Journal of the Neurological Sciences 375 (2017) 474–475

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Editorial

New hearts for Friedreich patients

Most individuals with Friedreich ataxia (FRDA) have an abnormal electrocardiogram and elevated serum concentrations of cardiac troponin 1. Many eventually develop cardiac hypertrophy, and heart failure is a frequent cause for their death. Histological evaluation of the heart shows enlarged cardiomyocytes encircled by fibrotic endomysium. Some of the enlarged cardiac myocytes, and also some macrophages that have accumulated in endomysium, contain iron-positive inclusions, but total cardiac iron content is not increased. Molecular studies have shown that frataxin deficiency impairs assembly of mitochondrial iron-sulfur cluster-containing subunits, thereby impeding mitochondrial electron transport and diminishing cardiac energy production [1,2,3,4].

Analysis of large North American and European FRDA cohorts has helped to clarify the evolution of cardiomyopathy in this disorder. In general, the onset of cardiac dysfunction occurs earliest in patients with the longest FXN GAA repeats and lowest tissue frataxin levels. However, cardiomyopathy tends to be less severe in the small proportion of FRDA patients who are double heterozygous for an expanded FXN GAA repeat and a null FXN mutation, despite the generally very low levels of frataxin in these patients [5,6].

Trials of anti-oxidants (vitamin E or idebenone), of a mitochondrial respiratory chain electron transport facilitator (coenzyme Q_{10}), or of an iron chelator (deferiprone) to prevent or slow progression of FRDA cardiomyopathy have thus far yielded minor or equivocal benefits. Combined therapy with coenzyme Q_{10} and vitamin E was initially reported to improve FRDA cardiac function, but this was not confirmed in a later double blind study. Both idebenone and deferiprone were reported to slow progress of cardiac hypertrophy in FRDA, but the favorable response to idebenone has not been consistently documented, and attempts to enhance the benefits of deferiprone by dose escalation appeared to worsen FRDA-associated neurological deficits [7,8].

What, then, can be done for FRDA patients with life-threatening cardiomyopathy, and in particular for those FRDA patients in whom neurological dysfunction has not yet become disabling? Counting the present series of 3 patients by McCormick et al. [9], a total of 7 FRDA patients with end-stage cardiomyopathy have undergone successful cardiac transplantation. Notably, the transplanted hearts showed no signs of cardiomyopathy during decades-long post-transplantation followup, providing strong evidence that FRDA cardiomyopathy develops independently of other manifestations of this systemic disease. The impact of the transplanted hearts on quality of life was large, even though there was no consistent evidence that the transplants themselves, or the immunosuppressive drugs administered thereafter to prevent graft rejection, slowed the progress of neurological dysfunction in these patients.

Can we hope for effective future interventions, other than cardiac transplantation, to ameliorate FRDA cardiomyopathy? Studies in FRDA patient-derived cell lines indicate that small molecule approaches to augmenting cardiac FXN transcription and frataxin expression might be possible [10]. It may also be possible to augment cardiac frataxin expression in FRDA patients by viral transduction [11], or, as in vivo gene editing techniques improve, by direct excision of the expanded FXN GAA repeat [12].

Conflicts of interest

None.

Acknowledgements

None.

References

[1] L.S. Friedman, K.A. Schadt, S.R. Regner, G.E. Mark, K.Y. Lin, T. Sciascia, M. St John Sutton, S. Willi, D.R. Lynch, Elevation of serum cardiac troponin I in a cross-sectional cohort of asymptomatic subjects with Friedreich ataxia, Int. J. Cardiol. 167 (4) (2013) 1622–1624.
[2] F. Weidmann, D. Liu, K. Hu, C. Florescu, M. Niemann, S. Herrmann, B. Kramer, S. Klebe, K. Doppler, N. Uceyler, C.O. Ritter, G. Ertl, S. Stork, The cardiomyopathy in Friedreich's ataxia – new biomarker for staging cardiac involvement, Int. J. Cardiol. 194 (9) (2015) 50–57.
[3] P.C. Kruger, K.X. Yang, P.J. Parsons, A.B. Becker, P.J. Feustel, A.H. Koeppen, Abundance and significance of iron, zinc, copper, and calcium in the hearts of patients with Friedrech ataxia, Am. J. Cardiol. 118 (7) (2016) 127–131.
[4] M. Bunse, N. Bit-Avragim, A. Riefflin, A. Perrot, O. Schmidt, F.R. Kreuz, R. Dietz, W.-I. Jung, J.K. Osterziel, Cardiac energetics correlates to myocardial hypertrophy in Friedreich's ataxia, Ann. Neurol. 53 (1) (2003) 121–123.
[5] M. Lazaropoulos, Y. Dong, E. Clark, N.R. Greeley, L.A. Seyer, K.W. Brigatti, C. Christie, S.L. Perlman, G.R. Wilmot, C.M. Gomez, K.D. Mathews, G. Yoon, T. Zesiewicz, C. Hoyle, S.H. Subramony, A.F. Brocht, J.M. Farmer, R.B. Wilson, E.C. Deutsch, D.R. Lynch, Frataxin levels in peripheral tissue in Friedreich ataxia, Ann. Clin. Transl. Neurol. 2 (8) (2015) 831–842.
[6] C.A. Galea, A. Huq, P.J. Lockhart, G. Tai, L.A. Corben, E.M. Yiu, L.C. Gurrin, D.R. Lynch, S. Gelbard, A. Durr, F. Pousset, M. Parkinson, R. Labrum, P. Giunti, S.L. Perlman, M.B. Delatycki, M.V. Evans-Galea, Compound heterozygous FXN mutations and clinical outcome in Friedreich ataxia, Ann. Neurol. 79 (3) (2016) 485–495.
[7] M. Kearney, R.W. Orrell, M. Fahey, R. Brassington, M. Pandolfo, Pharmacological treatments for Friedreich ataxia, Cochrane Database Syst. Rev. (8) (2016) CD007791.
[8] M. Pandolfo, J. Arpa, M.B. Delatycki, K.H. Le Quan Sang, C. Mariotti, A. Munnich, I. Sanz-Gallego, G. Tai, M.A. Tarnopolsky, F. Taroni, M. Spino, F. Tricta, Deferiprone in Friedreich ataxia: a 6-month randomized controlled trial, Ann. Neurol. 76 (4) (2014) 509–521.
[9] A. McCormick, J. Shinnick, K. Schadt, R. Rodriguez, L. Addonizio, M. Hirano, S. Perlman, K.Y. Lin, D.R. Lynch, Cardiac transplantation in Friedreich ataxia: extended follow up, J. Neurol. Sci. 375 (2017) 471–473.

http://dx.doi.org/10.1016/j.jns.2017.01.035
0022-510X/© 2017 Elsevier B.V. All rights reserved.

[10] Y.K. Chutake, C.C. Lam, W.N. Costello, M.P. Anderson, S.I. Bidichandani, Reversal of epigenetic promoter silencing in Friedreich ataxia by a class I histone deacetylase inhibitor, Nucleic Acids Res. 44 (11) (2016) 5095–5104.
[11] M. Perdomini, B. Belbellaa, L. Monassier, L. Reutenauer, N. Messaddeq, N. Cartier, R.G. Crystal, P. Aubourg, H. Puccio, Prevention and reversal of severe mitochondrial cardiomyopathy by gene therapy in a mouse model of Friedreich's ataxia, Nat. Med. 20 (5) (2014) 542–554.
[12] Li Y, Polak U, Bhalla AD, Rozwadowska N, Butler JS, Lynch DR, Dent SYR, Napienala M. Excision of expanded GAA repeats alleviates the molecular phenotype of Friedreich's ataxia. Mol. Ther. 23(6)1055–1065.

David Pleasure
Neurology, UC Davis, c/o Shriners Hospital, 2425 Stockton Blvd, Sacramento, CA 95817, United States
E-mail address: depleasure@ucdavis.edu.

6 January 2017