

## Prof. Gil I. Wolfe: don't be afraid to say "yes" even if you feel your plate is pretty full

Submitted May 31, 2018. Accepted for publication May 31, 2018.

doi: 10.21037/jtd.2018.06.14

View this article at: <http://dx.doi.org/10.21037/jtd.2018.06.14>

### Expert's introduction

Prof. Gil I. Wolfe, MD, FAAN, currently serves as Professor and Chairman of the Department of Neurology, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, New York. He is the Irvin and Rosemary Smith Professor and a University at Buffalo Distinguished Professor. Prior to this, he was Professor of Neurology at University of Texas Southwestern Medical School in Dallas, Texas; Co-Director of the Muscular Dystrophy Association Clinics; and Director of the Myasthenia Gravis and Peripheral Neuropathy Clinics at UT Southwestern.

Prof. Wolfe is board certified in neurology, neuromuscular medicine and neurophysiology. His research interests include myasthenia gravis (MG), and idiopathic and immune-mediated peripheral neuropathies. His research has received funding supports from various organizations including National Institute of Health (NIH), National Institute of Neurological Disorders and Stroke (NINDS), Muscular Dystrophy Association, Myasthenia Gravis Foundation of America, and Food and Drug Administration. Besides, he is actively involved in a number of professional associations. He is a former Councilor on the Executive Committee of the Association of University Professors of Neurology; a member of the Western ALS Study Group; and Medical Advisory Board Member and a Center of Excellence for the GBS/CIDP Foundation International, just to name a few. He has been named Doctor of the Year by the MG Foundation of America.

### Editor's note

As its name implies, MG is a Latin-Greek phrase meaning "grave or serious muscle weakness". It is a chronic autoimmune disease caused by a breakdown in the transmission of nerve impulses to muscles, resulting in rapid fatigue in the skeletal muscles that control movements of the body, including neck and limb movement, eye and eyelid mobility, facial expression, speech, chewing, swallowing and even breathing. There is so far no known cure but available treatments such as



**Figure 1** Prof. Gil I. Wolfe.

thymectomy, immunosuppressive drugs and anticholinesterase medications are proven to be capable of controlling symptoms and maintaining patients' quality of life.

Prof. Gil I. Wolfe from the Department of Neurology, University at Buffalo Jacobs School of Medicine & Biomedical Sciences (*Figure 1*) has wide interest in neuromuscular medicine with a focus on the management of MG. Over the years, he has been involved in a number of funded studies on MG including the thymectomy trial in non-thymomatous MG patients on prednisone, testing the safety and efficacy of eculizumab in subjects with refractory MG, and formulating international MG treatment guidelines. In this interview, Prof. Wolfe will share with us his experience in conducting the thymectomy trial on MG patients, the difficulties encountered in the meantime, the effectiveness of transsternal thymectomy, and his advice to young researchers.

### Interview

**JTD:** *You have conducted a thymectomy trial on MG patients. What were the goal, scope and geographic coverage of the study?*

**Prof. Wolfe:** In the thymectomy trial our goal was to

demonstrate whether the procedure using a transsternal approach benefitted patients with non-thymomatous MG. The hunch for some 75 years had been that it did, but it had never been proven in a formalized, randomized manner where medication was controlled. Over the decades, many had called for a formal trial. We received planning grant funding from the MDA and MG Foundation of America. After several reviews, we secured funding from NINDS/NIH for an international trial. We needed many sites to recruit a proper number of patients and an international scope was felt to be important. Most of the MG experts we contacted around the world felt it was important to do the study. John Newsom-Davis, my mentor and chair at Oxford at the time, who passed away during the trial recruitment phase, had trained many of the experts we used around the world as site investigators.

*JTD: To what extent is transsternal thymectomy effective to remedy MG?*

**Prof. Wolfe:** We showed in the MGTX trial published in *New England Journal* in August 2016 that transsternal thymectomy plus prednisone confers several benefits *vs.* a standardized prednisone protocol alone in MG. Not only does it significantly improve outcomes but it also reduces the need for corticosteroids over 3 years as well as requirements for steroid sparing agents such as azathioprine. It also by more than half reduced the need for hospitalizations for disease exacerbations and rescue type therapies.

*JTD: What are other available options to deal with the form of MG that cannot be tackled by thymectomy?*

**Prof. Wolfe:** There are many treatment options in MG starting with acetylcholinesterase inhibitors, then proceeding to immunosuppressive therapy. Other options in refractory cases include IVIG, plasma exchange, and nowadays, biological therapies such as monoclonal antibodies have entered the arena of treatment. Recently, eculizumab was approved by the FDA to treat generalized Ach antibody positive MG, the type of population we recruited for the thymectomy trial. But I wish to emphasize that it is appropriate to discuss the potential of thymectomy to improve the longer-term outcomes in this population of MG patients fairly early on in the management period. As we showed, it does confer benefits, some of which there was a signal for within a year or so. But definitely at three years,

and we also have data that the benefit persists even longer than that.

*JTD: As the principal investigator, how do you manage and monitor this study in a global context? What were the difficulties encountered?*

**Prof. Wolfe:** Monitoring of the research project such as this requires a large team and significant administrative and statistical infrastructure. This was provided for MGTX by the excellent biostatistics team at University of Alabama Birmingham, directed by Gary Cutter, PhD.

Given the international scope of the trial, we did encounter issues with certain countries amid requirements that the NIH made before they would agree to transfer funds to these sites. So yes, NIH monies can flow outside the boundaries of the USA, but you need to ensure the sites follow Good Clinical Practice guidelines, ethical standards of research, etc. For one country, we actually had to work on State Department clearance before NIH monies could be released. Then from the other side, a couple of countries refused to allow us to send them prednisone from the US, so we had to work around that issue as well carefully, since prednisone dosing was one of the dual primary outcomes. It did require quite a bit of effort and one member of the UAB team did a lot of travelling.

*JTD: Are there any studies going on to further enhance and optimize the surgical procedures of thymectomy?*

**Prof. Wolfe:** I am unaware of any randomized surgical studies for different types of thymectomy procedures. During the trial, minimally invasive approaches became more and more standard and we toyed with the idea of allowing other non-transsternal approaches. But in the end, it was decided that we had to stick to our guns and only allow that type of approach. If the trial had been negative and other approaches had been allowed, we would have been open to criticism that perhaps a complete thymectomy was not accomplished due to this or that type of minimally invasive approach. Now I will say that VATS or videoscopic approaches are practiced worldwide now. If the intention is to remove as much thymus as possible, and studies have shown reasonable similarity in thymus removal with these approaches compared to transsternal ones, then the outcomes we saw in MGTX can be anticipated for that patient. I really do think that is the case. And there are a number of series that show these less invasive approaches

require shorter hospital stays, less pain medication, and certainly the cosmetic effects are superior. And in both the surgical and neurological literature, the outcomes they are reporting after several years is on par with what we have observed with older, more invasive approaches.

*JTD: What are your future research directions?*

**Prof. Wolfe:** Future research directions mainly involve testing novel therapies for MG, particularly in the minority of patients, perhaps up to 20%, who do not respond well or do not tolerate well conventional approaches. For instance, attention is being paid to anti-CD20 and anti-complement molecules. And antagonism of FcRN receptors that would reduce the salvaging of immunoglobulin is also actively being looked at in MG. Now that eculizumab has proven the efficacy of an anti-C5 mechanism of action preventing its cleavage into C5b which would start the cascade to create the membrane attack complex which we know is crucial in the muscle membrane damage seen in anti-Ach receptor MG. There is further activity in this area. Companies are looking into a subcutaneous delivery of such molecules, so that patients do not need to receive what so far is very frequent intravenous infusion. Therefore, there is a good amount of excitement in this arena. I anticipate that the treatment of MG will continue to evolve and improve. Compared to where we were in the 1970's, things are much better now.

*JTD: You are actively involved in clinical work, research, and training younger physicians. How do you strike a balance whilst having such heavy workload?*

**Prof. Wolfe:** Striking a work life balance is not easy, and I do think the younger generations focus on this and for good reason. There is a good amount of fatigue or burnout in being a physician. But if you love what you do, it drives you and keeps you eager to tackle the next big question. But I would advise this: always have one or two activities that you love to do outside of medicine or neurology or healthcare. One of those two perhaps could be a form of exercise such as cycling, swimming, playing tennis—what you have. The other could be playing music, indulging in live artistic performances, being involved on a community board or other things. Then I am ALWAYS reading something on my Kindle that has nothing to do with medicine or neurology. I don't read much fiction anymore; history and biographies have been big on my list lately. Use those types

of things to balance your work responsibilities. Obviously, some of these can be pursued in the context of one's family.

*JTD: As an experienced trainer, what are the key things you would remind newcomers in your field?*

**Prof. Wolfe:** I have run several residency and fellowship training programs over my career. It is something I really enjoyed doing. I am still involved as a chairman, but I am not the direct administrative lead for our training programs. But what I can advise to younger physicians and scientists is this: Don't be afraid to say "yes" even if you feel your plate is pretty full. It is always better to have more things to do than too few. And some of those opportunities may blossom into something you had not anticipated, whether a neat answer or approach to a problem in medicine or a scientific relationship that will pay dividends in your career for many years. I think it is also important to align yourself with coaches or mentors who can help you along your way, introduce you to people or opportunities that can help your career. I am indebted to a handful of people who helped shape me. I won't name them here, but I make a point of thanking them. But that is one of the things that make academic medicine so special—the professional and even social relationships that develop due to your involvement with projects, whether they are clinical trials or other types of scientific study. I don't think that is something you really find in community practices. It is fairly unique to being in an investigative environment. And if you are part of multicenter studies, you will develop friendships all over the country or world, which is a very neat thing as well.

### Acknowledgements

We would like to express our sincerest gratitude to Prof. Gil I. Wolfe for sharing his insights and opinions with us.

### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

(Science Editor: Brad Li, JTD, jtd@amepc.org)

**Cite this article as:** Li B. Prof. Gil I. Wolfe: don't be afraid to say "yes" even if you feel your plate is pretty full. J Thorac Dis 2018;10(6):E493-E495. doi: 10.21037/jtd.2018.06.14