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MR Contrast Agents

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Macrocyclic GBCAs and Parkinson's Disease: Reassuring Evidence on Safety

Na-Young Shin

Severance Hospital, Korea

Gadolinium retention in the brain following administration of gadolinium-based contrast agents (GBCAs) was first brought to widespread attention through MRI studies demonstrating progressive T1 hyperintensity in the dentate nucleus and globus pallidus with cumulative linear GBCA exposure. Subsequent tissue analyses confirmed that gadolinium deposits preferentially in iron-rich regions implicated in various forms of parkinsonism. These observations naturally raised the question of whether gadolinium retention in motor-relevant brain areas might translate into clinically meaningful neurological consequences, particularly parkinsonian symptoms. However, histopathological studies and animal experiments conducted to date have largely failed to demonstrate significant structural brain damage or motor dysfunction attributable to gadolinium deposition, even at cumulative doses substantially exceeding those used in clinical practice. In vitro data have nonetheless suggested potential neurotoxic mechanisms, including gadolinium acting as a calcium antagonist given its similar atomic radius, with downstream effects on neurotransmission, energy metabolism, and synaptic signaling. The biological plausibility of neuronal dysfunction thus remained a concern that histological and preclinical studies alone could not fully resolve. Against this background, large-scale population-based studies were needed to evaluate whether GBCA exposure is associated with a measurable increase in the incidence of parkinsonism in real-world clinical populations. A previous population-based study reported no significant association between gadolinium exposure and incident parkinsonism; however, it did not stratify by GBCA type, leaving important questions unanswered. In our nationwide cohort study utilizing the Korean National Health Insurance Service database — encompassing 222,977 individuals aged 40 years or older who underwent first-ever MRI between 2011 and 2014 and were followed through 2022 — we investigated whether the risk of parkinsonism differed according to GBCA type. A key methodological consideration in our study was the appropriate definition of the control group: preliminary analyses demonstrated that individuals who underwent MRI, even non-enhanced MRI, had markedly higher rates of parkinsonism than those who had never undergone MRI, and that brain or spine MRI was specifically associated with elevated risk, likely reflecting ascertainment bias from prodromal symptom-driven imaging. Accordingly, individuals who underwent only non-enhanced, non-neuraxial MRI served as the reference group. Under this design, exposure to linear GBCAs was associated with a modest but statistically significant increase in the risk of all-cause parkinsonism (adjusted HR, 1.13; 97.5% CI, 1.08–1.19), while exposure to macrocyclic GBCAs was not (adjusted HR, 1.00; 97.5% CI, 0.95–1.05). The differential risk between linear and macrocyclic agents is consistent with their well-characterized physicochemical differences: linear GBCAs exhibit lower thermodynamic and kinetic stability, rendering them more susceptible to transmetallation and release of free Gd^{3+} ions, whereas macrocyclic agents encage gadolinium within rigid ring structures, substantially limiting dechelation and subsequent tissue deposition. These findings provide further reassurance regarding the neurological safety profile of macrocyclic GBCAs.

Keywords: *Gadolinium-based contrast agent, Macrocyclic, Linear, Parkinsonism, Brain retention, Safety, population-based cohort*