Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Natural history and survival in stage 1 Val30Met transthyretin familial amyloid polyneuropathy

In "Natural history and survival in stage 1 Val30Met transthyretin familial amyloid polyneuropathy," Coelho et al. reported improved survival in patients in Portugal with TTR-FAP treated with liver transplant or tafamidis compared with those who were untreated. They concluded that disease-modifying treatments profoundly change the long-term prognosis for patients with TTR-FAP. Because they found a 1-year mortality rate after liver transplant of 14%, they question Yamashita et al.'s report that 100% of patients with liver transplant in their series of Japanese patients with TTR-FAP did not die because of amyloidosis in the ensuing 10-year period. In response, Ueda and Yamashita et al. note that outcomes often vary by location and that their study included (1) patients with heterozygous Val30Met mutations, (2) mostly patients who received transplants from living donors, and (3) patients who were treated early. The Portugal team responds that although they reviewed all-cause mortality in patients with TTR-FAP (including deaths related to liver transplant), the Japan team focused their assessment of mortality on deaths related to amyloidosis. Finally, the Japan team also suggests that the Portugal team should carefully estimate the long-term effects of treatment based on their short-term findings. The Portugal team agrees that their results must be interpreted cautiously and emphasize that, when describing prognosis, they used the phrase "long-term" to emphasize the fact that with disease-modifying treatment, TTR-FAP becomes a chronic condition, rather than a fatal disease.

Ariane Lewis, MD, and Steven Galetta, MD
Neurology® 2019;93:228. doi:10.1212/WNL.0000000000007868

Reader response: Natural history and survival in stage 1 Val30Met transthyretin familial amyloid polyneuropathy

Mitsuharu Ueda (Kumamoto, Japan), Taro Yamashita (Kumamoto, Japan), Yohei Misumi (Kumamoto, Japan), Teruaki Masuda (Kumamoto, Japan), and Yukio Ando (Kumamoto, Japan)
Neurology® 2019;93:228–229. doi:10.1212/WNL.0000000000007870

In an observational study conducted in a single country, Coelho et al.¹ reported favorable survival of patients with transthyretin familial amyloidosis polyneuropathy (TTR-FAP) who underwent liver transplantation (LTx) or received tafamidis. This report is important to reconfirm the benefits of early treatments for patients with TTR-FAP. The authors also attempted to estimate long-term outcomes of patients treated with tafamidis based on short-term findings. In addition, they described a skeptical view of our outstanding outcome of Japanese patients with TTR-FAP treated with LTx.² We refute the following issues.

First, we never excluded patients with the heterogeneous Val30Met mutation in our previous study,² although we excluded patients with other types of TTR mutations to standardize the patients' genotypes.

Second, the authors should consider the great diversity of medical situations in each country or region. In other diseases, it is well documented that patients' outcomes differ greatly across different countries or regions.^{3,4} We performed living donor LTx for most patients with TTR-FAP.² Early treatments and no operation-related deaths contributed to the result.²

Finally, the authors should carefully propose the estimated long-term effects based on short-term findings because unexpected events could occur in the long term, which we learned from our experience with LTx.⁵

1. Coelho T, Inês M, Conceição I, et al. Natural history and survival in stage 1 Val30Met transthyretin familial amyloid polyneuropathy. *Neurology* 2018;91:e1999–e2009.
2. Yamashita T, Ando Y, Okamoto S, et al. Long-term survival after liver transplantation in patients with familial amyloid polyneuropathy. *Neurology* 2012;78:637–643.
3. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018;391:1023–1075.
4. Robinson BM, Akizawa T, Jager KJ, et al. Factors affecting outcomes in patients reaching end-stage kidney disease worldwide: differences in access to renal replacement therapy, modality use, and haemodialysis practices. *Lancet* 2016;388:294–306.
5. Ericzon BG, Wilczek HE, Larsson M, et al. Liver transplantation for hereditary transthyretin amyloidosis: after 20 years still the best therapeutic alternative? *Transplantation* 2015;99:1847–1854.

Copyright © 2019 American Academy of Neurology

Author response: Natural history and survival in stage 1 Val30Met transthyretin familial amyloid polyneuropathy

Mónica Inês (Lisbon), Teresa Coelho (Porto, Portugal), and João Costa (Lisbon)
Neurology® 2019;93:229. doi:10.1212/WNL.0000000000007876

In our study,¹ we evaluated all-cause mortality and a 76% survival rate at 10 years among Val30Met liver transplant (LTx)-treated patients (n = 957) was found. Notably, a previous study of Japanese patients with transthyretin-associated familial amyloid polyneuropathy Val30Met reported a 100% survival rate at 10 years among LTx-treated patients (n = 37).² In the Yamashita et al. study, deaths were classified as either related or unrelated to progressive amyloidosis. The different approaches followed by the 2 studies on how to analyze deaths can lead to completely different results because LTx per se (not related to progressive amyloidosis) is associated with an early excess mortality. We found a 14% mortality rate in the first year following LTx, similar in the Swedish LTx cohort (n = 108)³ and to what Ericzon et al.⁴ reported using data from the World Transplant Registry (n = 1,940), having described 14% deaths due to liver-related complications and 3% due to intraoperative mortality.

We agree that caution is required when interpreting the results from the comparative analysis because treatment follow-up was different (tafamidis, maximum 10 years; LTx, maximum 25 years). This limitation is clearly highlighted in the discussion. The “long-term” expression was carefully used to state that the advent of disease-modifying treatments (in particular LTx) dramatically changed the long-term prognosis from a fatal disease to a more chronic condition.

1. Coelho T, Inês M, Conceição I, et al. Natural history and survival in stage 1 Val30Met transthyretin familial amyloid polyneuropathy. *Neurology* 2018;91:e1999–e2009.
2. Yamashita T, Ando Y, Okamoto S, et al. Long-term survival after liver transplantation in patients with familial amyloid polyneuropathy. *Neurology* 2012;78:637–643.
3. Okamoto S, Wixner J, Obayashi K, et al. Liver transplantation for familial amyloidotic polyneuropathy: impact on Swedish patients' survival. *Liver Transpl* 2009;15:1229–1235.
4. Ericzon BG, Wilczek HE, Larsson M, et al. Liver transplantation for hereditary transthyretin amyloidosis: after 20 years still the best therapeutic alternative? *Transplantation* 2015;99:1847–1854.

Copyright © 2019 American Academy of Neurology

Editors' note: Residency Training: Enhancing resiliency in our residents: Combining the principles of business and neurobiology

In “Residency Training: Enhancing resiliency in our residents: Combining the principles of business and neurobiology,” Llinas et al. discussed business and neuroscientific perspectives on burnout and resiliency. They noted that sleep deprivation, stress, and depersonalization contribute to frontal lobe exhaustion leading to burnout, but that activities that promote spiritual, mental, emotional, and physical renewal can prevent burnout. Robbins applauds the authors for discussing burnout prevention strategies, rather than focusing on treatment of burnout. He further notes that the use of patient satisfaction scores to assess physician performance can contribute to burnout, particularly because these scores can be influenced by a number of factors external to the physician themselves. Llinas agrees that ungrateful patients demoralize physicians and adds that interactions with unprofessional colleagues and patients also lead to burnout. As there are many other factors that can cause burnout, further research is necessary to explore how to minimize burnout and enhance resiliency.

Ariane Lewis, MD, and Steven Galetta, MD
Neurology® 2019;93:230. doi:10.1212/WNL.0000000000007877

Reader response: Residency Training: Enhancing resiliency in our residents: Combining the principles of business and neurobiology

Nathaniel M. Robbins (Hanover, NH)
Neurology® 2019;93:230–231. doi:10.1212/WNL.0000000000007875

I read with interest Llinas et al.¹'s article that discussed burnout and resiliency. I appreciate the authors' emphasis on the primacy of systemic changes to address the problem, such as increasing opportunities for recognition and rewarding activities. This contrasts with efforts to mitigate burnout by teaching doctors strategies like meditation. The latter strategy blames the victim and ignores the fact that those without adequate stress coping skills would not have made it through medical school and residency in the first place.

Another important systems-level contributor to burnout that garners little attention is the burgeoning emphasis on patient satisfaction scores to measure physician performance. Anecdotally, we all face dissatisfied patients despite doing the right thing: diagnosing conversion disorder rather than misdiagnosing a neurologic condition, recommending watchful waiting rather than additional invasive tests, or refusing to prescribe opiates for chronic neuropathic pain. Evidence supports this anecdotal impression because higher “patient satisfaction” scores have been associated with increased utilization and higher mortality.^{2,3} Inherent patient biases, manifested as lower “knowledge” ratings for women and minorities compared with older white men, also undermine the validity and utility of physician rating.^{4,5}

Facilitating the ease with which (often unfair) negative patient feedback is disseminated demoralizes physicians who take pride in their work, perversely limits physician autonomy, undermines good medical care, and increases physician burnout by undermining the core emotional need to feel appreciated and valued.¹ I agree with the authors that combatting burnout requires resetting of the balance between effort and reward,¹ but I hope that future articles consider the contributing role of negative patient feedback in the burnout epidemic.

1. Llinas RH, Marsh EB, Gamaldo CE. Residency Training: enhancing resiliency in our residents: combining the principles of business and neurobiology. *Neurology* 2018;91:e1721–e1723.
2. Biondi EA, Hall M, Leonard MS, Pirraglia PA, Alverson BK. Association between resource utilization and patient satisfaction at a tertiary care medical center. *J Hosp Med* 2016;11:785–791.
3. Fenton JJ, Jerant AF, Bertakis KD, Franks P. The cost of satisfaction: a national study of patient satisfaction, health care utilization, expenditures, and mortality. *Arch Intern Med* 2012;172:405–411.
4. Chen JG, Zou B, Shuster J. Relationship between patient satisfaction and physician characteristics. *J Patient Exp* 2017;4:177–184.
5. Rogo-Gupta LJ, Haunschild C, Altamirano J, Maldonado YA, Fassiotto M. Physician gender is associated with patient satisfaction scores in outpatient gynecology. *Womens Health Issues* 2018;28:281–285.

Copyright © 2019 American Academy of Neurology

Author response: Residency Training: Enhancing resiliency in our residents: Combining the principles of business and neurobiology

Rafael H. Llinas (Baltimore)

Neurology® 2019;93:231. doi:10.1212/WNL.0000000000007874

I thank Dr. Robbins for the comment on our Residency Training article.¹ We agree with the concept that patients that appear ungrateful contribute to burn out. It does not serve as a victory, even if great effort and time is put into treating them. Furthermore, unprofessional interactions with our colleagues, as well our patients, contribute substantially to burn out.

1. Llinas RH, Marsh EB, Gamaldo CE. Residency Training: enhancing resiliency in our residents: combining the principles of business and neurobiology. *Neurology* 2018;91:e1721–e1723.

Copyright © 2019 American Academy of Neurology

CORRECTION

PCNT point mutations and familial intracranial aneurysms

Neurology® 2019;93:231. doi:10.1212/WNL.0000000000007524

In the article “PCNT point mutations and familial intracranial aneurysms” by Lorenzo-Betancor et al.,¹ published online ahead of print on November 9, 2018, Dr. Lorenzo-Betancor’s affiliations should have included the Veterans Affairs Puget Sound Health Care System and the University of Washington. The Disclosures section should have included: “O. Lorenzo-Betancor was supported in part by a postdoctoral fellowship award from the Department of Veterans Affairs.” In the Results section of the abstract, the value should read “p.V2811L.” Finally, in the abbreviations for figure 2, “Pact” should read “pericentrin-AKAP-450....” These items appear correctly in the December 4, 2018, issue. The publisher regrets the errors.

Reference

1. Lorenzo-Betancor O, Blackburn PR, Edwards E, et al. PCNT point mutations and familial intracranial aneurysms. *Neurology* 2018;91:e2170—e2181.

Neurology®

PCNT point mutations and familial intracranial aneurysms

Neurology 2019;93;231

DOI 10.1212/WNL.00000000000007524

This information is current as of July 29, 2019

Updated Information & Services

including high resolution figures, can be found at:
<http://n.neurology.org/content/93/5/231.2.full>

References

This article cites 1 articles, 1 of which you can access for free at:
<http://n.neurology.org/content/93/5/231.2.full#ref-list-1>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints

Information about ordering reprints can be found online:
<http://n.neurology.org/subscribers/advertise>

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2019 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.