shown in Fig. 2. Most characteristic was the progressive temporal lobe damage depicted by $ADC_{parallel}$ maps (Fig. 2). q-Space imaging was not able to detect this change. This is probably due to the already damaged white matter in widespread areas on MD maps, as shown in Fig. 5. This is in contrast with the ADC map, which still exhibits preserved regions (e.g., subcortical U-fibers). This, in turn, indicates that q-space imaging has much higher sensitivity to neuronal damage.

The visual assessment of the created maps indicated that there was relative sparing of the posterior parts of the brain, especially the occipital lobes (Fig. 4). Such occipital sparing has been pointed out in a couple of previous studies. A multi-institute study using conventional images has shown this trend [3]. A second, more recent study carried out computerized cortical thickness measurement on preclinical patients and found the trend for relative occipital sparing [21]. The results of these studies were drawn from group analysis, whereas the present observation of occipital lobe sparing was possible on an individual case basis, as illustrated in Fig. 4.

Some technical background of this q-space approach deserves comments. The effective diffusion time (i.e., $\Delta-\delta/3$) for q-space imaging is set to a much longer value than the regular clinical DWI/DTI. This leads to longer TE and thus a reduced SNR. In addition, use of extremely high b values leads to imaging data that are even more susceptible to noise. Thus, one has to use higher averaging during image acquisition. This leads to longer acquisition time, and in the present study, it took 25 min to obtain 12 slices. One can shorten the acquisition by reducing various factors, including averaging, b value increments, and gradient directions. One of the most common ways that has been used to resolve the problem is to reduce the gradient directions. For instance, a clinical study was carried out using only three orthogonal directions, which reduced the data acquisition time to 6.5 min [24]. There is, however, some criticism in reducing the MPG directions to the level where one can no longer reconstruct the tensor model.

Another limitation of "clinical" q-space imaging is that one cannot completely replicate the sequence design used in experimental conditions [6]. In the q-space formalism, the data are valid only when the following two conditions are fulfilled. The first condition is the short pulse gradient (SPG) approximation (i.e., $\delta \ll \Delta$ and δ to be infinitesimally short), and the second is the long diffusion time (i.e., $\Delta > a^2/2D$, where a is the size of the compartment, and D is the diffusion coefficient) [11]. These are not possible using a clinical scanner. Therefore, some of the clinical studies use much shorter diffusion time [24]. The advantage of this is the increase in SNR. However, it is well known that such suboptimal sequence design will lead to underestimation of compartment size [18, 19]. Our quantitative estimation of normal white matter (represented by MD_{radial}) was approximately 8.6 μm, which may thus be an underestimated value.

One of the limitations of this study includes the small number of patients. Especially, the number of preclinical patients was small (n=2), which would potentially make it difficult to assess the progressive nature of the disease. Despite such limitation, we were able to observe the statistically significant differences at some parts of brain, as indicated in Fig. 2. Another limitation of this study is the lack of direct histopathological correlation. The precise cause of the increased compartment size as measured by this technique remains unknown. There are a couple of conceivable causes, which include enlarged extracellular space due to loss of myelin/neurons and widening of perivascular space, which is known to be a unique microscopic feature of CADASIL [25]. The precise mechanism may be elucidated by future histological correlations.

In conclusion, the feasibility of demonstrating the progressive nature of white matter damage using the q-space technique in patients with CADASIL was shown. Since this method appears to be sensitive to the early damage, we believe it would aid in monitoring patients in the preclinical stage. Further longitudinal studies will be necessary to evaluate the true efficacy of this technique.

Acknowledgments This work was supported by JSPS KAKENHI Grant Number:22591348.

Conflict of interest We declare that we have no conflict of interest.

References

1. Okeda R, Arima K, Kawai M (2002) Arterial changes in CADASIL in relation to pathogenesis of diffuse myelin loss of cerebral white matter. Stroke 33:2565–2569
2. Chabriat H, Levy C, Taillia H, Iba-Zizen MT, Vahedi K, Joutel A et al (1998) Patterns of MRI lesions in CADASIL. Neurology 51:452–457
3. Singhal S, Rich P, Markus HS (2005) The spatial distribution of MR imaging abnormalities in CADASIL and their relationship to age and clinical features. AJNR Am J Neuroradiol 26:2481–2487
4. Holtmannspötter M, Peters N, Opherk C, Martin D, Herzog J, Brückmann H et al (2005) Diffusion magnetic resonance histograms as a surrogate marker and predictor of disease progression in CADASIL. Stroke 36:2559–2565
5. O'Sullivan M, Singhal S, Charlton R, Markus HS (2004) Diffusion tensor imaging of thalamus correlates with cognition in CADASIL without dementia. Neurology 62:702–707
6. Callaghan PT, Coy A, MacGowan D, Packer KJ, Zelaya FO (1991) Diffraction like effects in NMR diffusion studies of fluid in porous solids. Nature 351:467–469
7. Cory DG, Garroway AN (1990) Measurement of translational displacement probabilities by NMR. Magn Reson Med 14:435–444
8. Wu EX, Cheung MM (2010) MR diffusion kurtosis imaging for neural tissue characterization. NMR Biomed 23:836–848
9. Jensen JH, Helpern JA (2010) MRI quantification of non-Gaussian water diffusion by kurtosis analysis. NMR Biomed 23:698–710

10. Biton IE, Duncan ID, Cohen Y (2007) QSI and DTI of excised brains of the myelin-deficient rat. Magn Reson Med 58:993–1000
11. Nossin-Manor R, Duvdevani R, Cohen Y (2002) q-Space high b value diffusion MRI of hemi-crush in rat spinal cord. Magn Reson Imaging 20:231–241
12. King MD, Houseman J, Roussel SA, van Bruggen N, Williams SR, Gadian DG (1994) q-Space imaging of the brain. Magn Reson Med 32:707–713
13. King MD, Houseman J, Gadian DG, Connelly A (1997) Localized q-space imaging of the mouse brain. Magn Reson Med 38:930–937
14. Assaf Y, Mayzel-Oreg O, Gigi A, Ben-Bashat D, Mordohovitch M, Verchovsky R et al (2002) High b value q-space-analyzed diffusion MRI in vascular dementia. J Neurol Sci 203–204:235–239
15. Farrell JA, Smith SA, Gordon-Lipkin EM, Reich DS, Calabresi PA, van Zijl PC (2008) High b-value q-space diffusion-weighted MRI of the human cervical spinal cord in vivo. Magn Reson Med 59:1079–1089
16. Farrell JA, Zhang J, Jones MV, Deboy CA, Hoffman PN, Landman BA et al (2010) q-Space and conventional diffusion imaging of axon and myelin damage in the rat spinal cord after axotomy. Magn Reson Med 63:1323–1335
17. Mayzel-Oreg O, Assaf Y, Gigi A, Ben-Bashat D, Verchovsky R, Mordohovitch M et al (2007) High b-value diffusion imaging of dementia. J Neurol Sci 257:105–113
18. Biton IE, Duncan ID, Cohen Y (2007) q-Space diffusion of myelin-deficient spinal cords. Magn Reson Med 58:993–1000
19. Bar-Shir A, Avram L, Ozarslan E, Basser PJ, Cohen Y (2008) The effect of the diffusion time and pulse gradient duration ratio on the diffraction pattern and the structural information estimated from q-space diffusion MR. J Magn Reson 194:230–236
20. Ong HH, Wright AC, Wehrli SL, Souza A, Schwartz ED, Hwang SN, Wehrli FW (2008) Indirect measurement of regional axon diameter in excised mouse spinal cord with q-space imaging. Neuroimage 40:1619–1632
21. Stromillo ML, Dotti MT, Battaglini M, Mortilla M, Bianchi S, Plewnia K et al (2009) Structural and metabolic brain abnormalities in preclinical CADASIL. J Neurol Neurosurg Psychiatry 80:41–47
22. Liem MK, van der Grond J, Versluis MJ, Haan J, Webb AG, Ferrari MD et al (2010) Lenticulostriate arterial lumina are normal in CADASIL. Stroke 41:2812–2816
23. Miao Q, Paloneva T, Tuisku S, Roine S, Poyhonen M, Viitanen M, Kalimo H (2006) Arterioles of the lenticular nucleus in CADASIL. Stroke 37:2242–2247
24. Fatima Z, Motosugi U, Hori M, Ishigame K, Kumagai H, Ikenaga S et al (2010) q-Space imaging of the brain. Magn Reson Med Sci 9:109–110
25. Yamamoto Y, Ihara M, Tham C, Low RW, Slade JY, Moss T et al (2009) Neuropathological correlates of temporal pole white matter hyperintensities in CADASIL. Stroke 40:2004–2011

遺伝性脳小血管病およびその類縁疾患の診断基準の確立と治療法の研究班

区　　分	氏　　名	所　　属　　等	職　　名
研究代表者	小野寺 理	新潟大学脳研究所附属生命科学リソース研究センター	教　授
研究分担者	水野 敏樹	京都府立医科大学神経内科・神経内科学	准教授
	吉田 邦広	信州大学医学部神経難病学講座・神経内科学	教　授
	豊島 靖子	新潟大学脳研究所病理学分野・神経病理学	准教授
	池内　健	新潟大学脳研究所附属生命科学リソース研究センター	教　授
研究協力者	野崎 洋明	新潟大学医学部保健学科	助　教
事　務　局	高口 久美	新潟大学脳研究所神経内科 〒951－8585　新潟市中央区旭町通1番町757 TEL:025-227-0665　FAX:025-223-6646 E-Mail:secre1@bri.niigata-u.ac.jp	秘　書
経理事務担当者	渡辺 浩匡	新潟大学医歯学系脳研究所事務室会計係　〒 951－8585　新潟市中央区旭町通1番町757 TEL:025-227-0603　FAX:025-227-0507 E-Mail:hiromasa@adm.niigata-u.ac.jp	係　長