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Controversies in Multiple Sclerosis

Gadolinium should always be used to assess disease activity in MS – Yes

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Gadolinium-based contrast agents (GBCAs) have been approved for clinical use for over 30 years. Currently, GBCAs are frequently employed in the management of patients suffering from multiple sclerosis (MS), but recently this policy has been questioned.

Focal contrast enhancement (CE) on T1-weighted spin-echo or gradient-echo images after intravenous injection of GBCAs is a sign of blood–brain barrier disruption, which is part of the pathophysiological cascade in MS-related inflammatory demyelination.[1]

Beyond its biological relevance, the presence of CE in focal lesions of the central nervous system (CNS) is one of the criteria for MS diagnosis and differential diagnosis: indeed, the simultaneous presence of CE and non-CE lesions, or the presence of a CE lesion in a follow-up scan, helps determine "dissemination in time."[2] In addition, the identification of a CE lesion helps differentiate MS from MS mimics like migraine—where no CE is found—or from other pathologies with specific CE patterns that are different from those observed in MS (e.g. cortical ischemia, neuromyelitis optica spectrum disorders (NMOSD), Baló's concentric sclerosis, capillary telangiectasia, vasculitis, Susac syndrome).[1]

The presence of CE lesions also helps identify ongoing subclinical progression and provides a measure to monitor response to therapies. The recent European Committee of Treatment and Research in Multiple Sclerosis (ECTRIMS) recommendations for disease-modifying therapy (DMT) monitoring include the measurement of both new or unequivocally enlarging T2 lesions and CE lesions.[3] In addition, compared to new T2/enlarging lesions, CE can elucidate the timing of a new lesion, because enhancement in inflammatory demyelinating lesions is a short-lived feature (typically 2–8 weeks), whereas T2 hyperintensity persists for much longer.[1]

Beyond the tried and true, new reasons for assessing CE in MS continue to emerge. For example, the acquisition of a post-contrast T2-FLAIR (fluid-attenuated inversion recovery) sequence can reveal the presence of focal leptomeningeal enhancement, which has been associated with progressive disease.[4] And importantly, the presence of focal CE must be assessed during the monitoring of patients at risk to develop progressive multifocal encephalopathy (PML) and immune reconstitution inflammatory syndrome (IRIS).[5]

In recent years, the potential adverse effects of GBCAs have received considerable attention, notably the risk of nephrogenic systemic fibrosis (NSF) and of GBCA deposition in the body/brain. Nevertheless, the potential for adverse events varies greatly across GBCA types. There is universal agreement that some agent types carry a much lower risk of NSF than others. Indeed, a very recent meta-analysis provides striking evidence of this, showing that the risk of NSF from group II GBCA administration even in patients with late-stage chronic kidney disease is only 0.07%.[6] As to the accumulation of gadolinium in the body and in the brain, which has been increasingly reported in recent years, this effect appears to be substantially lower when macrocyclic compounds are used instead of linear chelates.[7] Moreover, to date, there are no data demonstrating the clinical significance of gadolinium deposition in the brain and in the body (outside of NSF), and the stated position of the Food and Drug Administration, the European Medicines Agency, and similar international organizations is that there are currently no associated known or proven harmful effects.[7]

There are some very promising new developments in the diagnosis and differential diagnosis of MS, such as the central vein sign (CVS) and the presence of cortical lesions (CLs), which may in the future inform the utility of CE.[8] The percentage of CVS in lesions is substantially higher in MS compared to non-MS patients, and CLs have not been shown in migraine and have only rarely been

detected in NMOSD.[8] However, both CVS and CLs are less conspicuous in images acquired with currently used pulse sequences at common clinical fields (1.5 and 3 T), which limits their application for now. While they may plan an important role in the future, neither CVS nor CLs are included in the current diagnostic criteria for MS.

A variety of non-contrast magnetic resonance imaging (MRI) techniques have been proposed as possible alternatives to detect CE in MS lesions, including diffusion weighting and susceptibility weighting.[9] There may also be information obtainable by modeling MRI signal intensity from conventional MRI sequences.[10] Alternative contrast agents, such as manganese, might become useful in the future. However, few studies have been performed in MS patients using these techniques, and their ultimate value remains uncertain. Thus, at present, there is no better or even comparable substitute to GBCAs for MS management and MS activity assessment.[9]

In summary, CE MRI is still necessary for measuring disease activity, diagnosing MS, monitoring therapy, and assessing therapy complications. In some MS patients with no evidence of radiological and clinical disease activity, the routine use of GBCA may prove less important. However, given all the exceptions one would have to make, if there were a policy for no gadolinium, CE MRI should remain the standard of care in MS.

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