Letter to the Editor

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Cortical Iron Deposition Is Multicausal, and Therefore Cannot Serve as a Biomarker for Early Cognitive Impairment

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We read with interest, the article by Kim et al. [1] on a retrospective magnetic resonance imaging (MRI) study of cortical iron deposition (CID) in 158 patients with mild cognitive impairment (MCI), 48 with Alzheimer's disease (AD), and 73 with normal cognition, measured using neuronal network-based quantitative susceptibility mapping (QSMnet). Susceptibility in the frontal, temporal, parietal, occipital, and cingulate cortices was higher in patients with MCI and AD than that in the controls [1]. Susceptibility in the cingulate and insular cortices was found to be an independent predictor of Mini Mental Status Examination [1]. Iron deposition in the cingulate and insular cortices may be an early imaging marker of cognitive impairment during neurodegeneration [1]. Although this study is impressive, some points require further discussion.

AD is a progressive disease; therefore, the amount and distribution of CID can depend largely on the disease stage. Thus, we should know how many patients with AD underwent QSMnet follow-up and showed a progressive CID pattern. Furthermore, it should be considered if susceptibility correlated with disease duration and if the included patients were all at the same disease stage.

A limitation of this study is that only certain cerebral diseases associated with CID, such as Parkinson's disease, multiple sclerosis, encephalitis, malignancy, stroke, and surgery, were excluded [1]. However, CID occurs not only in the cerebral disorders excluded from the study, but also in intracerebral bleeding, subarachnoid bleeding, stroke-like episodes, MOG-associated demyelinating disorders, amyotrophic lateral sclerosis, spasticity, dystonia, or inflammation [2]. Knowing whether the included patients had prior cerebral disease is crucial to avoid confusing CID caused by AD with CID caused by other causes.

Additionally, the indications for MRI must also be stated. For example: how many patients had indications other than cognitive impairment for MRI?

A second limitation is that the imaging findings did not correlate with serum iron, ferritin, transferrin saturation, or apoferritin levels. Before associating iron accumulation in the cortex with MCI and AD, it is important to rule out impairment of iron metabolism and previous cerebral diseases.

We should also be aware of the current medications. Knowing the current medications is important, as there are drugs for which iron deposition is a side effect. This is especially true for blood transfusions, ferrous sulfate, and drugs that cause hemolysis.

Another limitation is that the diet and nutrition of the included patients was not correlatd with MRI findings. Certain foods such as peppers, tomatoes, steaks, and lentils can increase iron levels. Therefore, the patients who prefer iron-rich foods should also be considered.

Because CID has also been reported in the context of physiological aging [3], it is important to determine whether susceptibility correlates with age in healthy controls.

Controls were defined as individuals with normal cognition; however, those with imaging abnormalities were not excluded. Therefore, we should be aware how many control participants showed abnormal MRI findings.

Before CID can be attributed to AD or MCI, alternative etiologies must be ruled out. The possibility that CID was

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due to an increased intake of iron-rich food, medications, or cerebral diseases not listed in the exclusion criteria must also be ruled out.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Josef Finsterer. Data curation: Josef Finsterer. Formal analysis: Josef Finsterer. Supervision: Josef Finsterer. Validation: all authors. Writing—original draft: Josef Finsterer. Writing—review & editing: all authors.

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