leading to abnormal posturing. Dystonias that affect discrete body parts, such as focal hand dystonia (FHD), may be task specific. Typically, FHD occurs in individuals who repeatedly perform very precise tasks for prolonged periods, usually under stressful conditions. As a result, musicians, typists, dart throwers, billiard players, and others can be affected with life-altering dysfunctions. Animal models have shown the importance of repetitive activities in the development of writer's cramp (WC).[1] Hereditary factors are also important.[2]

Task specificity in FHD is poorly understood. All other aspects of hand function are usually unaffected and the neurological examination is normal. Since the initial recorded description of task specificity in FHD by Sir Charles Bell[3] and the description of WC by Gowers[4] in the 1800s, this specificity has puzzled clinicians. The unusual task specificity led to it being classified as a psychogenic movement disorder until the 1980s, when it was recognized, together with other dystonias, as an organic entity.[5] Here, we describe 4 patients who had "extreme task specificity" as an early manifestation of WC. Three of the four initially were thought to have a psychogenic movement disorder.

Patients and Methods

Patient 1

A 55-year-old right-handed Caucasian male presented with a 1-year history of difficulty in signing his name. He signed his name 200 to 1,000 times per day for the past several years under stressful conditions where deadlines had to be met and employees and bills had to be paid. His initial symptom was difficulty with initiating his signature, which starts with the letter "J" (Video 1). Only in the context of signing his name was this difficult. Initially, when he printed or wrote this letter in other contexts, there were no

Additional Supporting Information may be found in the online version of this article.

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problems. Later, he began to have trouble with the letter "J" even in other contexts, and a diagnosis of WC was more obvious.

On examination, he used excessive pressure while writing and had mirror movements with his right hand when he wrote with the left; his neurological examination was otherwise normal. Using a stamp to sign his name has been very helpful.

Patient 2

A 49-year-old left-handed Caucasian male presented with a 3-year history of progressive difficulty in writing the number "7." He only had trouble making the vertical line down. This progressed to involve the number "9" and the letter "C," in the same manner. He felt a cramping sensation in the forearm while making these vertical lines. Writing the number "1" was not a problem. He later had difficulty with all aspects of writing (Video 2). He was a mechanic for over 20 years. Three years ago, he started carving birds for 2 hours daily. His free time was spent carving, which required him to make very precise short vertical movements with his hands, using the right index finger and thumb to stabilize the carving tool. He had to be gentle yet forceful when making these repetitive movements of the arm, hand, wrist, and finger. Ultimately, he had difficulty carving.

His neurological examination showed mirror movements in his left hand while writing with his right hand. He held the pen in an awkward position with fingers and wrists flexed (Video 2). He stretched his hands frequently while writing.

He tried medicines without benefit, including primidone, gabapentin, propranolol, or carbidopa/levodopa. He was told by physicians, neurologists, and psychiatrists that the ailment was psychological. Approximately 2 years after the onset of symptoms, he was diagnosed with WC. Currently, using a thick pen helps alleviate the cramping sensation and carving remains a problem.

Patient 3

A 52-year-old right-handed Caucasian woman presented with a 10-year history of trouble writing the letters "m" and "n." She was an accounting executive and her job required a great deal of writing with lots of stress and frequent deadlines. She worked 70 to 80 hours weekly. The writing later affected all letters and numbers, and she had difficulty writing even short thank-you notes and frequently broke pens because of the amount of pressure she exerted. She never had difficulty writing on a blackboard. Her ability to play the piano was unaffected. She had normal electrodiagnostic studies and MRI of the brain and cervical spine. She saw many physicians and her symptoms were considered a manifestation of underlying emotional stress, so she stopped working.

Her neurological examination was normal. With writing, her thumb, fingers, and wrist flexed and she felt a cramping sensation in her forearm (Video 3). She used excessive pressure when writing. With continued writing, the pen fell out of her hand. She had mirror movements with her right hand as she wrote with her left.

Patient 4

A 52-year-old right-handed Caucasian man presented with an 8-year history of trouble writing. He was an accountant and cartographer for the National Guard. He participated in daily drills where he had to make a dot on a map and circle the dot and then write a couple of words where bombing practice was to occur. Although these were just practice drills, they were very tense situations. He started having difficulty making the dot. He would try to make a dot, but could not place the pen on the map. His superiors told him the problem was stress related. He soon developed difficulty writing words. He then sought the help of physicians, psychiatrists, and orthopedic surgeons without any answers. He was also a banjo player, and subsequently noticed that his fingers would curl while playing. He was diagnosed with FHD approximately 11 years after onset.

The patient's neurological examination was notable for awkward posturing with hyperextension at the wrist joint and fingers, causing frequent change in his grip while writing (Video 4). With playing the banjo, his fingers curled and he was unable to extend them (Video 4). He had mirror movements with the right hand while he wrote with the left hand.

For several years BTX helped, but this later became ineffective. He has stopped playing the banjo and began typing.

Discussion and Conclusion

Although task specificity in focal dystonias is a well-known phenomenon, the nature of this specificity is not well understood. Because of the curious nature of task specificity, patients are sometimes thought to have a psychogenic problem, leading to significant frustration until a diagnosis is established. Only 1 of the 4 patients was diagnosed in a relatively short period of time. The other 3 patients went from one physician to the next until a diagnosis was established. In one case, it took more than 10 years. Early recognition can be life altering,[6] may decrease frustration in an already disheartened individual, and may allow the patient to function with appropriate treatment.

Some clinicians may argue that patient 1 may have had writer's block, which might be a psychological phenomenon, but WC would seem more likely. Pressured writing and history of repetitive movement are seen in patients with WC. The development of dystonia in the right hand when he was asked to write with the left hand represents a phenomenon called "mirror dystonia," which is frequently seen in patients with WC. Jedynak et al. reported that it was seen in 44% of the 65 patients they studied with WC.[7] This patient represents a good example of how WC diagnosis can be confusing, even for experts, in the earliest stage of the disease.

In the etiology of FHD and WC, performing a very precise repetitive task for prolonged periods is a frequent trigger. Epidemiological studies in musicians who are required to perform very precise repetitive movements for prolonged periods under stressful conditions[8] have supported this notion. The importance of performing repetitive activity in patients with WC was recognized even in the earliest description of the disease in the late 1800s.[4] All 4 of our patients performed repetitive activities for long periods. For patient 2, daily carving and mechanical activities may have triggered the FHD. None of our patients had affected family members.

Unusual task specificity can be seen in other focal dystonias and can be considered bizarre, leading to a psychogenic diagnosis. Perhaps it was this bizarre exceptional specificity that led to the descriptive term "professional neuroses," which was later confused as a psychological phenomenon.[9] Unusual task specificity can be seen in many focal dystonias.[10–14] With embouchure dystonia, trumpet players may begin with dystonia with certain ranges of notes, which later generalizes to all notes.[14] The underlying mechanism leading to loss of specificity over time is not clear. Loss of surround inhibition in patients with FHD may lead to abnormal plasticity of other parts of the brain over time.[15]

It is important for physicians and, especially, neurologists and psychiatrists to be wary of the fact that WC can start as a very task-specific problem involving only a single letter or number in patients performing repetitive writing or fine motor tasks during stressful situations. Early recognition can help allay frustration for patients and provide some explanation to an already disheartened individual.

Legends to the Video

Video 1. Extreme task-specificity in writer's cramp: video 1. Dystonic features of patient 1 are depicted here. He uses excessive pressure when he writes, as noted by his hands turning red while writing.

Video 2. Extreme task specificity in writer's cramp: video 2. There are two video clips of the patient depicting dystonic features. The first clip demonstrates the problems with writing certain numbers. The second clip is a follow-up after more than 1 year, which illustrates his writing posture with generalized writer's cramp.

Video 3. Extreme task specificity in writer's cramp: video 3. Dystonic features of patient 3 are depicted here. She had to change her handgrip to allow her to write. The video depicts the only hand grip that would allow her to write. Otherwise, she is unable to write.

Video 4. Extreme task specificity in writer's cramp: video 4. Dystonic features of patient 4 are depicted here. The first video clip illustrates the problems with writing and the second with playing the banjo. ■

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References

1. Byl NN, Merzenich MM, Cheung S, Bedenbaugh P, Nagarajan SS, Jenkins WM. A primate model for studying focal dystonia and repetitive strain injury: effects on the primary somatosensory cortex. Phys Ther 1997;77:269–284.
2. Tarsy D, Simon DK. Dystonia. N Engl J Med 2006;355:818–829.
3. Bell C. The Nervous System of the Human Body. Washington, DC: Duff Green; 1833.
4. Gowers W. A Manual of the Diseases of the Nervous System. Philadelphia: P. Blakiston; 1888.
5. Sheehy MP, Marsden CD. Writers' cramp—a focal dystonia. Brain 1982;105:461–480.
6. Pullman S, Hristova A. Musician's dystonia [editorial]. Neurology 2005;64:186–187.
7. Jedynak PC, Tranchant C, de Beyl DZ. Prospective clinical study of writer's cramp. Mov Disord 2001;16:494–499.
8. Frucht SJ. Focal task-specific dystonia in musicians. Adv Neurol 2004;94:225–230.
9. Marsden CD, Sheehy MP. "Writer's cramp." Trends Neurosci 1990;13:148–539.
10. Sachdev P. Golfers' cramp: clinical characteristics and evidence against it being an anxiety disorder. Mov Disord 1992;7:326–332.
11. Song IU, Kim JS, Kim HT, Lee KS. Task-specific focal hand dystonia with usage of a spoon. Parkinsonism Relat Disord 2008;14: 72–74.
12. Scolding NJ, Smith SM, Sturman S, Brookes GB, Lees AJ. Auctioneer's jaw: a case of occupational oromandibular hemidystonia. Mov Disord 1995;10:508–509.
13. Bonanni L, Thomas A, Scorrano V, Onofrj M. Task-specific lower lip dystonia due to mantra recitation. Mov Disord 2007;22: 439–440.
14. Ilic TV, Potter M, Holler I, Deuschl G, Volkmann J. Praying-induced oromandibular dystonia. Mov Disord 2005;20:385–386.
15. Frucht SJ. Embouchure dystonia—portrait of a task-specific cranial dystonia. Mov Disord 2009;24:1752–1762.
16. Hallett M. Neurophysiology of dystonia: The role of inhibition. Neurobiol Dis 2011;42:177–184.