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LETTER

Integrity of cerebral white matter in type 1 diabetes. Reply to Wessels AM [letter]

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Abbreviation
WMHs white matter hyperintensities

To the Editor: We appreciate the valuable comments of Dr Wessels [1] on our recent article in *Diabetologia* [2]. We specifically sought to study the impact of white matter hyperintensities (WMHs) on brain structure in relatively young patients (age 32±4 years) with diabetes of long duration (20±4 years) (mean ± SD). As Wessels noted, our large sample of patients did not differ from non-diabetic controls in terms of severity of white matter lesions. Indeed, our results are similar to those of Brands et al. [3], who studied cognition and WMHs in older type 1 diabetic adults with disease of longer duration associated with more complications. Taken together, these studies suggest that the incidence of WMHs in type 1 diabetes is not likely to be high. Using voxel-based morphometry, we have also found that, compared with non-diabetic controls, patients with type 1 diabetes had lower grey matter density and this was associated with both higher HbA_{1c} levels and an increased number of severe hypoglycaemic events [4]. This finding suggests that more sensitive measures of brain structure would reveal changes induced by type 1 diabetes.

Wessels notes that type 1 diabetes leads to changes in cognition, which may be mediated by hyperglycaemia, hypoglycaemia and/or vascular disease. The literature on these points is far from conclusive. We observed only small differences in cognition when comparing type 1 diabetic patients to non-diabetic controls [2]. Our results are consistent with a meta-analysis that found modest effects of type 1 diabetes on cognition, characterised by slowing of mental processing and diminished mental flexibility [5]. Furthermore, our cognitive data were consistent with recent results from an 18 year longitudinal study of type 1 diabetic patients enrolled in the Diabetes Control and Complications Trial [6], which found only minimal changes in psychomotor efficiency and motor speed over time among those with the highest HbA_{1c} levels.

Wessels' suggestion that we examine our WMH findings in relation to total white matter volume measurements in patients with and without retinopathy is of interest and would be a useful complementary design. Our goal is to utilise multiple methods of assessing the grey and white matter compartments of the brain, to develop a more precise understanding of the 'signature' of type 1 diabetes.

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We have some reservations about considering the categorical rating method as being a less sensitive method than a fully quantitative volumetric analysis, as Wessels suggests [1]. To our understanding, categorical and quantitative assessments of WMH lesions have different purposes, and both methods have strengths and weaknesses.

Volumetric analysis, using both manual segmentation methods [7] and recent automated procedures [8] to measure WMH volumes, has several methodological limitations, including inter-rater reliability, partial volume effects (especially problematic in the T2-weighted images, the slice thickness of which is usually >3 mm), intensity distortion caused by magnetic field inhomogeneity and issues in processing low-quality MR images such as those obscured by motion artefacts. Some of these factors can be efficiently taken into consideration when the images are evaluated by neuroradiologists. Furthermore, we note that automatic and semiautomatic volumetric procedures have generally been validated using visual inspection scales or clinical variables as reference standards [8], which also introduces a subjective component. On a related note, the Fazekas classification system we adopted in our analysis as our primary scoring system has been histopathologically validated [9].

Although controversy exists [10], WMHs in the brain are likely to have different effects on neurological and psychiatric symptomatology according to their specific locations [11]. The visual inspection scale that we used also provides information regarding the locations of the lesions.

In conclusion, our study examined WMHs using current standard imaging techniques in a large sample of diabetic patients and matched non-diabetic controls, and the results add to our knowledge of the relationship, or lack thereof, between these lesions and diabetes or cognitive deficits. Minimal white matter lesions were found, and these were not associated with diabetes or cognition. However, newer, more sensitive imaging techniques may find differences in brain structure, metabolism or function between those with and without diabetes.

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