Deciphering the contributions of neuroinflammation to neurodegeneration: lessons from antibody-mediated encephalitis and coronavirus disease 2019

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Purpose of review
Does neuroinflammation promote neurodegeneration? Does neurodegeneration promote neuroinflammation? Or, is the answer to both questions, *yes*? These questions have proven challenging to answer in patients with typical age-related neurodegenerative diseases in whom the onset of neuroinflammation and neurodegeneration are largely unknown. Patients recovering from diseases associated with abrupt-onset neuroinflammation, including rare forms of antibody-mediated encephalitis (AME) and common complications of novel coronavirus disease 2019 (COVID-19), provide a unique opportunity to untangle the relationship between neuroinflammation and neurodegeneration. This review explores the lessons learned from patients with AME and COVID-19.

Recent findings
Persistent cognitive impairment is increasingly recognized in patients recovering from AME or COVID-19, yet the drivers of impairment remain largely unknown. Clinical observations, neuroimaging and biofluid biomarkers, and pathological studies imply a link between the severity of acute neuroinflammation, subsequent neurodegeneration, and disease-associated morbidity.

Summary
Data from patients with AME and COVID-19 inform key hypotheses that may be evaluated through future studies incorporating longitudinal biomarkers of neuroinflammation and neurodegeneration in larger numbers of recovering patients. The results of these studies may inform the contributors to cognitive impairment in patients with AME and COVID-19, with potential diagnostic and therapeutic applications in patients with age-related neurodegenerative diseases.

Keywords
antibody-mediated encephalitis, biomarkers, coronavirus disease 2019, neurodegeneration, neuroinflammation, severe acute respiratory syndrome coronavirus 2

INTRODUCTION

Neuroinflammatory changes may promote the accrual and propagation of neuropathological changes associated with Alzheimer disease (AD) and AD-related dementias (ADRD). Autopsy studies attest to the relationship between inflammatory mediators (cytokines, chemokines, prostaglandins, complement cascade proteins) and breakdown in the blood-brain-barrier [1–6], while depicting the association between reactive glia, and cerebral plaques and tangles. In cellular models, activated microglia and astrocytes induce amyloid-beta and tau pathology, while deletion of microglial receptors prevents inflammation and ameliorates amyloid accumulation [7–9]. In mouse models, microglial activation occurs months before neurofibrillary tangle formation [10]. Genetic evidence further strengthens this relationship in humans, with variants affecting microglia or astrocyte activation linked to neurodegeneration (e.g., *TREM2* mutations in Nasu–Haloka disease; microglial-expressed progranulin mutations in patients with frontotemporal lobar degeneration, FTLD

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KEY POINTS

- The relationship between neuroinflammation and neurodegeneration is challenging to decipher in patients with typical age-related neurodegenerative diseases.
- Clinical observations, neuroimaging and biofluid biomarker measures, and pathological studies suggest that acute neuroinflammation associated with antibody-mediated encephalitis (AME) and coronavirus disease 2019 (COVID-19) precedes neurodegeneration and contributes to persistent cognitive impairment.
- Knowledge gained through the study of patients with AME and COVID-19 may inform the relationship between neuroinflammation and neurodegeneration with potential diagnostic and therapeutic applications in patients with age-related neurodegenerative diseases.

[11,12]). Taken together these findings suggest that neuroinflammation drives neurodegeneration. Yet, an equally robust literature suggests that neurodegenerative changes promote neuroinflammation. The aggregation of various neurodegeneration-related proteins triggers inflammatory processes, including microgliosis, microglial 'priming' (an activated state leading to exaggerated responses), cytokine release, and complement activation [4,13–17]. Additionally, population-based prospective studies suggest that the sustained use of nonsteroidal anti-inflammatory drugs negatively associated with the development of AD [18] (although prospective treatment trials failed to prove this [19]). Clearly, the relationship between neuroinflammation and neurodegeneration is complex.

Unraveling this complex relationship in patients with age-related neurodegenerative diseases is challenging. In humans, disease-associated pathology accumulates over decades, at variable rates, with various effects. Furthermore, the inability to directly measure histopathologic changes early in the course of AD/ADRD has confounded efforts to decipher the temporal ordering of neuroinflammation and neurodegeneration. Although animal models may address some of these limitations, current models fall far short of the human experience. Models relying on overexpression of genes or protein products may drive excessive pathology, without time for a compensatory response, while single gene 'knock-in' (or out) approaches may result in changes that are too mild to elicit measurable changes, particularly if animals are not allowed to age sufficiently [20–22]. New models and new approaches are needed to address this challenge.

Patients with diseases associated with the abrupt onset of substantial neuroinflammation offer one possible solution to this problem: providing an opportunity to study the relationship between neuroinflammation and neurodegeneration in a cohort where the direction of effect is known. On this front, experience with increasing numbers of patients recovering from rare forms of antibody-mediated encephalitis (AME) or common complications of novel coronavirus disease 2019 (COVID-19) may inform the short- and long-term consequences of neuroinflammation on neurodegeneration, including the effects of neuroinflammation on the formation and propagation of age-associated neurodegenerative diseases in susceptible individuals.

ANTIBODY-MEDIATED ENCEPHALITIS

Neuroinflammation in antibody-mediated encephalitis: cause?

Rare diseases associated with autoantibodies against central nervous system (CNS) cell-surface *N*-methyl-D-aspartate receptors (NMDAR) or components of the voltage-gated potassium channel complex (e.g., leucine-rich glioma-inactivated 1; LGI1) provide unique insights into the effects of targeted neuroinflammation. Acutely, the immune-mediated pathological process is marked by inflammatory changes in the cerebrospinal fluid (CSF), including pleocytosis, immunoglobulin synthesis, and clonal expansion of disease-specific autoantibodies; with transient changes on magnetic resonance neuroimaging (MRI), including T2-fluid-attenuated inversion recovery (FLAIR) and contrast-enhancing abnormalities in cortical and subcortical regions [23–27]. In AME associated with NMDAR and LGI1 autoantibodies, these changes correspond to the emergence of prominent behavioral and psychiatric symptoms, including memory loss, altered mental status, hallucinations, psychoses, and affective disturbances. Movement disorders, seizures, and autonomic dysfunction may also occur, contributing to morbidity and mortality [26,27]. The link between acute neuroinflammation and clinical presentation is supported by cellular models demonstrating antibody-mediated disruption in neuronal signaling associated with autoantibody exposure [26,28–30]; animal models recapitulating clinical findings with intraventricular infusion of CSF from AME patients [31,32]; and, most convincingly, by the high potential for recovery in AME patients treated with immune-suppressing therapies [24–26].

The longer-term consequences of neuroinflammation are increasingly understood in recovering patients. Persistent deficits in attention, memory,

and executive function are common in recovering NMDAR and LGI1 AME patients [33–38]. Cognitive deficits are noted in 80% of recovering NMDAR AME patients assessed between 2 and 5 years from disease onset [39], and at least 65% of patients recovering from LGI1 AME assessed a median of 39 months following disease onset [40]. Poor cognitive outcomes are more likely in patients with marked CSF pleocytosis or MRI abnormalities at presentation, and in those who experience delays from symptom onset to initiation of immunosuppressant therapies [39–41], implying that the severity and duration of neuroinflammation is associated with long-term outcomes. Importantly, long-term cognitive deficits are seen in the absence of concurrent neuroinflammation [42], raising questions concerning the mediators of impairment in recovering AME patients.

Neurodegeneration in antibody-mediated encephalitis: effect?

Early in the disease course, CSF biomarkers of neurodegeneration (total tau, VILIP-1) are similar in patients with AME and healthy controls [43▪,44] suggesting that neuronal integrity is acutely maintained. By contrast, markers of neuroinflammation (YKL-40, tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, IL-10 [43▪,45]) and neuro-axonal injury (neurofilament light chain, NfL) [43▪,46▪,47,48] are elevated, whereas markers of synaptic function (SNAP-25 and neurogranin) are decreased [43▪,46▪]. If neuronal integrity is acutely maintained in AME patients, then long-term outcomes may reflect the protracted effects of neuroinflammation, neuroaxonal injury, and synaptic dysfunction. Longitudinal studies increasingly support this hypothesis (Table 1).

Functional MRI confirms acute network dysfunction, loss of intrinsic activity [49], and widespread connectivity alterations in patients with NMDAR AME [36,50]. These deficits persist in patients with behavioral and cognitive dysfunction [36,51]. Similarly, structural neuroimaging, although normal at presentation in many patients [24,36], may become abnormal in follow-up (Fig. 1). Diffuse cerebral atrophy is recognized in longitudinal imaging in AME, with disproportionate effects on the hippocampi [52,53], which may be most prominent in patients with persistent deficits in verbal and visual memory [34]. Deep [54] and superficial [55] white matter disruption is also reported on diffusion tensor MRI in recovering patients with memory and visuospatial dysfunction.

The long-term drivers of structural and functional changes in recovering AME patients are

Table 1. Biomarkers of neurodegeneration following AME

Biomarkers	Acute findings	Long-term findings
MRI		
Structural & functional	Normal in most cases [36] Mild hippocampal atrophy [52] Impaired functional connectivity of the hippocampus [50] Loss of intrinsic activity: reduction in the amplitude of spontaneous BOLD fMRI fluctuation [49]	Diffuse cerebral and bilateral hippocampal atrophy [34,52,53] Widespread deep white matter damage [54] Superficial white matter damage predominant in the frontal and temporal lobes [55] Impaired hippocampal connectivity; decoupling of the medial temporal and default-mode networks; an overall impairment of frontotemporal connections [36] Alteration in default mode network with aberrant structure–function relationship with damaged hippocampus; impairments in sensorimotor, salience and higher visual networks [51]
CSF		
Markers of neuroinflammation	Elevated YKL-40, TNF-α, IL-6, IL-10 [43▪,45]	Normalization of YKL-40 levels [45]
Markers of neurodegeneration	Normal t-tau, VILIP-1 [43▪,44]	Normal t-tau [44]
Markers of neuroaxonal injury	Elevated NfL [43▪,46▪,47,48]	Normalization of NfL levels [44]
Molecular PET		
Tau PET	Not reported	Prominent [^{18}F]flortaucipir retention within the temporal lobes, correlating to hippocampal atrophy [65▪]

AME, antibody-mediated encephalitis; BOLD, blood oxygen level dependent; CSF, cerebrospinal fluid; IL, interleukin; MRI, magnetic resonance imaging; NfL, neurofilament light chain protein; TNF-α, tumor necrosis factor-α; T-tau, total tau; VILIP-1, visinin-like protein 1.

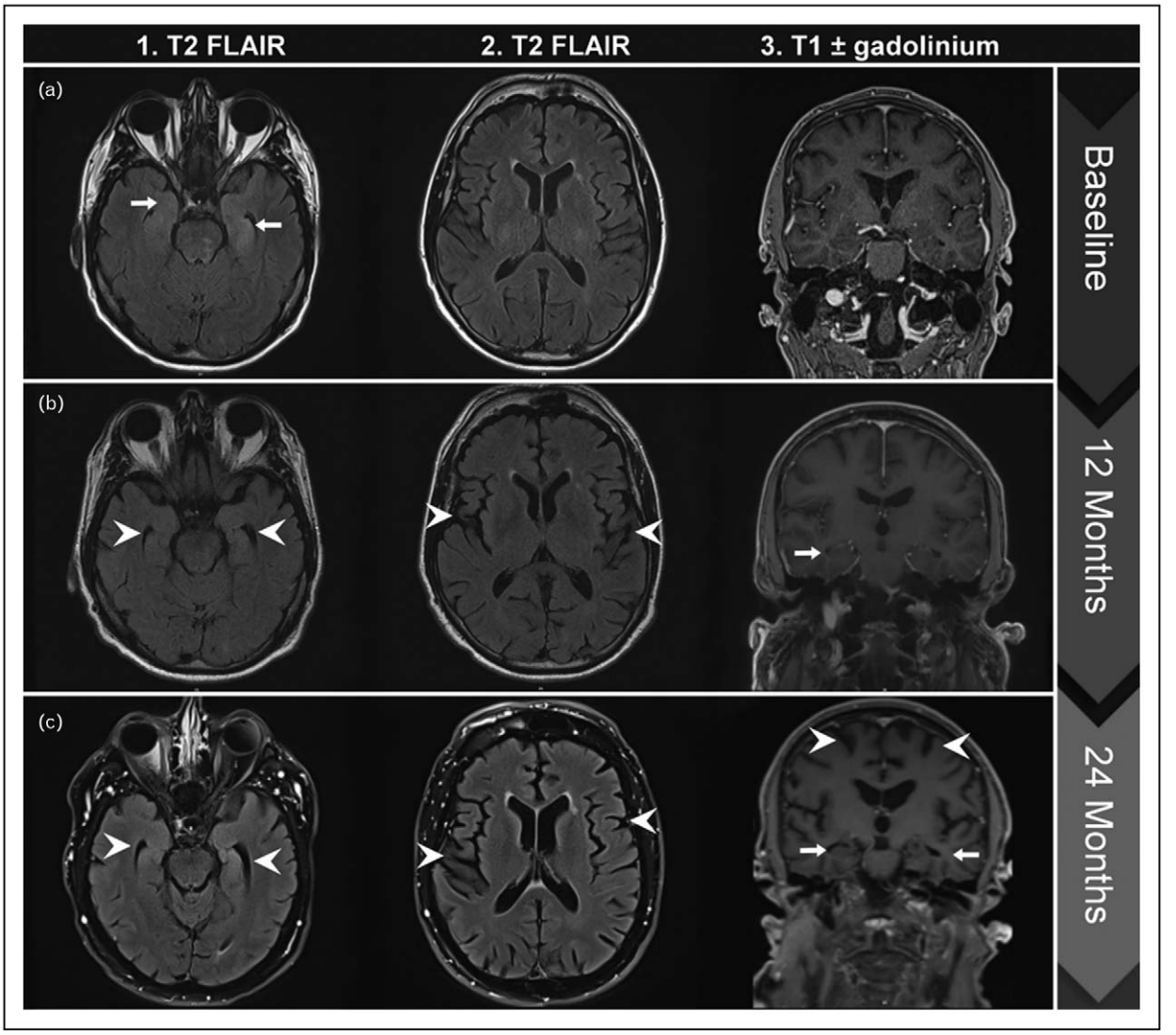

FIGURE 1. A 68-year-old man presented with the subacute onset of personality changes, irritability, confusion, and a convulsion. Subtle bitemporal T2-FLAIR hyperintensities were observed on brain MRI (A1, white arrows), without enhancement (A3). LGI1 autoantibodies were detected in the serum and spinal fluid, establishing the diagnosis of *definite* LGI1 antibody-mediated encephalitis. He was treated with plasmapheresis within 5.5 weeks of symptom onset, and subsequently rituximab leading to resolution of acute confusion. Cognitive impairment persisted, characterized by deficits in orientation and memory, difficulty with word retrieval, spelling errors, and slow deductive reasoning, meeting diagnostic criteria for 'autoimmune dementia' [33]. No inflammation was found on repeat CSF studies or neuroimaging, although diffuse cerebral (white arrowheads) and focal hippocampal atrophy (white arrows) were evident on neuroimaging obtained 12- (B1–3) and 24-months (C1–3) following symptom onset. Memory deficits remain stable 36-months following symptom onset. CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

unclear. Extensive pathological studies are lacking in AME, owing to favorable outcomes in treated patients. The few studies available almost exclusively report findings in patients with severe, treatment-refractory forms of disease who died during the acute phase of the illness. These studies confirm gliosis, microglial activation, and infiltrating leukocytes and antibody-secreting cells, with acute neuronal loss [56–60]. Antibody-mediated complement activation with T-cell infiltration may be a unique feature in patients with LGI1 AME [56,61], providing a plausible pathway for immune-mediated neuronal destruction and degeneration leading to progressive atrophy in these patients [62]. Less is known in NMDAR AME.

Findings from biofluid biomarkers, neuroimaging, and highly selected autopsy series raise important questions concerning the long-term neuropathological consequences of AME. Longitudinal studies culminating in neuropathological assessment are

needed to address these questions. In lieu of such studies, novel applications of emergent molecular PET tracers may provide insights into antemortem brain changes, providing an opportunity to evaluate the distribution and accumulation of amyloid (e.g., ^{18}F-florbetaben (Neuraceq), ^{18}F-florbetapir (Amyvid), ^{18}F-flutemetamol (Vizamyl) [63]) and tau neuropathology (e.g., ^{18}F-flortaucipir, Tauvid [64]), and to study the relationship between cognitive symptoms and neuropathology. To date, molecular imaging studies are limited to a single series including four patients with LGI1 AME [65▪]. Increased ^{18}F-flortaucipir tau-PET retention was noted in two recovering patients, who both exhibited protracted cognitive impairment with hippocampal atrophy. In the patient with highest accumulation, molecular imaging findings were confirmed at autopsy [66]. Although preliminary, these findings suggest that accumulating tau neuropathology may contribute to cognitive complaints and structural and functional changes observed in recovering AME patients. Future studies incorporating tau-PET imaging at multiple intervals in larger cohorts are required to replicate these findings and determine whether AME-associated neuroinflammation influences the formation and propagation of tau neuropathology in susceptible individuals.

CORONAVIRUS DISEASE 2019

Neuroinflammation in coronavirus disease 2019: cause?

Neurological deficits are common in recovering COVID-19 patients, with headache, nausea, anosmia, ageusia, myalgia/fatigue, confusion, or disorientation recognized in 36% of patients in some series [67]. More serious neurologic consequences are reported in 13.5% of patients, including encephalopathy, stroke, seizures or hypoxic injury [68]. Rates of cognitive impairment may be even higher with some studies reporting acute deficits in 80% of patients [69], and persistent complaints in 35.5% [70]. As with AME, the risk of impairment increases with disease severity, with higher prevalence of impairment noted in patients who require hospitalization, intensive care unit admission, and intubation [70–72].

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus infiltrates epithelial cells of the respiratory and gastrointestinal tract via the angiotensin converting enzyme 2 (ACE2) functional receptor. ACE2 is also expressed within CNS neurons and glia [73], providing a possible pathway through which SARS-CoV-2 may invade the CNS [74]. Evidence of axonal transport, neuron-to-neuron propagation, and detection of virus RNA in brain autopsy samples supports direct dissemination of SARS-COV-2 within the CNS as one cause of neurologic sequelae [75]. However, the absence of virus in most CSF samples and tissues specimens in autopsy series implicates other *indirect* drivers of cognitive impairment [76,77], namely neuroinflammation. Indeed, a substantial proportion of COVID-19 patients with CNS-localizing neurological symptoms have evidence of neuroinflammation in the CSF (positive SARS-CoV-2 antibodies with evidence of intrathecal synthesis (12%), pleocytosis (15%), elevated cerebral fluid protein (31%) [76]). Cases of SARS-CoV-2-related encephalitis are also recognized, with CSF examination demonstrating elevations in NfL, t-tau, YKL-40 and higher concentrations of cytokines such as IL-1β, IL-6, IL-8, and TNF-α compared to healthy controls [78]. The cytokine storm associated with COVID-19 infection may also promote cognitive dysfunction by contributing to blood-brain-barrier disruption (via IL-6 mediated endothelial dysfunction and vascular permeability), and through IL-1 mediated acceleration of the formation and propagation of underlying age-related neuropathology in susceptible individuals [16,79].

Neurodegeneration in coronavirus disease 2019: effect?

Biomarker studies provide compelling evidence of neurodegeneration in moderate and severely ill COVID-19 patients (Table 2). Serum biomarkers of neuroaxonal injury (e.g., NfL) are higher in patients with severe COVID-19 versus healthy controls [80], while biomarkers of neurodegeneration (e.g., t-tau, p-tau$_{181}$, NfL, and UCHL1) appear to rise during the acute phase of illness [81], normalizing months later [82,83]. Higher markers may identify patients with greater neurological symptoms and illness severity [82]. Brain imaging provides further insights. Abnormal brain imaging findings in acutely ill COVID-19 patients may be harbingers of chronic vascular pathology [84,85], with few reports suggesting focal hippocampal atrophy in selected patients with new-onset seizures [86]. One study leveraging diffusion tensor MRI found possible disruption to microstructural integrity in the recovery stages of COVID-19 patients compared to healthy controls, with changes in olfactory- and limbic-related regions correlating with memory loss [87]. In the UK Biobank COVID-19 re-imaging study [88▪▪], 401 participants tested positive for SARS-CoV-2 infection between two MRI scans (mean 3.2 ± 1.6 years between scans). Compared to controls, infected participants had greater global atrophy and tissue damage in limbic regions, which was associated with greater cognitive decline [88▪▪]. As COVID-19 remains a new illness, longitudinal

Table 2. Biomarkers of neurodegeneration following COVID-19

Biomarkers	Acute findings	Long-term findings
MRI		
Structural & functional	Chronic vascular lesions: nonspecific white matter microangiopathy, chronic infarcts [84,85] Acute vascular lesions: ischemic infarcts or hemorrhage [84,85] Focal hippocampal atrophy in selected patients [86]	Disruption to micro-structural and functional brain integrity, including enlarged olfactory cortices, insulas, Rolandic operculum, cingulate gyrus, Heschl's gyrus, hippocampi, corona radiata, external capsule, and superior frontal-occipital fasciculus [87] Reduced cortical thickness and contrast in the lateral orbitofrontal region and para-hippocampal gyrus; a relative increase of diffusion indices in the regions of the brain functionally-connected to the piriform cortex, anterior olfactory nucleus, and olfactory tubercle; reduction in global measures of brain size and increase in CSF volume [88▪▪]
CSF		
Markers of neuroinflammation	Elevated YKL-40, TNF-α, IL-6, IL-8, IL-1β [78]	Not reported
Markers of neurodegeneration	Elevated t-tau [78,82]	Not reported
Markers of neuroaxonal injury	Elevated levels of NfL [78,81,82]	Normalization of NfL levels [83]

COVID-19, coronavirus disease 2019; CSF, cerebrospinal fluid; IL, interleukin; MRI, magnetic resonance imaging; NfL, neurofilament light chain; TNF-α, tumor necrosis factor-α; T-tau, total tau.

biomarker data are lacking. Longitudinal studies are needed to inform the long-term consequences of neuroinflammation and the relationship between early biomarker changes, and later neurodegeneration and cognitive function.

Neuropathological findings to date have exclusively reported findings from patients who died in the acute phase of COVID-19 [89▪,90]. As expected, these studies codify the presence of neuroinflammation, describing abundant reactive astrogliosis, microgliosis, T-cell invasion, hypoxic injury, and rare cases with leptomeningeal inflammation [89▪]. Although most patients in neuropathological series died before neurodegenerative changes would be expected to manifest, select patients exhibited brainstem neuronal loss ($n = 4$) and axonal degeneration ($n = 3$) [90]. As with AME, neuropathological studies in recovered patients are needed to decipher the drivers of long-term complications of COVID-19. Molecular PET studies offer an opportunity to track the effect of COVID-19 associated neuroinflammation on the formation and propagation of age-related neuropathology. However, no studies have been published reporting amyloid- and tau-PET measures in recovering patients.

INFORMING THE LINK BETWEEN NEUROINFLAMMATION AND NEURODEGENERATION

Experience with recovering AME and COVID-19 patients inform the relationship between acute neuroinflammation, neurodegeneration, and cognitive impairment. Clinical observations, neuroimaging and biofluid biomarkers, and pathological studies imply a link between the severity of acute neuroinflammation, subsequent neurodegeneration, and disease-associated morbidity. Although much remains to be determined before cause and effect can be established, these early findings inform key hypotheses that may be tested through future studies. Neuroinflammation may mediate some effects acutely (i.e., by direct cellular damage reflected in acute elevation in neurodegenerative biomarkers in subsets of patients with severe illnesses). However, long-term sequelae likely extend from the long-term effects of neuroinflammation, which may include blood-brain-barrier disruption, vascular stress, immune dysregulation, and glial activation. The cumulative effects of these changes may trigger the formation of and/or promote the propagation of typical age-related pathology in susceptible individuals (e.g., individuals with existing preclinical pathology, or disease-associated genetic variants such as *APOEε4* and *TREM2*).

Longitudinal studies incorporating biofluid, neuroimaging, and molecular biomarkers of neuroinflammation and neurodegeneration are needed to explore these hypotheses. In this respect, the COVID-19 pandemic offers a unique opportunity to study the chronic effects of time-locked neuroinflammation in large numbers of patients. As in AME, it will be particularly interesting to consider how neuroinflammation associated with severe COVID-19 contributes to the formation and propagation of age-related neuropathology in susceptible individuals.

CONCLUSION

Clinical observations, neuroimaging and biofluid biomarker measures, and pathological studies suggest that acute neuroinflammation predates the emergence of neurodegeneration in recovering AME and COVID-19 patients. Knowledge gained through the study of unique patients with diseases associated with abrupt onset of neuroinflammation may inform the complex relationship between neuroinflammation and neurodegeneration, with potential diagnostic and therapeutic applications that extend well beyond patients with AME and COVID-19.

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Conflicts of interest

Dr. Shir reports no conflicts of interest. Dr. GS Day owns stock (>$10,000) in ANI Pharmaceuticals (a generic pharmaceutical company). He serves as a topic editor for DynaMed (EBSCO), overseeing development of evidence-based educational content; and as a consultant for Parabon Nanolabs Inc. on a NIH-sponsored grant supporting the development of smartphone-based cognitive testing. He is the Clinical Director of the Anti-NMDA Receptor Encephalitis Foundation (Inc, Canada; uncompensated).

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