Letter to the Editor

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

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I on behalf of the coauthors of our study [1] am grateful for Dr. Finsterer's thoughtful engagement with our study and welcome the opportunity to address the concerns raised.

Dr. Finsterer correctly notes the potential implications of cortical iron deposition (CID) variability across the different stages of disease [2]. While our cross-sectional design provides a snapshot of CID, it inherently cannot capture its progression over time. Acknowledging this limitation, we advocate for longitudinal studies to elucidate the trajectory of CID over time.

In our paper, we delineated our study population: individuals attending our hospital's memory clinic, which focuses on memory impairment and neurodegenerative disorders, rather than a random sample of patients with various neurological conditions such as intracerebral hemorrhage or multiple sclerosis. This selection, reinforced by stringent inclusion and exclusion criteria, yielded a group characterized by having cognitive challenges stemming predominantly from neurodegenerative processes.

We performed MR examinations at our memory clinic to evaluate brain atrophy and the presence of co-pathologies in patients with subjective or objective cognitive impairment.

We posited that cortical iron is an indicator of neurodegenerative change, not a pathognomonic marker for specific proteinopathies such as amyloidosis or tauopathies [3]. This is comparable to the role of hippocampal atrophy, a hallmark of Alzheimer's dementia that is also observed across a spectrum of other neurological conditions [4].

Dr. Finsterer's concerns about the absence of systemic iron level analysis are noted. Our study design presumes the exclusion of systemic iron-related disorders at the outset. Given the blood-brain barrier's regulation of iron, serum levels may not accurately reflect cerebral iron homeostasis, which is intricately linked to neurodegenerative processes in Alzheimer's disease. Neurotoxin-induced neurodegeneration is reported to increase brain iron levels [5].

Another limitation identified is the lack of detailed current medication data. Our cohort excluded patients undergoing treatments that could significantly alter systemic iron levels, such as blood transfusions and iron chelation therapies. Admittedly, the dietary habits and nutritional statuses of our subjects were not cataloged.

The association between cerebral iron and aging is indeed complex. Recent studies suggest a variable correlation across different brain regions. Our data revealed a modest correlation between whole cortex iron levels and age which did not reach statistical significance. Nevertheless, we factored in age as a covariate when comparing cortical iron levels across the three groups.

We hope this response adequately clarifies the points and concerns raised by Dr. Finsterer and further highlights the strengths and limitations of our study.

Conflicts of Interest

The author has no potential conflicts of interest to disclose.

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