Disputes & Debates: Editors' Choice

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Editors' Note: Prospective Natural History Study in 24 Adult Patients With LGMDR12 Over 2 Years of Follow-up: Quantitative MRI and Clinical Outcome Measures

De Wel et al. prospectively studied 24 patients with autosomal recessive limb-girdle muscular dystrophy type 12 (LGMDR12). Patients with LGMDR12 had no appreciable clinical worsening over a 2-year period according to repeated standardized clinical assessments, such as the 6-minute walk distance, 10-meter walk test, or Medical Research Council sum scores of muscle power. However, for patients with LGMDR12 and intermediate-stage fatty replacement of muscle tissue (20%–70% proton density fat fraction), there was a significant worsening of Biodex Isometric Dynamometry even after 1 year. The investigators conclude this quantitative tool may be useful in monitoring clinical progression and response to targeted treatments for LGMDR12. Dr. Kawada expresses a concern regarding lead-time bias in the cohort (unclear time of disease onset in a recessive condition) which may have confounded any differences in the various qualitative and quantitative assessments over time. In response, the investigators confirmed that patients were included at the time of clinical symptom onset. Both investigators agree that sex-related differences in disease progression are less well understood, and additional studies are suggested to explore reasons for the variability in prognosis between sexes and age groups.

James E. Siegler, MD, and Steven Galetta, MD
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Reader Response: Prospective Natural History Study in 24 Adult Patients With LGMDR12 Over 2 Years of Follow-up: Quantitative MRI and Clinical Outcome Measures

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De Wel et al. conducted a prospective study to evaluate prognosis in 24 patients with limb-girdle muscular dystrophy autosomal recessive type 12 (LGMDR12).[1] They prepared 24 healthy controls by way of an age- and sex-matching procedure. Biodex(R) isometric dynamometry showed a significant decrease of muscle strength in the right quadricep muscles for all patients after 1 year. In contrast, outcomes from the 6-minute walk distance, 10-meter walk test, and Medical Research Council sum scores did not change significantly, even after 2 years. The authors recognized that thigh muscle proton density fat fraction imaging was a sensitive indicator to track progressive muscle fat replacement.

The difficulty of the determination of disease onset and the 1–2 years between follow-up may have biased the observational period. In addition, a total of 20 patients were men and there is a wide range in age at onset. By distilling patient data, stable estimates by multivariate analysis would be possible.

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By conducting a meta-analysis, 3/4 of patients with LGMDR12 are men, whereas skeletal and/or cardiac muscle atrophy is less progressive in women.[2] Although LGMDR12 is caused by recessive mutations in the anoctamin-5 gene (ANO5), ANO5 myopathy is not an X-chromosome linked disease. There may be a wide variability in ANO5-related myopathies,[3] and sex difference on the prognosis in patients with LGMDR12 should be specified by further studies.

1. De Wel B, Huysmans L, Peeters R, et al. Prospective natural history study in 24 adult patients with LGMDR12 over 2 years of follow-up: quantitative MRI and clinical outcome measures. *Neurology*. 2022;99(6):e638-e649.
2. Foltz S, Wu F, Ghazal N, Kwong JQ, Hartzell HC, Choo HJ. Sex differences in the involvement of skeletal and cardiac muscles in myopathic *Ano5*-/- mice. *Am J Physiol Cell Physiol*. 2022;322(2):C283-C295.
3. Vázquez J, Lefeuvre C, Escobar RE, et al. Phenotypic spectrum of myopathies with recessive anoctamin-5 mutations. *J Neuromuscul Dis*. 2020;7(4):443-451.

Author Response: Prospective Natural History Study in 24 Adult Patients With LGMDR12 Over 2 Years of Follow-up: Quantitative MRI and Clinical Outcome Measures

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We read with interest the comments by Professor Kawada on our article.[1] As described in the article, all participants were evaluated 3 times within strict 1-year intervals; there were no missed visits or missing data. Furthermore, we defined disease onset as the start of clinical symptoms of limb-girdle muscular dystrophy autosomal recessive type 12 (LGMDR12) and thereby excluded patients with isolated hyperCKemia for increased phenotypic homogeneity.

We noted that LGMDR12 is less frequent and severe in women, as described in the study by Khawajazada et al.[2] We did not evaluate this in our article because our subjects consisted of 20 men and 4 women, which made the latter group too small for reliable statistical analyses, especially when considering the disease stage subgroups we examined and described in the limitations section. The man to woman ratio in our article was nonetheless quite representative for the general LGMDR12 patient population, and our results would have been similar if only men had been analyzed.

In addition, a wide range in age at onset is very characteristic for LGMDR12, as is represented in our article. We suggest that future studies should attempt to explain the large heterogeneity in disease severity and progression in LGMDR12.

1. De Wel B, Huysmans L, Peeters R, et al. Prospective natural history study in 24 adult patients with LGMDR12 over 2 years of follow-up: quantitative MRI and clinical outcome measures. *Neurology*. 2022;99(6):e638-e649.
2. Khawajazada T, Kass K, Rudolf K, et al. Muscle involvement assessed by quantitative magnetic resonance imaging in patients with anoctamin 5 deficiency. *Eur J Neurol*. 2021;28(9):3121-3132.

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Editors' Note: Association of Sleep, Neuropsychological Performance, and Gray Matter Volume With Glymphatic Function in Community-Dwelling Older Adults

In their analysis of 84 community-dwelling elderly adults, Dr. Siow et al. evaluated the relationship between diffusion tensor imaging along the perivascular space (DTI-ALPS), sleep, and cognitive performance. As an emerging surrogate indicator of glymphatic function, the DTI-ALPS was strongly associated with sleep in this analysis. The investigators also found that higher DTI-ALPS indices were associated with better language and memory recall scores and concluded the DTI-ALPS could serve as an imaging biomarker for cognitive disorders. Dr. Piantino contests the notion that DTI-ALPS is a validated indicator of glymphatic function, which exhibits regional variability and lacks a gold standard test for quantitating glymphatic function. Furthermore, distinguishing between perivascular and nonperivascular spaces may be challenging on DTI. This exchange highlights the potential shortcomings of DTI as surrogate markers of glymphatic function. Additional studies are necessary to validate imaging markers of glymphatic activity and to better understand the relationship between the glymphatic system, sleep, and cognitive dysfunction.

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Reader Response: Association of Sleep, Neuropsychological Performance, and Gray Matter Volume With Glymphatic Function in Community-Dwelling Older Adults

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In this article, Siow et al.[1,2] used diffusion tensor imaging along the perivascular space (DTI-ALPS) as a marker of glymphatic function in community-dwelling older adults. We raise 4 notes of caution in interpreting the findings from studies using DTI-ALPS to measure human brain glymphatic function. First, the relationship between the DTI-ALPS index and gold standard contrast-based glymphatic imaging has not yet been rigorously defined. In addition, glymphatic exchange occurs throughout the brain volume and exhibits regional variability. The relationship between diffusion parameters at a single anatomical location and glymphatic function throughout the rest of the brain is currently unknown.

In addition, the resolution of DTI may not allow precise delineation of perivascular vs nonperivascular spaces. Because partial volume effects from free water compartments obscure DTI measurements,[3] it is possible that any age-related correlations found may be because of cell rarefaction or edema. Last, the authors loosely interpret the methodology for measuring the DTI-ALPS index using 2 fiber bundles without ascertaining the location or orientation of the associated perivascular spaces, resulting in further ambiguity as to the relationship between this measure and glymphatic perivascular transport.

We recommend that until DTI-ALPS is substantially validated, studies using DTI-ALPS should avoid suggesting that its outcomes are synonymous with glymphatic function.

1. Siow TY, Toh CH, Hsu JL, et al. Association of sleep, neuropsychological performance, and gray matter volume with glymphatic function in community-dwelling older adults. *Neurology*. 2022;98(8):e829-e838.

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2. Taoka T, Masutani Y, Kawai H, et al. Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. *Jpn J Radiol*. 2017;35(4):172-178.
3. Pasternak O, Sochen N, Gur Y, Intrator N, Assaf Y. Free water elimination and mapping from diffusion MRI. *Magn Reson Med*. 2009; 62(3):717-730.

Author Response: Association of Sleep, Neuropsychological Performance, and Gray Matter Volume With Glymphatic Function in Community-Dwelling Older Adults

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We appreciate the insightful comments on our study.[1] Contrast-based imaging allows direct visualization of the glymphatic system and assessment of its function based on the pharmacokinetics of contrast agents. However, quantifications of glymphatic activity in individual fluid compartments may require other techniques.

Expanding research has shown the potential of the diffusion tensor imaging along the perivascular space (DTI-ALPS) index in reflecting glymphatic function. A search in PubMed revealed about 40 articles on this topic, including studies on Parkinson disease, small vessel disease, sleep disorders, and so forth. More studies are needed to establish the relationship between the DTI-ALPS index and glymphatic function in different regions of the brain.

With the typical resolution of diffusion MRI, any parameters derived from DTI are likely to reflect the result of partial volume averaging of the water motion in different compartments of biological tissues. The DTI-ALPS index incorporates the projection area (Dyyproj) and association area (Dzzassoc) into the denominator, potentially normalizing the effect of cell rarefaction or edema.[2] Although the anatomy of human medullary veins has been well described,[3] future studies may consider applying susceptibility-weighted imaging to better determine the venous orientation.

We agree that further validation of existing techniques can better clarify the strengths and weaknesses of each tool, which is important when studying the human glymphatic system.

1. Siow TY, Toh CH, Hsu JL, et al. Association of sleep, neuropsychological performance, and gray matter volume with glymphatic function in community-dwelling older adults. *Neurology*. 2022;98(8):e829-e838.
2. Taoka T, Masutani Y, Kawai H, et al. Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. *Jpn J Radiol*. 2017;35(4):172-178.
3. Taoka T, Fukusumi A, Miyasaka T, et al. Structure of the medullary veins of the cerebral hemisphere and related disorders. *Radiographics*. 2017;37(1):281-297.

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