DOI: 10.1111/cei.13670

Clinical & Experimental Immunology
The Journal of Translational Immunology
British Society for immunology

EDITORIAL

REVIEW SERIES: IMAGING IMMUNOLOGICAL PROCESSES IN NEUROINFLAMMATORY DISEASES

Series Editor: Sandra Amor

Imaging immune responses in neuroinflammatory diseases

Abstract

Innate and adaptive immune responses in the central nervous system (CNS) play critical roles in the pathogenesis of neurological diseases. In the first of a two-part special issue, leading researchers discuss how imaging modalities are used to monitor immune responses in several neurodegenerative diseases and glioblastoma and brain metastases. While comparative studies in humans between imaging and pathology are biased towards the end stage of disease, animal models can inform regarding how immune responses change with disease progression and as a result of treatment regimens. Magnetic resonance imaging (MRI) and positron emission tomography (PET) are frequently used to image disease progression, and the articles indicate how one or more of these modalities have been applied to specific neuroimmune diseases. In addition, advanced microscopical imaging using two-dimensional photon microscopy and *in vitro* live cell imaging have also been applied to animal models. In this special issue (Parts 1 and 2), as well as the imaging modalities mentioned, several articles discuss biomarkers of disease and microscopical studies that have enabled characterization of immune responses.

Future developments of imaging modalities should enable tracking of specific subsets of immune cells during disease allowing longitudinal monitoring of immune responses. These new approaches will be critical to more effectively monitor and thus target specific cell subsets for therapeutic interventions which may be applicable to a range of neurological diseases.

The role of innate and adaptive immune responses in neurodegenerative and neuroinflammatory diseases has become a focus for many researchers, not least because of the ageing community, and therefore the increase in age-related neurodegenerative diseases [1,2]. That the average life expectancy exceeds the eighth decade in many parts of the world has highlighted the role what has been termed 'inflammageing' [3], the chronic, low-grade, subclinical inflammatory processes coupled to biological ageing in many neurodegenerative disorders. Additionally, the immune system plays a critical role in shaping the brain during development [4] and in repair processes [5], but also in the response to tumours. For these reasons monitoring immune responses during disease progression, as well as how such responses change and as a result of therapy, is increasingly important.

In this special issue, imaging in its broad sense has been used to cover microscopy approaches, magnetic resonance imaging (MRI), positron emission tomogtaphy (PET), magnetic resonance spectroscopy (MRS) (Table 1) and optical coherence tomography (OCT). These studies provide an insight into the various approaches used to aid our current understanding of immune processes in central nervous system (CNS) diseases.

In this two-part review series we have collated articles that cover a range of neurodegenerative and neuroinflammatory diseases and the current approaches used to monitor disease and assess efficacy of treatment regimens. In Part 1 of the series, leading researchers in the field of neuroimmunology review how PET targeting 18 kDa translocator protein (TSPO) has been used to detect microglia [6], and imaging of the immune system has been applied to pathological processes in amyotrophic lateral sclerosis (ALS) [7], neuromyelitis optica (NMO) [8], myelin oligodendrocyte glycoprotein (MOG) immunoglobulin (Ig)G antibody-associated

OTHER ARTICLES PUBLISHED IN THIS REVIEW SERIES

Magnetic resonance imaging in neuromyelitis optica spectrum disorder. Clinical and Experimental Immunology 2021, 206: 251–265.
Clinical and neuroimaging findings in MOGAD-MRI and OCT. Clinical and Experimental Immunology 2021, 206: 266–281.
Towards PET imaging of the dynamic phenotypes of microglia. Clinical and Experimental Immunology 2021, 206: 282–300.
Imaging immunological processes from blood to brain in amyotrophic lateral sclerosis. Clinical and Experimental Immunology 2021, 206: 301–313.
Neuroinflammation and immunoregulation in glioblastoma and brain metastases: Recent developments in imaging approaches. Clinical and Experimental Immunology 2021, 206: 314–324.
'A picture is worth a thousand words': The use of microscopy for imaging neuroinflammation. Clinical and Experimental Immunology 2021, 206: 325–345.

TABLE 1 Types of imaging approaches

Imaging modality	Principal	Comments
Positron emission tomography (PET)	Uses radiolabelled ligand that binds to selected target, e.g. translocator protein (TSPO) and F-FIMP an L-type amino acid transporter 1 (LAT1)-specific PET probe	TSPO was widely considered to represent pathogenic proinflammatory microglia, but more recent studies report that TSPO PET rather represents microglial density in the brain F-FIMP is an L-type amino acid transporter 1 (LAT1)-specific PET probe that allows better differentiation between tumour tissue and inflammation
Magnetic resonance imaging (MRI)	1. Voxel-based morphometry 2. Diffusion tensor imaging 3. Magnetic resonance spectroscopy 4. Susceptibility weighted imaging 5. Functional MRI	In general, these approaches determine the extent of axonal injuries across different axonal tracts More specifically, they can determine the levels of increased iron accumulation in microglia and astrocytes
Biological fluids [e.g. blood, cerebrospinal fluid (CSF), urine]	Various methods, e.g. proteomics, can identify changes in immune markers as well as levels of central nervous system (CNS) proteins, e.g. neurofilament (Nf) light	Many do not fully distinguish different neurological diseases

disorders (MOGAD) [9] and brain tumours [10]. Part 1 also includes a paper that covers microscopic approaches to monitor disease [11]. Part 2, which will be published in 2022, will include imaging of infectious and other neurodegenerative diseases. However, as discussed below and in the mini-reviews, several questions remain to be addressed.

As with both the adaptive and innate immune systems, whether these responses are beneficial or detrimental in neurological conditions depend upon the disease, type and magnitude of the response and the level of immune regulation in the CNS. For example, in viral infections adaptive immune responses are generally considered to be beneficial to eradicate the virus although, as seen in SARS-CoV-2, the innate arm of the immune response leads to tissue damage even after the infectious virus has been eliminated. In contrast, tumours of the brain and brain metastases induce changes that lead to immunosuppression and trigger an inflammatory response within the tumour microenvironment [11].

During development the innate immune response in the CNS is responsible for synaptic pruning by microglia, as well as phagocytosis of debris and apoptotic cells – steps that are critical for homeostasis and repair. The development of transcriptomic and single nucleus RNA sequencing has revealed the vast complexity of microglial phenotypes as well as other innate immune cells in the CNS [12,13]. This has generated great interest in identifying and monitoring these cells *in situ* to more effectively correlate the phenotypes with disease processes. In their article, Beanio and colleagues review how PET imaging can be applied to image microglia phenotypes [6].

The identification of biomarkers and imaging techniques for diagnosis, to monitor disease processes and assess efficacy of therapies in neurodegenerative disorders is a rapidly emerging field. The limited access to the CNS necessitates proxy approaches such as blood and cerebrospinal fluid biomarkers or imaging techniques. In the paper by Clarke *et al.* [8] the authors discuss the clinical aspects of neuromyelitis optica spectrum disorder (NMOSD), an inflammatory disease of the CNS associated with antibodies directed to a water channel: aquaporin-4 (AQP4). Given the differences in therapeutic approaches to treat closely related diseases the authors focus on magnetic resonance imaging (MRI), which has been key to distinguishing the disease using imaging technology and immune assays to assess AQP4 antibodies. A closely related disease to NMOSD is the new group of demyelinating diseases MOGAD. Serologically, MOGAD is diagnosed by the presence of serum IgG autoantibodies against MOG. In their review, Bartels *et al.* [9] discuss the different MRI and OCT approaches from multi-centred studies. Lastly, Amor *et al.* [7] discuss MRI, MRS and PET approaches as well as serological biomarkers of inflammation in amyotrophic lateral sclerosis (ALS) and those arising from the animal models of ALS. In contrast to classical neurodegenerative diseases, Roesler *et al.* review approaches to image inflammation in association with brain tumours and brain metastases that have aided diagnosis of primary tumours versus inflamed and necrotic brain lesions [11].

The development of imaging approaches to probe specific immune pathways during neurological diseases will be key to monitoring disease progression and discriminating specific diseases. As well as those questions and perspectives given in the reviews, we have outlined several important considerations:

1. When applying and thus reporting data on imaging modalities in neurodegenerative diseases the studies should include the patient cohort sizes and the relevant control cohorts. Large cohorts are critical if it is necessary to segregate subgroups of patients.
2. The emerging technology in ultra-high field and resolution functional MRI and time-of-flight PET/MRI offers new possibilities. Advances in imaging performance with increased sensitivity and specificity will enable higher spatial and temporal resolution and detection of targets with low endogenous expression.
3. Biomarkers of innate and adaptive immune responses need to be specific to more effectively segregate the expanding numbers of neuroinflammatory and neurodegenerative diseases.

As repeatedly reported [14,15], a fundamental consideration remains how relevant a specific experimental animal model is to the human neurodegenerative disease it is modelling.

In summary, imaging modalities can inform on various aspects of CNS pathology; for example, by measuring brain atrophy, myelin damage and levels of innate immune activation reflected by biomarkers in blood and CSF. Emerging evidence indicates that many neurodegenerative diseases may share common pathological mechanisms that involve the interplay between resident innate immune cells, neurones, glia and, in some conditions, the immune cells recruited from the periphery. The link between the changes in immune responses with ageing and the increased incidence of neurodegenerative diseases in the ageing population could provide important insights into this interplay and thus it is crucial to further develop imaging approaches to monitor these during life.

Many questions still need to be answered, and the future development of imaging approaches should provide more insight into the role of immune responses in neurodegenerative diseases in general and provide tools to monitor novel therapeutic strategies targeting innate immune responses in the CNS.

KEYWORDS

amyotrophic lateral sclerosis, central nervous system, imaging, inflammation, innate immune system, microglia, neuroimmunology, PET

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