

Viewpoints

The Roles and Uses of Extracellular Vesicles in Neuroimmunologic Diseases

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Neuroimmunology is a field of neurology focused on the diagnosis and treatment of diseases where the immune system causes inflammation or injury to the nervous system. This includes diseases such as multiple sclerosis, myelin oligodendrocyte glycoprotein antibody-associated disease, neuromyelitis optica spectrum disorder, autoimmune encephalitis, autoimmune ataxia, stiff person syndrome spectrum disorder, and neuro-rheumatologic diseases such as neuropsychiatric lupus. Over the past couple decades, there have been significant advancements in the diagnostic methods for several neuroimmunologic diseases. Despite these achievements, major needs remain for additional methods to facilitate earlier diagnosis, monitor disease activity and treatment, and elucidate disease mechanisms to aid in the development of novel or tailored treatment strategies. Currently, there is often a trade-off between the invasiveness of neurodiagnostic testing and the level of detail that can be obtained from the test without causing an iatrogenic injury. Here, we discuss the potential of extracellular vesicles (EVs), especially CNS-derived EVs obtained from peripheral blood, as a promising avenue for advancing research and clinical care in neuroimmunology. This article provides a review of the key clinical features and approaches to care for the most common neuroimmunologic diseases. We identify gaps that remain in our current understanding of these conditions. We then highlight how ongoing research in the EV field may address these existing gaps. Finally, we examine the challenges that must be overcome before EV analysis can be more widely adopted in both research and clinical care in this field.

Key words: autoimmune encephalitis; biomarker; exosomes; multiple sclerosis; neuroimmunologic disease

Introduction

The field of neuroimmunology is focused on diseases in which the immune system attacks the nervous system—especially the central nervous system (CNS). Primary neuroimmune diseases are those in which the autoimmune process is primarily focused on the nervous system. These include primary demyelinating diseases [such as multiple sclerosis (MS), myelin oligodendrocyte glycoprotein (MOG) autoantibody-associated disease (MOGAD), and anti-aquaporin-4 (APQ4)-positive neuromyelitis optica spectrum disorder (NMOSD)], as well as autoimmune encephalitis, autoimmune ataxias, and stiff person syndrome spectrum disorder. Conversely, neuro-rheumatologic diseases are neuroimmune diseases in which systemic autoimmunity and inflammation are often co-occurring and/or driving the neurologic inflammation or injury (Govoni and Hanly, 2020). In this article, we review the most common neuroimmunologic diseases, the current unmet gaps in their understanding and clinical care, and current work and future directions to improve care through the application and analysis of extracellular vesicles (EVs).

Multiple Sclerosis

MS is the most common primary neuroimmune disease with an estimated prevalence of 2.8 million persons worldwide and an incidence of 2.1 per 100,000 persons/year (Walton et al., 2020). MS is a chronic disease characterized by recurrent relapses of demyelination in the CNS. These relapses result in focal neurologic deficits such as vision or sensory loss, paresis/paralysis, coordination issues, and ataxia. Although they are followed by periods of remission (Jakimovski et al., 2024), damage accumulates with each relapse, and with ongoing subclinical inflammation disability can progress even without relapse. High rates of chronic cognitive dysfunction and fatigue are also seen. As a result, MS is considered one of the leading causes of disability from neurologic disease in young and middle-aged adults (Jakimovski et al., 2024).

There are several forms of MS, including clinically isolated syndrome (CIS), relapsing-remitting MS, secondary progressive MS, and primary progressive MS (Haki et al., 2024; Montalban et al., 2025). CIS is a term that is used to denote a person who has a single event of demyelination but does not yet meet criteria for MS. Relapsing-remitting MS is characterized by a series of relapses with at least partial recovery (remittance) in between relapses. Primary and secondary progressive MS shows a gradually progressive disability that occurs independent of relapses. Progressive MS is the most disabling form of MS, with many individuals requiring walking aids or wheelchairs (Haki et al., 2024; Montalban et al., 2025).

There is no single diagnostic test for MS at present. Instead, people are diagnosed through the McDonald clinical criteria.

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This requires evidence of demyelination on magnetic resonance imaging (MRI) or clinical flares in typical locations for MS (optic nerve, periventricular, juxtacortical, infratentorial, or spinal cord) and evidence of either multiple relapses, chronic inflammation in the cerebrospinal fluid (CSF) determined by the presence of multiple CSF-unique oligoclonal bands, or other evidence suggesting a high risk of recurrent disease. An exclusion of mimics of MS, such as MOGAD or NMOSD, may also be needed (Montalban et al., 2025). The lesions in MS may appear as T2 hyperintensities, indicating either current inflammation and demyelination or chronic damage to the white matter, while gadolinium contrast enhancement of lesions can point to active inflammation. Accelerated atrophy of white or gray matter in the brain is commonly seen in MS or after a severe demyelinating attack (Barkhof et al., 2025).

Immunotherapy is a cornerstone in the treatment of MS, helping to limit injury and neurologic deficits from the disease. Acute inflammation in demyelinating disease is treated with high-dose corticosteroids or plasmapheresis. Relapses or progression of MS are prevented through long-term maintenance preventative immunotherapy (disease-modifying therapy), such as fingolimod, natalizumab, or anti-CD20 medications like rituximab and ocrelizumab (Haki et al., 2024).

Myelin Oligodendrocyte Glycoprotein Autoantibody-Associated Disease

MOGAD is a disease that often mimics MS, having both a demyelinating and encephalitic form (Banwell et al., 2023). Presentations of demyelinating MOGAD disease include optic neuritis, transverse myelitis, and brainstem inflammation. This disease has an estimated prevalence of >100,000 persons and an incidence of 0.3–0.5 per 100,000 persons/year (Hor and Fujihara, 2023). Diagnosis is based on the presence of serum or CSF anti-MOG antibodies at high titers, in addition to a consistent clinical phenotype. This disease may have a monophasic or a relapsing course similar to MS. However, it often shows more significant impairment during relapses than MS and a better recovery afterward with little or no progression between relapses (Sechi et al., 2022). It is not yet clear who will develop a relapsing course at the time of the first attack, and relapses may be years apart. Therefore, the appropriate time to start maintenance preventative immunotherapies, their duration, and their type are still not known. When started, rituximab, intravenous immunoglobulin, antiproliferative medications such as azathioprine or mycophenolate, or anti-interleukin-6 medications such as tocilizumab are the most frequently used interventions (Cacciaguerra and Flanagan, 2024).

Anti-aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder

Anti-AQP4-positive NMOSD is an astrocytopathy causing demyelinating lesions, often presenting as a longitudinally extensive transverse myelitis or optic neuritis. While less common than MS, with an estimated prevalence of 25,000–820,000 persons and an annual incidence of 0.3–10 per 100,000 persons (Papp et al., 2021), its relapses are often devastating and patients are left with permanent disabilities (Yang et al., 2014). Anti-AQP4-positive NMOSD is a chronic disease, with many patients remaining on lifelong maintenance preventative immunotherapies that include complement inhibition with eculizumab or ravulizumab, inebilizumab (anti-CD19),

or anti-interleukin-6 medications such as satralizumab (Cacciaguerra and Flanagan, 2024).

Autoimmune Encephalitis

Autoimmune encephalitis is characterized by the acute to subacute onset of neuropsychiatric symptoms due to neuroinflammation from autoantibodies against neuronal cell surface synaptic channels or through destruction of the neurons by cytotoxic T-cells (Dalmau and Graus, 2018). Autoimmune encephalitis often presents with a new onset of encephalopathy or cognitive deficits, significant psychiatric disease such as catatonia or psychosis, seizures, movement disorders, autonomic dysfunction, or coma. It has an estimated prevalence of 13.7 per 100,000 persons, and an annual incidence of 0.8 per 100,000 persons, similar to that of infectious encephalitis (Dubey et al., 2018). While these symptoms may improve with immunotherapy, a number of individuals are left with chronic cognitive or psychiatric sequelae or epilepsy (Brenner et al., 2024; Jia et al., 2025).

Anti-N-methyl-D-aspartate receptor encephalitis (NMDARE) is one of the more well-known forms of autoimmune encephalitis, although MOGAD is also being recognized as another frequent cause of autoimmune encephalitis (Dalmau and Graus, 2018; Dubey et al., 2018). Herpes simplex virus encephalitis (HSVE) has been noted as a potential trigger for some forms of NMDARE. It is thought that the initial injury to the brain from HSVE exposes neuronal antigens to the immune system, with NMDAR antibodies and NMDARE developing within several weeks later (Swayne et al., 2022). A subset of NMDARE are also paraneoplastic, most commonly associated with ovarian teratomas (Dalmau and Graus, 2018).

Autoimmune Cerebellar Ataxia

Autoimmune cerebellar ataxia is a disease with a subacute to chronic onset of gait abnormalities, ataxia, and coordination issues, usually without encephalopathy or other significant neurologic symptoms. There are multiple causes, including paraneoplastic cerebellar degeneration or opsoclonus-myoclonus-ataxia syndrome. Autoimmune cerebellar ataxia has a variable response to immunotherapy, and outcomes often include permanent neurologic deficits (Meira et al., 2023).

Stiff Person Syndrome Spectrum Disorder

Stiff person syndrome spectrum disorder is a chronic neurologic disease characterized by immunotherapy-responsive painful muscle spasms and progressive stiffness of the axial > appendicular musculature. This disease has a prevalence of ~2 per 100,000 persons and an annual incidence of 0.3 per 100,000 persons (Crane et al., 2024). Diagnosis is often delayed an average of 3 years from symptom onset due to subtle onset of symptoms or their overlap with other neurologic diseases. While immunotherapy and muscle relaxants help ease the morbidity of this disease, many remain significantly affected in daily life and require assistive devices for mobility (Wang et al., 2024b).

Neuro-rheumatologic Diseases

Neuro-rheumatologic disease refers to neuropsychiatric complications occurring from a systemic rheumatologic disease. This contrasts with the primary neuroimmune diseases discussed above, where autoimmunity and damage are focused on the nervous system. A number of rheumatologic diseases can develop neurologic involvement, including systemic lupus erythematosus

(SLE; Govoni and Hanly, 2020), sarcoidosis (Bradshaw et al., 2021), Sjogren's syndrome (Perzyńska-Mazan et al., 2018), rheumatoid arthritis (Villa et al., 2021), and vasculitis (Sherri et al., 2024). Depending on the underlying rheumatologic disease, the neurologic manifestations can be diverse—including demyelination, encephalitis, strokes, movement disorders, seizures, meningitis, confusion, and neuropathy. The treatment for these is usually a more intensive immunosuppressive protocol typical for that systemic rheumatologic disease (Govoni and Hanly, 2020).

Neuropsychiatric Diseases with Unclear Neuroimmune Involvement

There are also neuropsychiatric syndromes whose status as neuroimmune diseases is still being debated, but for which neuroimmunologists may be called upon to evaluate and provide treatment recommendations. This includes Down syndrome regression disorder (Santoro et al., 2022a,b) and pediatric acute-onset neuropsychiatric syndrome (AAP, 2025).

Down syndrome regression disorder is a severe neuropsychiatric disorder that can affect adolescents and young adults with Down syndrome. In this disorder, the individual has a subacute onset of developmental regression, new autistic features, a loss of skills of daily living, mutism, and catatonia or hallucinations (Santoro et al., 2022a,b). A subset shows signs of neuroinflammation on neurodiagnostic evaluation, but there is a variable response to both psychiatric medications and immunotherapies with or without evidence of neuroinflammation (Santoro et al., 2022a,b).

Pediatric acute-onset neuropsychiatric syndrome is a disorder which affects children and results in an abrupt onset of severe obsessive-compulsive disorder, anorexia, tics, school difficulties, anxiety, or other disabling psychiatric symptoms. While neuroimaging and cerebrospinal fluid testing are often normal, a portion show significant improvements with immunotherapy—raising debate on the involvement of the immune system for at least a subset of these patients (Frankovich et al., 2017; AAP, 2025).

Animal Models of Neuroimmunologic Diseases

Experimental autoimmune encephalomyelitis (EAE) is a set of animal models most often used to study demyelinating diseases, in particular MS and MOGAD. In the most common EAE models, mice or other mammals are actively immunized with CNS autoantigens such as myelin basic protein, proteolipid protein, or myelin oligodendrocyte glycoprotein, together with complete Freund's adjuvant and pertussis toxin (Baker and Amor, 2014; Lassmann and Bradl, 2017; Dedoni et al., 2023). This results in acute or chronic demyelination with features that overlap those seen in human demyelinating disease.

Animal models of different stages of autoimmune encephalitis have also been developed through passive antibody transfer or active immunization using neuronal cell surface receptor subunits. These models recapitulate several of the clinical and immunologic features of the disease (Levite, 2014; Dalmau et al., 2019). Similarly, immunization models of acute neuropsychiatric SLE have been created using autoantigens related to SLE (Polis et al., 2024).

However, as with every model system, there are dissimilarities in the disease course, effective treatments, and immune mechanisms observed between these animal models and human diseases, which may limit the translation of the findings (Baker

and Amor, 2014). For example, in EAE there is greater axonal injury, spinal cord demyelination, and T-cell-predominant inflammation than is seen in human patients with multiple sclerosis. In addition, a number of compounds that are effective in treating EAE models of disease do not succeed in human trials (Lassmann and Bradl, 2017; Dedoni et al., 2023). These differences may be due to the process of disease induction, choice of autoantigen, or species-related differences in immune responses or neural repair mechanisms (Lassmann and Bradl, 2017; Polis et al., 2024).

Unmet Needs in Neuroimmunology

Diagnosis

Although the diagnosis of several neuroimmune diseases has advanced significantly over the past several decades (Dalmau et al., 2017; Banwell et al., 2023), challenges remain. The most common neuroimmunologic disease, multiple sclerosis, still does not have a specific biomarker for diagnosis and thus can be misdiagnosed as a different demyelinating disease (Montalban et al., 2025). Over half of NMDARE cases have normal MRIs, with 14% having “normal” standard CSF testing (cell count, protein, and oligoclonal bands), leaving neuroinflammation and NMDARE to only be confirmed upon the return of their autoantibody testing (Hébert et al., 2020). Additionally, between 14 and 45% of autoimmune encephalitis cases are antibody negative (Moreno-Estébanez et al., 2021; Mojžišová et al., 2023; Gao et al., 2024). Therefore, these cases must be diagnosed through additional diagnostic testing to search for evidence of neuroinflammation (Graus et al., 2016; Cellucci et al., 2020). These challenges in using standard tests of neuroinflammation can result in a delayed diagnosis and treatment of these diseases.

The challenges of traditional biomarkers of neuroinflammation also affect the diagnosis and treatment of neuro-rheumatologic disorders such as neuropsychiatric systemic lupus erythematosus (NPSLE). The heterogeneity in clinical presentation of these disorders can result in inconsistent CSF or MRI findings, often delaying diagnoses in subtle or evolving disease (Emerson et al., 2023; Kammeyer et al., 2024). For some diseases such as CNS vasculitis or neurosarcoidosis, brain or spine biopsy remains the gold standard of diagnosis despite the potential injury that can result from these biopsies (Rice and Scolding, 2020; Lackey et al., 2024). There is an urgent need to develop new and less invasive diagnostic biomarkers for these neuro-rheumatologic diseases to provide a safer and earlier diagnosis and better outcomes (Govoni and Hanly, 2020).

Treatment selection

Predictive biomarkers to assist in selecting the most efficacious and targeted treatment for an individual are needed. The current immunotherapy treatments for neuroimmunologic diseases include immunosuppression with corticosteroids, antiproliferative medications such as mycophenolate mofetil, monoclonal antibodies such as rituximab, or other disease-modifying therapies or immunomodulation with intravenous immunoglobulin or plasma exchange (Abboud et al., 2021; Lee and Chan, 2024). Given the risk of systemic side effects and the broad action of many of the current interventions, there is an intense interest in identifying more targeted and mechanistically focused therapies that have fewer off-target side effects. The development of regenerative treatments and/or treatments that address the etiology of residual chronic symptoms are also highly desired by both providers and patients, given the frequency of disability or chronic symptoms in these diseases.

Monitoring for treatment response and progression

Novel tools are also urgently needed for the monitoring of treatment response and/or disease progression in neuroimmunology. Early detection of inadequate treatment or of disease progression is essential to provide more targeted treatment prior to a clinical relapse or worsening of disability. While clinical or composite measures of disease severity and disease control exist for use in autoimmune encephalitis and several demyelinating diseases, these rely, at least in part, on subjective clinical assessment (Kappos et al., 2016; Lim et al., 2019). These may not adequately predict future relapses or disease progression in an individualized manner or identify subtle changes (Rotstein et al., 2022; Weinstock-Guttman et al., 2022; Lai et al., 2024). These also cannot determine whether ongoing neuropsychological symptoms post intervention are residual from the initial injury or caused by smoldering neuroinflammation whose treatment might improve outcomes for that individual.

Given the limitations of solely clinical measures for monitoring, complementary biological markers are needed. Currently, serum or plasma cytokines as well as other systemic markers of inflammation are often inconsistent and/or unreliable for monitoring neuroinflammation in primary autoimmune neurologic disease (Ma et al., 2022). They are also difficult to interpret in systemic rheumatologic diseases, which commonly have concurrent systemic inflammation (Hirohata and Kikuchi, 2021). Traditional CSF markers of inflammation, such as cell count, oligoclonal bands, autoantibody titers, and cytokines, may more directly evaluate inflammatory disease activity (Leypoldt et al., 2015). However, these can be inconsistent, even during relapse (Gresa-Arribas et al., 2014; Ciano-Petersen et al., 2025). Also, relying on periodic invasive sampling of the CSF prevents close monitoring and tailoring of immunotherapy treatments. New and minimally invasive biomarkers are essential to improve our ability to monitor treatment response(s) and develop new therapeutic approaches.

Disease mechanisms

Our knowledge of disease mechanisms for neuroimmunologic diseases remains limited. The mechanisms underlying several primary neuroimmune diseases are gradually being elucidated, providing important insights that have translated into clinical care and treatment (Huang et al., 2022; Charabati et al., 2023; Michalski et al., 2024). However, the role of each individual brain cell type (neurons, microglia, astrocytes, oligodendrocytes, etc.) in pathogenesis or disease manifestation has largely been evaluated through animal models of disease or immunohistopathology from biopsied or autopsied human CNS tissue (Huang et al., 2022; Charabati et al., 2023; Michalski et al., 2024). The development of less invasive methods to analyze alterations in individual CNS cell types is needed to complement or assist in the validation of findings from mechanistic studies with animal models.

In addition, the etiology and underlying mechanistic cause of several neuroimmune diseases or the neuro-rheumatologic diseases remain unclear. For example, the normal or inconsistent findings from standard neurodiagnostic testing and the variable response to immunotherapy of Down syndrome regression disorder and pediatric acute-onset neuropsychiatric syndrome suggest that either multiple subtypes of disease exist (with both inflammatory and noninflammatory mechanisms) or that additional work is needed to elucidate the specific role of the immune system in their pathogenesis. For neuro-rheumatologic diseases, the mechanisms are often assumed to be similar to that of the systemic disease, yet how the CNS becomes involved is a topic of

ongoing research. New methods to evaluate the mechanisms in these diseases would greatly advance our understanding of the appropriate treatments for each.

Extracellular Vesicles—Characteristics and Isolation

The analysis of EVs or one of their subsets—such as CNS-derived exosomes in plasma or serum—may provide methods to address these unmet needs and improve the treatment and care for patients with neuroimmune diseases.

EVs are nonreplicative lipid bilayer particles that are secreted from every living cell in the body and range in diameter from 30 to 5,000 nm (Jeppesen et al., 2023). EVs may be subcategorized in several ways, including by size, fluid or tissue source, subcellular origin, cell of origin, and/or molecular content. Approximate characterizations by size include “small” (<200 nm) and “large” EVs (>200 nm; Welsh et al., 2024). EVs present in the blood are cleared rapidly (within several hours) through hepatic or renal routes (Lai et al., 2014), although systemic inflammation may impair clearance and increase plasma half-life (Pavlova et al., 2026).

Several terms have been used to group EVs by their subcellular origin. These include apoptotic bodies, microvesicles, and exosomes (Fig. 1). Apoptotic bodies are thought to occur when a portion of the plasma membrane of a dying cell is separated from its cytoskeleton, forming a separate vesicle or “bleb” that contains membrane proteins, cytosolic proteins, nucleic acids, and organelles. The content and location of these bodies are random and the size of these bodies variable (50–5,000 nm), although typically in the “larger” size range (Gregory and Rimmer, 2023).

In contrast, microvesicles are smaller than most apoptotic bodies, ranging between 100 and 1,000 nm in diameter, resulting in the exclusion of most larger organelles (Yates et al., 2022). They are formed by a direct outward budding and pinching off from the plasma membrane. This budding is coordinated by a directed redistribution of lipid components of the plasma membrane, through flippase and floppase, which in turn affects the curvature of the membrane and contributes to microvesicle formation (Tricarico et al., 2017; Clancy et al., 2021). ADP-ribosylation factor 6 (ARF6) can selectively recruit proteins and endosomes for incorporation into these microvesicles and coordinate actomyosin contraction across the neck of the microvesicle to facilitate its pinching off and release. With respect to their contents, multiple forms of nucleic acids (DNA, mRNA, microRNA) can be trafficked to and incorporated into microvesicles, along with cytosolic proteins and plasma membrane-associated proteins and lipids (Clancy et al., 2021).

Exosomes are generally reported as vesicles that are 30–150 nm in diameter and are considered a form of “small” EV. They are reported to originate from the endosomal system, in particular from multivesicular bodies (MVBs) within this system. As shown in Figure 1, early endosomes may be formed by endocytosis of extracellular contents (including EVs from other cells) or products from the Golgi complex. Invagination of the endosomal membrane results in the formation of multiple intraluminal vesicles (ILVs; Primorac et al., 2026). This matured and ILV-containing endosome is termed an MVB. The ILVs in the MVB have three main potential fates; they can be sent to the lysosome for degradation, reintegrated into the MVB membrane, or trafficked to the cell membrane using cytoskeletal and Rab GTPase mechanisms (Eden and Futter, 2021; Xu et al., 2023; Primorac et al., 2026). At the cell membrane, SNARE and SNAP proteins assist in the fusion of MVBs with the cell

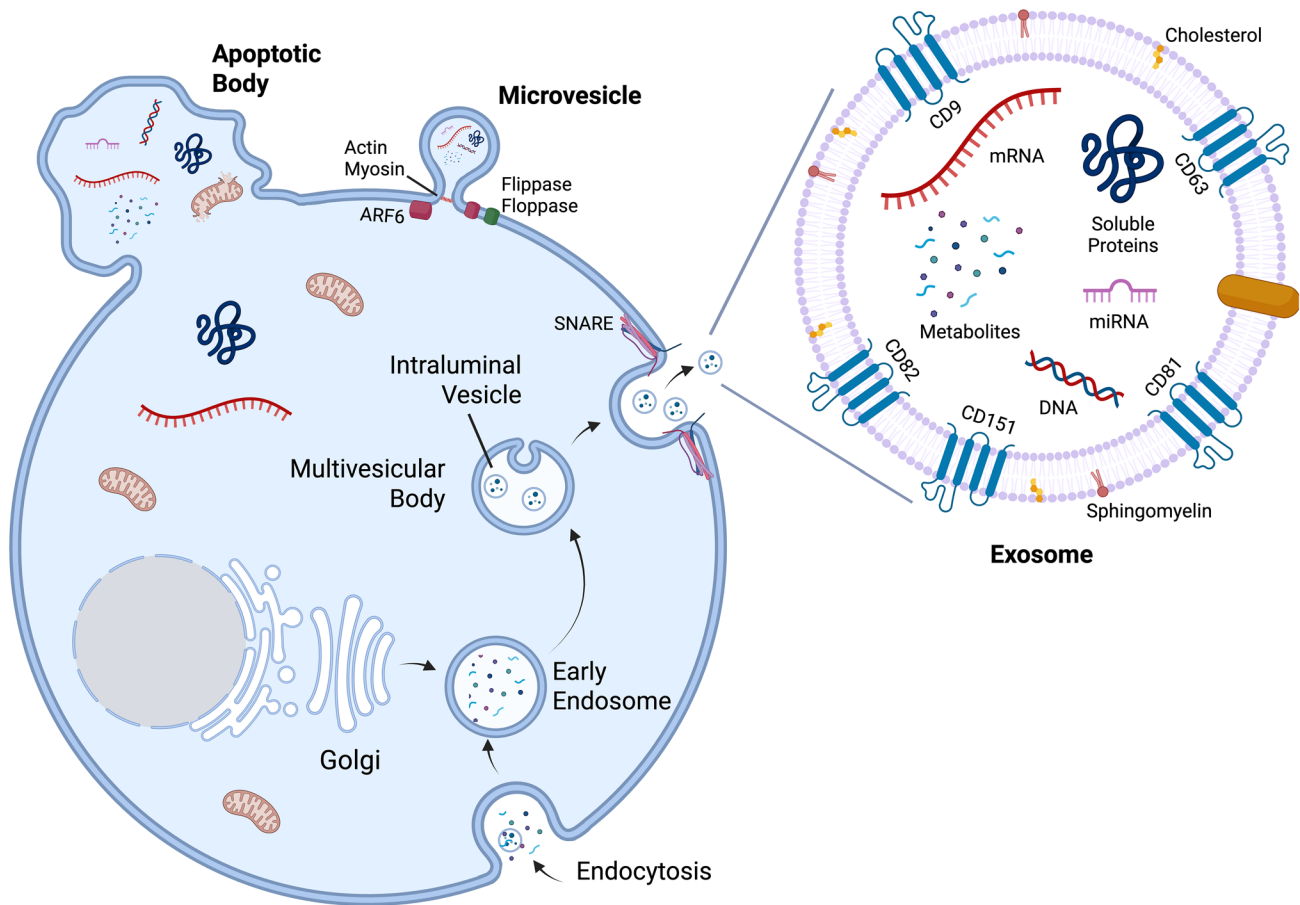


Figure 1. Theorized biogenesis and contents of extracellular vesicles: apoptotic bodies, microvesicles, and exosomes. ARF6, ADP-ribosylation factor 6; CD, cluster of differentiation; DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid; miRNA, microRNA. Created in BioRender. Coughlan, C. (2026). BioRender.com/e4q8fxr

membrane, releasing their ILVs into the extracellular space (Liu et al., 2023). These released ILVs are now considered exosomes (Doyle and Wang, 2019; Primorac et al., 2026). How and why the ILVs are directed to each pathway is the focus of many research studies.

With respect to the cargo transported by these EVs, microvesicles and exosomes can both carry cytosolic and membrane proteins, metabolites, DNA, mRNA, and microRNA. Given the nature of their formation, microvesicles are proposed to have greater enrichment of plasma membrane proteins and lipids than exosomes (Yates et al., 2022). In contrast, the lipids enriched in exosomes include cholesterol, sphingolipids, and sphingomyelin as well as free fatty acids (Skotland et al., 2025). Exosomes are also enriched in transmembrane tetraspanin proteins, including cluster of differentiation (CD) markers CD9, CD63, CD81, CD82, and CD151 (Rubinstein et al., 2025) that may, along with the endosomal sorting complex required for transport (ESCRT) complexes, determine the protein cargo sorted into ILVs from intracellular locations and the plasma membrane (Primorac et al., 2026).

In practice, it is difficult to isolate and study pure forms of these three EV subtypes. While exosomes are generally reported as vesicles that are 30–150 nm in diameter, and thus considered a form of “small” EV, the overlapping size range of exosomes and microvesicles makes it challenging to obtain fully pure samples of each vesicle type using size alone. Additionally, there is an overlap of the expected contents and surface markers of these EV subtypes, especially between microvesicles and exosomes

(Yates et al., 2022). Exosomes are often considered to be “isolated” by tetraspanin content, but given tetraspanins are present on the plasma membrane, they can be present on a larger range of EVs than just those originating from the endosomal system (Welsh et al., 2024).

Given the challenges in isolating EVs into their subtypes and conclusively proving their subcellular origin, EVs is the recommended term to be used in most studies (Welsh et al., 2024). For the purpose of this review, we will use the term EVs or exosomes depending on the term used in a given publication, while recognizing that in many of these studies the subcellular origin was not definitively identified and only theorized by EV content and size.

EVs can be isolated from source fluids by several approaches, each with their own benefits and shortfalls. The most commonly used methods to date include ultracentrifugation, ultrafiltration, size exclusion chromatography, immunoaffinity-based capture, and precipitation-based methods (Coughlan et al., 2020; Dilsiz, 2024; Suresh and Zhang, 2025). Ultracentrifugation approaches, especially if accompanied by a subsequent density gradient separation, are labor- and time-intensive (18–20 h) and may damage or induce aggregation of the EVs (Dilsiz, 2024; Suresh and Zhang, 2025). Ultrafiltration uses a series of filters and pressure to force a sample fluid through membranes with pores based on an expected diameter or molecular weight for a chosen EV size. This process can be quick compared with ultracentrifugation and can be automated, but EV deformation or lysis may occur (Dilsiz, 2024). Size exclusion chromatography may be

used alone or with an ultracentrifugation pretreatment step to gently isolate EV-sized particles, with a higher yield of intact EVs compared with repeated ultracentrifugation (Dilsiz, 2024; Suresh and Zhang, 2025). Immunoaffinity methods use unique surface proteins found on EVs, such as the highly enriched tetraspanin proteins. Antibody-coated magnetic beads with affinity for these proteins are added to the EV sample in solution and the EVs that bind to these beads are magnetically separated and subsequently eluted from the beads. This method is useful for small sample volumes and has a high specificity for EVs once the surface markers of these EVs are accurately identified (Veerman et al., 2021). However, it has a lower yield compared with other methods since not all EVs will contain the specific markers used in the capture technique (Dilsiz, 2024). Precipitation methods use highly hydrophilic polymers, such as polyethylene glycol, that bind to water molecules, reducing the solubility of the EVs in solution, resulting in their precipitation as a pellet. To reduce contamination of the EV pellet with cell debris or platelets, centrifugation of supernatants and human biofluids is performed prior to precipitation. This method is rapid and inexpensive and produces a high yield of intact EVs with small sample volumes (Coughlan et al., 2020; Veerman et al., 2021; Dilsiz, 2024). When followed by immunoaffinity methods, this method can produce high yields of EVs purified for distinct subpopulations.

The Enrichment and Application of CNS-Derived Extracellular Vesicles

Because EVs bidirectionally cross the blood–brain barrier, a subset of EVs in peripheral blood originate from cells in the CNS (Zou et al., 2022). Thus, using unique surface protein markers and immunoaffinity-based approaches, EVs from the CNS can be selected for and isolated from total EVs in the blood. The analysis of these CNS-derived EVs can then provide valuable information about the physiology and pathology occurring in the CNS for a specific neurologic or autoimmune disease (Zheng et al., 2022; Palacio et al., 2023; Coughlan et al., 2024). In neurodegenerative diseases such as Alzheimer's disease, the evaluation of CNS-derived EVs has provided new diagnostic and therapeutic biomarkers (Hamlett et al., 2017; Chinnathambi et al., 2025) as well as a greater understanding of the underlying mechanisms of disease (Coughlan et al., 2024). This is also true for traumatic brain injury, where elevation of proteins associated with neurologic injury (total tau, $\alpha\beta 42$) and inflammation (interleukin-6) occurs within neuron-derived plasma exosomes and associates with clinical post-concussion symptoms (Gill et al., 2018; Goetzl et al., 2019).

This isolation of CNS-derived EVs provides a minimally invasive method for analyzing the brain from a blood test, avoiding the risks and limitations of other more invasive approaches such as lumbar punctures or brain biopsies. Targeting CNS-derived EVs may also serve to improve the sensitivity and selectivity of the biomarkers currently used in the identification and detection of neurologic disease, generating “liquid biopsies” for CNS pathologies (Malhotra et al., 2023; Chen et al., 2025). The rapid clearance of EVs from the circulation also suggests that CNS-derived EVs from the blood may provide a more dynamic snapshot of the neurologic environment than current biomarkers with slower clearance such as neurofilament light (Lai et al., 2014; Holmegaard et al., 2024).

The identification and validation of reliable markers of CNS-derived EVs is an important ongoing avenue of research in this field. Various surface markers with varying degrees of

CNS cell-type specificity have been proposed and used to enrich EVs from each CNS cell type. This includes L1 cell adhesion molecule (L1CAM) or neural cell adhesion molecule (NCAM) for neuron-derived exosomes/EVs, Tmem119, P2RY12, Iba1, and TREM2 for microglia-derived exosomes/EVs, glutamate aspartate transporter (GLAST) for astrocyte-derived exosomes/EVs, and MOG for oligodendrocyte-derived exosomes/EVs, among others (Gabrielli et al., 2022; Roseborough et al., 2023; Bravo-Miana et al., 2024). The reliability of the chosen surface markers in enrichment for CNS-derived EVs is a key remaining challenge in their use. For example, while L1CAM was initially widely used to identify neuron-derived exosomes, it was later identified in other CNS cells, in systemic cell types, and in a soluble form that is not membrane associated (Bravo-Miana et al., 2024; Kadam et al., 2025), thus decreasing its specificity as a “neuronal marker.” Other candidate markers for enrichment have been evaluated, but there is not yet consensus on which markers are optimal for each cell type in the CNS.

Extracellular Vesicles in Neurophysiology and Neuropathology

Our understanding of the roles of EVs and exosomes in the human body is constantly expanding. Current data supports important roles for exosomes in maintaining intracellular homeostasis and intercellular communication between all brain cell types (Kalluri and Lebleu, 2020). EVs can also transfer proteins, RNA, and other forms of cargo to a receiving cell with the internalization of EVs through endocytosis (Frühbeis et al., 2012; 2013). EVs also bidirectionally cross the blood–brain barrier, allowing communication between the brain and systemic cell types (Banks et al., 2020).

This communication has a functional impact on the brain and adjacent tissues in neurologic diseases. For example, after herpes zoster reactivation, plasma exosomes have been found to induce prothrombotic states and trigger proinflammatory cytokine production by human brain vascular adventitial fibroblasts (Bubak et al., 2023), potentially contributing to the higher risk of stroke after infection. Furthermore, exosomes derived from glioblastoma multiforme tumors induce permeability of the blood–brain barrier (Zhao et al., 2018) and alter cytokine release from astrocytes (Wang et al., 2024a). In addition, serum-derived exosomes in systemic inflammatory states activate microglia, astrocytes, and cerebral endothelial cells, and exosomes from activated glial cells may induce injury or neuroinflammation in adjacent brain or endothelial cells (Mukherjee et al., 2019; Ozansoy et al., 2023; Kodali et al., 2024).

Given the ability of EVs to cross the blood–brain barrier, their role in intercellular communication, and their targeted uptake by certain recipient cells, EVs are also being explored for their potential in targeted drug delivery, repairing CNS tissue, and/or modifying neuropathology (Kalluri and Lebleu, 2020; Zhai et al., 2022; Wang et al., 2023; Hasaniani et al., 2024; Kråkenes et al., 2024; Saleem et al., 2024; Askari et al., 2025; Zonouz et al., 2025). To achieve this potential, additional work determining the role of EVs in the communication between cell types within the CNS and their role in neuropathology is essential.

Extracellular Vesicles in Neuroimmunologic Diseases

The unique properties of EVs and their role in intercellular communication make them ideal candidates for studying

neuroimmunologic diseases and developing new biomarkers. The unmet needs in neuroimmunologic care include the need for minimally invasive biomarkers for diagnosis, treatment selection, treatment monitoring, and disease progression, along with the identification of mechanisms of disease or of chronic residual neuropsychological symptoms. These needs can be met, at least in part, through the study of EVs. For example, CNS-derived plasma or serum EVs may contain microRNAs or proteins correlating with recent and active inflammation, allowing minimally invasive measurements of this inflammation without a lumbar puncture, thereby assisting in diagnosis and treatment monitoring (Torres Iglesias et al., 2024). The rapid turnover of EVs in circulation and rapid changes in response to treatments can provide dynamic markers of disease (Lai et al., 2014; Sáenz-Cuesta et al., 2018). In those with disease progression or chronic residual neuropsychiatric symptoms, the analysis of proteins, microRNAs, or metabolites in EVs associated with oxidative stress or metabolic dysfunction could also assess if these pathways are involved in the pathogenesis of these symptoms (Ladakis et al., 2022). Given their role in intercellular communication, EVs also likely play active roles in modulating the neuroinflammatory environment and its recovery after neuroinflammation—potentially providing insights for new treatments or identifying novel mechanisms that contribute to these diseases and their comorbidities (Benjamins et al., 2019). Further examples of the potential role of EVs and their analysis in addressing the unmet needs in neuroimmunology are provided in the following sections.

The majority of the current work evaluating EVs in neuroimmunologic disease has focused on total EV or exosome populations from the blood or CSF, primarily in the demyelinating disease of MS. Thus, there are very few studies evaluating CNS-derived plasma or serum EVs in the field of neuroimmunologic disease relative to the immense number of total studies concerning these diseases each year.

Multiple sclerosis

Total EVs and exosomes from the serum or plasma of MS patients have unique microRNA, protein, and lipid profiles compared with healthy controls (Tables 1, 2). These may provide new biomarkers for predicting or monitoring response to immunotherapies. For example, a decrease in serum exosomal miR-150-5p, which directly targets sphingosine-1-phosphate, is associated with a positive clinical and radiologic response 6 months postintervention with the immunotherapy fingolimod (sphingosine-1-phosphate inhibitor; Ebrahimkhani et al., 2020). Similarly, a serum exosomal miRNA panel was identified that was associated with positive responses to interferon- β treatment (Manna et al., 2018). Expanding more broadly, a composite measure of pretreatment oligodendrocyte (MOG+) and neuron-derived (L1CAM+) serum EV concentrations and two exosomal miRNAs predicted early treatment responses to multiple immunotherapies (Torres-Iglesias et al., 2025).

Potential biomarkers of relapses and disease activity in MS have been identified through the analysis of EVs. Myelin basic protein is reported to be elevated in oligodendrocyte-derived EVs in persons with progressive and relapsing MS compared with controls, with levels correlating with disease activity (Agliardi et al., 2023; Torres-Iglesias et al., 2023). Similarly, serum exosomal MOG protein was elevated in relapse and correlated with active MRI lesions (Galazka et al., 2018). Excitatory amino acid transporter 2 (EAAT2) on plasma EVs, primarily an astrocytic protein involved in regulating glutamatergic signaling, has been advanced as a potential biomarker of MS relapses

(D'Ambrosio et al., 2024) as well. These identified biomarkers of disease activity fit well with the known pathology of MS relapses, which include demyelination and excitotoxicity (Vercellino et al., 2007).

EV-based markers of disability in MS have also been identified in multiple studies. These include CSF-derived exosomal acid sphingomyelinase and CD11c and oligodendrocyte-derived exosomal purinergic P2X7 receptor, each of which correlates with disability levels (Pieragostino et al., 2018; Agliardi et al., 2024; Iwahara et al., 2025). Each of these provides insights into the potential pathways related to disability in MS and new treatment targets.

Diagnostic panels have also been developed to assist in distinguishing between or predicting relapsing and progressive MS courses. A panel including three plasma EV miRNAs (miR-760, miR-191-5p, and miR-146a-5p) showed promise for distinguishing between stable RRMS and SPMS [area under the curve (AUC) = 0.942; Wasilewska et al., 2026]. Another study identified a panel of nine serum exosomal microRNAs that predicted relapsing versus progressive MS with high accuracy and validated them in a small pilot group (Ebrahimkhani et al., 2017). With larger validation, these panels may assist clinicians in identifying patients at high risk for progressive disease so that highly efficacious immunotherapy can be prescribed earlier.

The size and concentration of EVs may also serve as useful metrics in MS. An increase in mean plasma EV size was seen in multiple demyelinating diseases—MOGAD, NMOSD, and RRMS—compared with controls, perhaps reflecting a shift toward a greater proportion of microvesicles or apoptotic bodies in the setting of inflammation or injury (Lim Falk et al., 2025). Supporting this, another study reported that a larger size of oligodendrocyte-derived EVs was related to motor and cognitive impairments in persons with MS (Torres Iglesias et al., 2023). The size and concentration of neuron-derived EVs also positively correlate with relapses and new lesions on MRI and decrease after immunotherapy, possibly reflecting an increase in release during injury and local inflammation (Anandan et al., 2025; Torres-Iglesias et al., 2025). These studies suggest the size and concentration of EVs provide additional relevant information and may relate to disease activity.

The analysis of EVs may also provide new insights into the pathophysiology underlying MS and its symptoms. For example, plasma exosomes in MS display an upregulation of microRNA *let-7i*, which suppresses regulatory T-cell induction (Kimura et al., 2018). Exosomes derived from regulatory T-cells in MS also show impaired suppression of conventional T-cell proliferation compared with controls (Azimi et al., 2018), an effect that has been attributed to the level of miR-142-3p, a microRNA that can downregulate T-cell growth and effector functions (De Rosa et al., 2025). Functionally, B-cell-derived exosomes from MS induce the death of oligodendrocytes responsible for myelination (Benjamins et al., 2019), and serum exosomes contain proteins derived from the Epstein-Barr virus that can activate macrophages (Mrad et al., 2021). The findings of these studies parallel the known involvement of B- and T-cells within MS but also demonstrate additional mechanisms by which exosomes may directly induce injury or precipitate inflammation.

An interplay between synaptic protein changes and mitochondrial/metabolic dysfunction in MS is also displayed upon the analysis of EVs. For neuron-derived plasma EVs, several synaptic proteins are lower in people with MS compared with controls (Bhargava et al., 2021), with changes in these proteins being related to altered mitochondrial function and brain or

Table 1. Studies evaluating total extracellular vesicle (EV) or exosome populations in multiple sclerosis (MS)

Article	Sample fluid source	Major findings
Moyano et al. (2016)	Plasma	Significant increase of C16:0 sulfatide in exosomes from MS compared with healthy controls. Similar protein content and exosomal markers between groups
Ebrahimkhani et al. (2017)	Serum	Significantly increased in exosomes from relapsing-remitting MS (RRMS) compared with healthy controls: miR-15b-5p, miR-30b-5p, miR-451a, miR-342-3p. Significantly increased microRNAs (miRNA) in exosomes from progressive MS compared with healthy controls: miR-127-3p, miR-370-3p, miR-409-3p, miR-432-5p, miR-15b-5p, miR-223-3p, miR-23-3p. Nine exosomal miRNAs predicted RRMS vs progressive MS with high accuracy in a validation set. Significantly enriched pathways of exosomal miRNAs in MS included the neurotrophin signaling pathway, focal adhesion, and T-cell receptor signaling
Selmaj et al. (2017)	Serum	Significantly downregulated in exosomes from RRMS compared with controls, and in RRMS with active brain/spinal lesions: Hsa-miR-122-5p, hsa-miR-196b-5p, hsa-miR-301a-3p, hsa-miR-532-5p. Significantly downregulated in exosomes from MS relapse compared with remission: hsa-miR-122-3p, hsa-miR-196b-5p, hsa-miR-532-5p
Galazka et al. (2018)	Serum, cerebrospinal fluid (CSF)	Myelin oligodendrocyte glycoprotein (MOG) protein was significantly elevated in serum exosomes from MS in relapse and secondary progressive MS (SPMS) compared with healthy controls, correlating with active MRI lesions. Serum exosomes from RRMS in relapse or from SPMS induced MOG-TCR T-cell proliferation compared with healthy controls
Kimura et al. (2018)	Plasma	let-7i miRNA is increased in exosomes from MS compared with healthy controls, and levels negatively correlate with regulatory T-cell frequency
Sáenz-Cuesta et al. (2018)	Plasma	miRNA cargo in EVs from MS patients changed after a dose of an immunotherapy, fingolimod with decreased immune regulatory activity
Manna et al. (2018)	Serum	Fourteen exosomal miRNAs were significantly downregulated and two were upregulated in RRMS patients who responded to interferon-beta therapy compared with those without response
Bhargava et al. (2019)	Serum	Lower concentration of Toll-like receptor 3 (TLR3); higher concentration of TLR4 on extracellular vesicles (EVs) of MS patients compared with controls
Ebrahimkhani et al. (2020)	Serum	Combinations of exosomal miRNAs predicted disease activity after starting immunotherapy with fingolimod
Mrad et al. (2021)	Serum	Exosomes derived from active MS showed greater abundance of Epstein–Barr Nuclear Antigen 1 (EBNA1), latent membrane protein 1 (LMP1), and LMP2A than healthy controls and stable MS
Mohammadinasr et al. (2023)	Serum, CSF	Significantly upregulated in serum and CSF exosomes of RRMS compared with healthy controls: Let-7g-5p, miR-18a-5p, miR-145-5p, miR-374a-5p, miR-342-3p. Significantly downregulated in serum and CSF exosomes of RRMS compared with healthy controls: miR-132-5p, miR-320a-5p
D'Ambrosio et al. (2024)	Plasma, CSF	Both plasma and CSF EVs of patients with MS showed significant enrichment of proteins enriched in the synaptic transmission pathway. One plasma exosomal protein, excitatory amino acid transporter 2, was significantly associated with MS relapses and correlated with disability
Lim Falk et al. (2025)	Plasma	Lower density of EVs in RRMS than healthy controls. Increased mean EV sizes in RRMS, NMOSD, and MOGAD compared with controls
Maimaitijiang et al. (2025)	Serum	Exosomes from MS had higher GJA1-29k than in NMOSD, other inflammatory neurologic diseases, and healthy controls. This increased at relapse and correlated positively with disability. Hsa-miR-133b was significantly lower in SPMS than in controls and negatively correlated with disability
Palazzo et al. (2025)	Serum	Exosomes from RRMS showed significantly lower phosphatidic acid and increased content of lysophosphatidylcholine (LPC) species compared with healthy controls
Saba et al. (2025)	Serum	Human endogenous retrovirus type W envelope protein (pHERV-W-ENV) was increased in exosomes from active RRMS, decreased at follow-up, and was related to greater clinical and MRI disease activity
Wasilewska et al. (2026)	Plasma	Four miRNAs from plasma EVs were significantly different in stable RRMS and SPMS: miR-760, miR-98-5p, miR-301a-3p, miR-223-3p. A combination of fibroblast growth factor—basic, miR-760, miR-191-5p, and miR-146a-5p—showed high ability to distinguish between RRMS and SPMS (AUC = 0.942)
Lee et al. (2016)	CSF	Multiple proteins from exosomes were highly expressed in MS and NMO, in pathways related to cellular adhesion, immune response, and cellular structure
Pieragostino et al. (2018)	CSF	Higher number of exosomes in MS compared with other neurologic diseases, with exosome number correlating to CSF acid sphingomyelinase activity
Geraci et al. (2018)	CSF	Increased number of C-C chemokine receptor type 3 (CCR3) ⁺ , CCR5 ⁺ , CD4 ⁺ /CCR3 ⁺ , CD4 ⁺ /CCR5 ⁺ , and CC3 ⁺ /CCR5 ⁺ EVs in RRMS with active lesions, and reduction in CD19 ⁺ /CD200 ⁺ EVs during relapse
Ragonese et al. (2020)	CSF	EVs from MS induced cell death in cultured astrocytes from rats
Iwahara et al. (2025)	CSF	EVs from MS had higher levels of integrin alpha-4, integrin alpha-X (ITGAX), CD20, and CD3E compared with other neurologic diseases, with ITGAX levels showing potential use in prognostication
Jank et al. (2025)	Postmortem tissue—white matter	EVs from normal-appearing white matter in persons with MS had decreased synaptic and mitochondrial and increased complement and inflammation-related proteins and pathways compared with controls

CSF, cerebrospinal fluid; EV, extracellular vesicle; EAE, experimental autoimmune encephalomyelitis; GLAST, glutamate aspartate transporter; miRNA, microRNA; NMOSD, neuromyelitis optica spectrum disorder; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

retinal atrophy (Ladakakis et al., 2022; 2024). Analysis of EVs derived from postmortem tissue samples of normal-appearing white matter in persons with MS also indicates synaptic and

metabolic dysfunction, along with elevated complement and inflammatory proteins (Jank et al., 2025). The relationship of these alterations in synaptic proteins and mitochondrial function

Table 2. Studies evaluating specific cell type-derived extracellular vesicle (EV) or exosome populations in multiple sclerosis (MS)

Article	Sample fluid source	Major findings
Benjamins et al. (2019)	PBMC, B-cells	Exosomes derived from B-cells of persons with multiple sclerosis (MS) induced the death of oligodendrocytes in vitro
Azimi et al. (2018)	PBMC, T-reg cells	Treg-derived exosomes from persons with MS induced less suppression of T-cell proliferation compared with controls
Azimi et al. (2019)	PBMC, T-cells	Exosomes derived from T-cells of persons with RRMS showed increased expression of miR-326 compared with controls
De Rosa et al. (2025).	PBMC, T-reg cells	Treg-derived EVs from persons with MS contain less miR-142-3p, resulting in less suppression of T-cell proliferation compared with controls. Levels of miR-142-3p in Treg EVs also inversely correlate with active inflammatory lesions and disability levels
Torres Iglesias et al. (2023)	Blood, B-cell derived (CD20) and T-cell derived (CD3)	Complement 1s and gelsolin were lower in B-cell-derived EVs in MS compared with controls. Total concentration of T-cell-derived EVs and associated alpha-1-microglobulin/bikunin precursor and fibrinogen beta chain are increased in relapse compared with stable disease in MS
Bhargava et al. (2021)	Plasma, neuron-derived (L1CAM ⁺), and astrocyte-derived (GLAST ⁺)	Neuron-derived exosomes from MS had lower synaptopodin and synaptophysin compared with healthy controls. Astrocyte-derived exosomes showed higher levels of complement cascade components compared with healthy controls
Ladakis et al. (2022)	Plasma, neuron-derived (L1CAM ⁺)	Mitochondrial complex IV activity from exosomes was positively correlated with T2 lesion volume; complex IV and V activity levels were correlated with brain volume atrophy rates
Agliardi et al. (2023)	Serum, oligodendrocyte-derived (MOG ⁺)	Myelin basic protein was significantly increased in oligodendrocyte-derived EVs from MS compared with healthy controls and correlated with disability. This was also significantly elevated in PPMS compared with RRMS and CIS
Torres Iglesias et al. (2023)	Blood, neuron-derived (L1CAM ⁺) and oligodendrocyte-derived (myelin oligodendrocyte glycoprotein—MOG ⁺)	Smaller size of neuron-derived EVs were associated with MS relapse. Smaller size of oligodendrocyte-derived EVs related to cognitive or motor impairments in MS. Higher abundance of Talin-1 in oligodendrocyte-derived EVs. Myelin basic protein in oligodendrocyte EVs correlated with MS disease activity
Ladakis et al. (2024)	Plasma, neuron-derived (L1CAM ⁺)	Rate of change of synaptopodin and synaptophysin in exosomes were associated with whole brain and cortical gray matter atrophy
Duan et al. (2024)	Plasma, microglia-derived EVs (CX3CR1 ⁺ /UCHL1 ⁺)	Elevated EVs in MS compared with controls, which increased in the first 5 years of MS disease
Agliardi et al. (2024)	Serum, oligodendrocyte-derived (MOG ⁺)	P2X7R was increased in oligodendrocyte-derived EVs in PPMS compared with RRMS and healthy controls. In all MS, this protein correlated positively with disability scores
Torres Iglesias et al. (2024)	Plasma, neuron-derived (L1CAM ⁺) and oligodendrocyte-derived (MOG ⁺)	Patients with MS who responded to immunotherapy initiation had higher collagen alpha-1(VI) chain and lower collagen alpha-1(XIV) chain proteins from oligodendrocyte-derived EVs, along with higher SPNT and neural adhesion molecule (NCAM) and lower laminin subunit alpha-5 (LAMAS) levels in neuron-derived EVs pretreatment compared with 3 months post treatment. Proteasome 20S subunit beta-5 (PSB5) was higher and hypoxanthine-guanine phosphoribosyltransferase (HPRT) was lower in oligodendrocyte-derived EVs from responders compared with nonresponders
Anandan et al. (2025)	Serum, neuron-derived (L1CAM ⁺)	Higher concentration of neuron-derived EVs in untreated MS compared with healthy controls, with a significant reduction in this concentration after 6 months of rituximab immunotherapy
Torres-Iglesias et al. (2025)	Serum, neuron-derived (L1CAM ⁺) and oligodendrocyte-derived (MOG ⁺)	Lower levels of neuron-derived EVs in persons with MS without clinical or MRI evidence of disease activity. Larger neuron-derived EVs were found in MS with new MRI lesions. Lower levels of oligodendrocyte-derived EVs were found in MS with progressive of disability compared with stable patients. A combination of neuron-derived EV levels and associated miR-144-5p and miR-126-5- had high accuracy in developing a therapeutic response predictive model
Verderio et al. (2012)	CSF, myeloid-derived (isolectin B4—IB4 ⁺)	Myeloid microvesicle (MV) concentration was significantly increased in relapsing MS, EAE, and clinically isolated syndrome compared with controls. A threshold concentration of 1.6 MVs/μl provided >80% sensitivity and specificity for distinguishing clinically isolated syndrome from controls, and stable from relapsing MS

CSF, cerebrospinal fluid; EV, extracellular vesicle; GLAST, glutamate aspartate transporter; IB4, isolectin B4; L1CAM, L1 cell adhesion molecule; MV, microvesicle; MS, multiple sclerosis; MOG, myelin oligodendrocyte glycoprotein; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary-progressive MS; UCHL1, ubiquitin carboxyl-terminal hydrolase L1.

to brain atrophy could underlie the chronic cognitive dysfunction and symptoms of fatigue that are common in MS. Further studies are needed to assess their relationship to these chronic symptoms, which may provide novel targets for their treatment.

These studies on MS demonstrate the promise of EVs in developing new biomarkers to aid in MS diagnosis, predicting immunotherapy response, monitoring outcomes of treatment, and prognosticating those at high risk for the development of progressive forms of MS. These studies have also generated novel insights into the potential pathophysiology of MS and its related chronic and disabling symptoms such as cognitive dysfunction.

Future research in this area may validate some of these identified potential biomarkers and biomarker panels in MS in larger cohorts and assist in the development of novel therapeutic strategies for both reducing neuroinflammation and aiding recovery.

Anti-AQP4-positive NMOSD

Fewer studies have evaluated EVs in anti-AQP4-positive NMOSD (Table 3). In NMOSD, antibody fragments and proteins related to complement pathway activation from exosomes in post-plasmapheresis fluid are reported to decrease after multiple treatments. However, several proteins increase over the course of

Table 3. Studies evaluating extracellular vesicle (EV) or exosome populations in the demyelinating diseases of neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)

Article	Sample fluid source	Major findings
Neuromyelitis optica spectrum disorder (NMOSD)		
Chen et al. (2020)	Serum	Seventeen differentially expressed miRNA were found in acute vs remitting anti-AQP4-positive NMOSD, including higher hsa-miR-122-3p and hsa-miR-200a-5p. These miRNAs also showed moderate positive correlation with disability scores. Enriched pathways for these miRNAs include MAPK, Ras, and Wnt signaling, pathways in cancer, and regulation of stem cell pluripotency
Lim Falk et al. (2025)	Plasma	Increased mean EV sizes in anti-AQP4-positive NMOSD, MOGAD, and relapsing-remitting multiple sclerosis (RRMS) compared with controls
Lee et al. (2016)	CSF	Multiple proteins from exosomes were highly expressed in NMO and MS, in pathways related to cellular adhesion, immune response, and cellular structure
Iwahara et al. (2025)	CSF	EVs from anti-AQP4-positive NMOSD had higher levels of integrin alpha-4 compared with MS
Ma et al. (2020)	Post-plasmapheresis collection fluid	Antibody fragments and complement pathway proteins decreased after plasmapheresis treatment; these proteins were involved in two pathways—primary immunodeficiency and systemic lupus erythematosus. Several proteins increased after plasmapheresis: complement factor H-related protein 5, bridging integrator 2, neuroplastin, pigment epithelium-derived factor, ficolin-1, extracellular matrix protein 1, fatty acid-binding protein 5
Maimaitijiang et al. (2025)	Serum	Exosomes from NMOSD in relapse had higher SNORD37, SNORD95, SNORD97, and Linc01560 and were negatively correlated with disability
Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)		
Kim et al. (2025)	Serum	Seventy-seven miRNAs were dysregulated in exosomes from MOGAD compared with healthy controls. A three microRNA (miRNA) panel had a high ability to distinguish MOGAD from MS and NMOSD. Within MOGAD, exosomal Hsa-miR-924 had high correlation with disability, and hsa-miR-548i had high correlation with relapse rate
Lim Falk et al. (2025)	Plasma	Increased mean EV sizes in MOGAD, NMOSD, and RRMS compared with controls

AQP4, aquaporin-4; CSF, cerebrospinal fluid; EV, extracellular vesicle; miRNA, microRNA; MS, multiple sclerosis; MOGAD, MOG antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorder; RRMS, relapsing-remitting MS.

treatment, including complement factor H-related protein 5 (CFHR5) and pigment epithelium-derived factor (PEDF). CFHR5 is involved in protection from complement system attack, while PEDF has anti-inflammatory properties (Ma et al., 2020). This study highlights the critical role of complement activation in the pathogenesis of NMOSD and provides potential biomarkers of treatment effectiveness and pathways to evaluate for new therapeutic strategies.

Analysis of serum exosomes in NMOSD has also identified unique miRNAs related to disease relapse and disability. Serum exosomal hsa-miR-122-3p and hsa-miR-200a-5p distinguished between NMOSD in relapse versus remittance in one study, while also revealing moderate positive correlations with disability scores. The target genes for miR-122-3p are enriched in the mitogen-activated protein kinase (MAPK) pathway, and those for miR-200-a-5p are enriched in pathways for pluripotency of stem cells, pathways in cancer, and the Ras and Wnt signaling pathways. As the Wnt signaling pathway may impair remyelination, the increased expression of miR-200-a-5p may impair remyelination and recovery after relapse (Chen et al., 2020; Kim et al., 2025). In addition, serum exosomal small nucleolar RNAs and long intergenic noncoding RNAs correlate negatively with disability during NMOSD relapse, suggesting that these RNAs may have a specific role in limiting damage or inflammation during relapse (Maimaitijiang et al., 2025).

The analysis of CSF-derived EVs and exosomes has provided additional insights for NMOSD. CSF-derived EVs from NMOSD show higher levels of integrin alpha-4, a lymphocyte marker, which may reflect the higher concentration of lymphocytes typically found in the CSF of NMOSD compared with MS (Iwahara et al., 2025). CSF-derived exosomal proteins also display a higher enrichment of pathways involved in the complement cascade, cellular adhesion, and regulation of cytoskeletal proteins in oligodendrocyte differentiation and myelination, compared with idiopathic longitudinally extensive transverse myelitis (negative for

anti-AQP4 and anti-MOG antibodies) or multiple sclerosis (Lee et al., 2016). C4b-binding protein—an inhibitory protein for the complement cascade—and haptoglobin-related protein were also significantly elevated in exosomes from NMOSD but not in MS or idiopathic myelitis in this study, suggesting that these proteins may serve as potential biomarkers specific to NMOSD. These findings further highlight the role of the complement cascade in NMOSD pathogenesis compared with MS or idiopathic myelitis and identify several potential biomarkers for future study.

Given the significant disability caused by relapses of anti-AQP4-positive NMOSD, the ability to evaluate mechanisms causing injury in this disease using EVs may assist in the development of new therapies to improve recovery after relapse. This is a serious unmet need in this disease. Additionally, biomarkers allowing for more frequent and targeted monitoring of treatment effectiveness will assist in improving long-term outcomes and disability after relapse. While studies evaluating EVs in NMOSD are sparse, their potential for addressing these needs is becoming realized.

Myelin oligodendrocyte glycoprotein autoantibody-associated disease

While there is also a dearth of studies on EVs in MOGAD (Table 3), those that exist report that serum small EVs show a number of dysregulated microRNAs between patients and healthy controls (Kim et al., 2025). This study identified panels consisting of three microRNAs that provided excellent discrimination of MOGAD from MS, NMOSD, and healthy controls (AUC > 0.9). One of these microRNAs, hsa-miR-346, is downregulated in MOGAD compared with MS and is enriched in GABAergic signaling pathways. This may relate to the seizures commonly observed in MOGAD but rarely seen in MS. Another of the microRNAs, hsa-miR-924, shows a strong negative correlation with disability levels. This miRNA inhibits Wnt

pathway signaling, with Wnt pathway signaling impairing remyelination. Therefore, higher expression of this miRNA may result in greater remyelination and less disability (Kim et al., 2025), which is similar to the relationship of the Wnt pathway to disability in NMOSD (Chen et al., 2020).

As a more recently identified and studied disease, MOGAD has many unmet needs. This includes a need for improving diagnosis for those with low-titer serum anti-MOG or CSF anti-MOG antibodies, improved discrimination between MOGAD and other demyelinating diseases, improved prediction of future relapse risk and the need for maintenance immunotherapy, and improved understanding of the mechanistic differences between demyelinating and encephalitic forms of MOGAD. Work performed to date shows the potential for accomplishing several of these through the analysis of EVs, with validation of the current proposed panel as one future direction to advance the clinical care for MOGAD.

Autoimmune encephalitis

Several studies have evaluated EVs in autoimmune encephalitis (Table 4), identifying relevant pathways related to inflammation and cell death connected to disease severity and outcomes, as well as identifying novel mechanisms of inflammation and injury. For example, CSF-derived exosomes from anti-gamma-aminobutyric acid (GABA)-B receptor encephalitis contain higher expression of miR-92a-3p than controls, with higher miR-92a-3p also

relating to worse clinical outcomes. miR-92a-3p regulates expression of IL-6 and cell death through ferroptosis, perhaps contributing to worse clinical outcomes through these mechanisms. When these exosomes were applied to rat-derived hippocampal neurons, they increased oxidative stress, iron accumulation, and neuronal death, compared with both CSF from healthy controls and CSF-derived IgG from anti-GABA-B receptor encephalitis (Zhang et al., 2025). This suggests a mechanism by which neurons are injured in autoimmune encephalitis through the influence or uptake of exosomes, which may be greater than that seen from pathogenic autoantibodies alone. This injury to neurons by exosomes may relate to the long-term sequelae of encephalitis such as epilepsy.

The analysis of EVs in autoimmune encephalitis also suggests new potential mechanisms of autoantibody formation that directly involve EVs. A study of several autoimmune encephalitis subtypes associated with specific anti-neuronal cell surface antibodies (including anti-NMDAR) showed that the surface of serum- and CSF-derived exosomes in these diseases contained increased expression of subunits of those specific neuronal antigens. Interestingly, when mice were immunized with these exosomes, they showed pathogenic autoantibody formation against these antigens (Gu et al., 2021).

Distinguishing between types of encephalitis in the acute setting is often challenging. Attempting to address this, one study found that serum exosomal miRNA 140-5p had an acceptable AUC of 0.748 for distinguishing between NMDARE and viral encephalitis. In EAE, this miRNA is involved in regulating Th1 differentiation and may be involved in the activation of B-cells, perhaps explaining why it is elevated in a B-cell-driven autoimmune encephalitis compared with a viral encephalitis (Liu et al., 2022).

New markers of neuroinflammation involving EVs may aid in the diagnosis of antibody-negative autoimmune encephalitis or in the monitoring of neuroinflammation during treatment. CSF exosomal miR-155-5p is elevated in multiple types of autoimmune encephalitis compared with healthy controls (Li et al., 2022). MiR-155-5p is proinflammatory in the CNS, targeting multiple pathways associated with both innate and adaptive immune responses (Jafarzadeh et al., 2021). In plasma exosomes, multiple miRNAs that regulate inflammatory pathways are decreased in autoimmune encephalitis compared with controls and negatively correlate with severity of disease (Xie et al., 2025). These differences in inflammatory pathway-related exosomal miRNAs may lead to new markers of neuroinflammation and assist in diagnosis or treatment monitoring. These will require validation in longitudinal studies and across encephalitis types.

Specific ongoing needs in the care of autoimmune encephalitis include diagnostic biomarkers for autoantibody-negative encephalitis, distinguishing between viral and autoimmune encephalitis, predicting response to specific immunotherapies, monitoring of treatment response, and evaluation of the mechanisms of disease to find new methods to reduce long-term neurologic and psychiatric sequelae. Although only a few studies have been completed at present, these studies are already showing the promise of EV analysis in identifying autoimmune encephalitis and new mechanisms of disease that may provide new treatment targets. Future research is needed to identify microRNAs for aiding in diagnosis or treatment monitoring and assess methods for blocking autoantibody production or neurotoxicity caused by exosomes in autoimmune encephalitis.

Table 4. Studies evaluating extracellular vesicle (EV) or exosome populations in autoimmune encephalitis

Article	Sample fluid source	Major findings
Liu et al. (2022)	Serum	MicroRNA MiR-140-5p was significantly upregulated in exosomes from anti-NMDA receptor encephalitis (NMDARE) compared with healthy controls and viral encephalitis
Xie et al. (2025)	Plasma	Expression of exosomal miR-432-5p, miR-4433b-5p, and miR-599 were significantly lower in NMDARE than healthy controls. miR-432-5p and miR-4433-5p correlated negatively with disease severity. Pathways enriched in NMDARE included neuroinflammation and glutamatergic signaling, rhythmic processes, and the cell surface receptor protein tyrosine kinase signaling pathway
Zhang et al. (2025)	CSF	In exosomes from persons with anti-GABA-B receptor encephalitis (GABABRE), miR-92a-3p was upregulated compared with healthy controls, and correlated with poor outcome. CSF-derived exosomes from GABABRE increased oxidative stress, iron accumulation, and cell death in cultured neurons compared with CSF from healthy controls and CSF IgG from GABABRE
Li et al. (2022)	CSF	miR-301-5p, miR-21-5p, miR-34a-5p, miR-132-5p, miR-29b-5p, miR-128-5p, miR-155-5p, miR-326-5p had significantly higher expression in exosomes from autoimmune encephalitis than in healthy controls. MiR-20a-5p showed lower expression
Gu et al. (2021)	Serum, CSF	NMDAR and other neurotransmitter receptor subunits were elevated in exosomes derived from that related to autoimmune encephalitis. Antibodies against these subunits developed when mice were immunized with these human-derived exosomes

CSF, cerebrospinal fluid; EV, extracellular vesicle; GABABRE, anti-gamma-aminobutyric acid receptor B encephalitis; miRNA, microRNA; NMDARE, anti-N-methyl-D-aspartate receptor encephalitis.

Animal models of neuroinflammation

EVs have also been studied in animal models of neuroinflammation, including EAE and those of NMOSD and autoimmune encephalitis (Table 5).

The study of EVs in EAE may lead to, or support, new markers for monitoring immunotherapy treatment. A study found that myeloid-derived (microglia/macrophage) EVs were increased in the CSF of an EAE model compared with controls and that these levels normalized upon treatment with fingolimod (Verderio et al., 2012). Additionally, exosomal GJA1-29k, a connexin, is also increased in EAE, MS, and NMOSD during relapse and positively correlates with disability (Maimaitijiang et al., 2025). If these exosomal populations and proteins are shown to correlate with clinical disease activity as well, this may lead to new methods of monitoring the effectiveness of immunotherapy through biologic measures.

EVs have been shown to directly influence the pathology of, and disease activity in, EAE models. Plasma EVs in an EAE model induced CD8⁺ T-cell responses and relapsing disease (Willis et al., 2019). Similarly, serum exosomes obtained during pregnancy in EAE models suppressed T-cell activation, which is notable because pregnancy is a period of time when clinical disease activity is usually lowered in MS (Gatson et al., 2011).

A direct pathologic role of EVs is also shown in other animal models of neuroinflammation. Astrocyte-derived exosomes in a rodent model of anti-AQP4-positive NMOSD led to demyelination in optic nerve tissue (Xie et al., 2023). In CSF-derived exosomes from animals inoculated with herpes simplex virus 1 (HSV1), subunits of NMDAR and other neurotransmitter

receptors were elevated (Li et al., 2022). Given that immunization of mice with these exosomes induces autoantibody formation against these antigens (Gu et al., 2021), these studies suggest a new mechanistic link between HSV1 infection and the development of autoantibodies in autoimmune encephalitis.

Together, the study of EVs and exosomes in animal models of inflammation has shown that, rather than being passive by-products of disease activity, EVs and exosomes may have an active role in the development or relapse of neuroinflammation. These studies have also identified potential mechanisms for the clinical features of these diseases. Further research studying EVs and exosomes in these animal models may lead to insights into novel mechanisms of disease and treatment approaches.

Potential Therapeutic Applications of Extracellular Vesicles in Neuroimmunologic Diseases

EVs have also been studied for their potential role in the treatment of neuroimmunologic diseases. EVs display several ideal characteristics for targeted treatment of CNS disorders, including low immunogenicity, the ability to cross the blood–brain barrier, targeted uptake by specific CNS cell types, and possible lipid bilayer encapsulation for a designated drug or treatment (Sun et al., 2022). Multiple studies have identified the intranasal or intravenous delivery of EVs or exosomes derived from mesenchymal stem cells (without additional drug) to decrease inflammation in EAE and to promote remyelination (Li et al., 2019; Fathollahi et al., 2021; Zhang et al., 2022; Qin et al., 2024; Rossi et al., 2025; Wu et al., 2025). EVs and exosomes have also been successfully engineered to enrich specific microRNA sequences (Shi et al., 2024; Shahryari et al., 2025), cytokines (Casella et al., 2018), or myelin growth factors (Xiao et al., 2022) for targeted treatment of neuroinflammation, as well as optimized to increase uptake by the CNS and specific CNS cell types (Casella et al., 2020; Xiao et al., 2022; Wang et al., 2023).

These approaches are also being developed for human trials. A systematic review and meta-analysis of EV-based clinical trials in 2024 found 21 completed trials. These trials were primarily phase I or II, with a focus on treatment in cancer, infectious disease, and regenerative/skin healing. Serious adverse effects were rare, and preliminary efficacy was demonstrated in a majority of the participants included in these studies (Van Delen et al., 2024). New clinical trials are currently ongoing. For neuroimmunologic diseases specifically, there is one active phase I/IIa study evaluating intranasal human umbilical mesenchymal stem cell-derived exosomes for the treatment of autoimmune encephalitis (NCT07131683), along with one observational study (NCT07145502). It is anticipated that clinical trials using EVs will increase in subsequent years for all neurologic diseases, as we learn more about the physiologic and pathophysiologic role of EVs, and the methods to improve their uptake, targeted specificity, and potency (Sun et al., 2022).

Challenges in Studying Extracellular Vesicles in Neuroimmunologic Diseases

Several challenges exist for analyzing EVs in neuroimmunologic diseases. First and most importantly, the ideal surface markers used to purify or enrich these vesicles from specific CNS cell types are still debated. As mentioned previously, this is an area of active and vital research since reliable and validated markers are essential to ensure accurate enrichment of CNS-derived EVs from a peripheral biofluid such as blood (Norman et al., 2025). While

Table 5. Studies evaluating extracellular vesicle (EV) or exosome populations in animal models of neuroimmunologic diseases		
Article	Sample fluid source	Major findings
Experimental autoimmune encephalomyelitis (EAE), mouse		
Gatson et al. (2011)	Serum	Exosomes from pregnant mice with EAE suppressed T-cell activation in vitro
Willis et al. (2019)	Plasma	Plasma EVs in EAE induced relapsing-remitting disease, driven by CD8 ⁺ T-cells and requiring fibrinogen
Maimaitijiang et al. (2025)	Serum	EAE showed increased exosomal GJA1-43k and GJA1-29k. Exosomal GJA1-29k was also increased in MS, especially at the time of relapse and correlated positively with disability
Verderio et al. (2012)	CSF, myeloid-derived (isolectin B4—IB4 ⁺)	CSF-derived myeloid microvesicle (MV) concentration was significantly increased in EAE, relapsing MS, and clinically isolated syndrome compared with controls. Fingolimod immunotherapy treatment decreased CSF myeloid MVs to normal in EAE
Other animal models of neuroimmune disease		
Xie et al. (2023)	Cultured rat astrocytes	Exosomes derived from cultured rat astrocytes exposed to AQP4-IgG resulted in demyelination of the rat optic nerve
Li et al. (2022)	Serum	The N-methyl-D-aspartate receptor (NMDAR) and other neurotransmitter receptor subunits were elevated in exosomes derived from serum of an intranasal HSV-1 treated mice compared with healthy controls

AQP4, aquaporin 4; CSF, cerebrospinal fluid; EAE, experimental autoimmune encephalomyelitis; EV, extracellular vesicle; IB4, isolectin B4; MS, multiple sclerosis; MV, microvesicle; NMDAR, N-methyl-D-aspartate receptor.

current studies have found potential biomarkers or mechanistic insights from non-CNS-derived EVs in the blood, CNS-derived EVs are most likely reflective of direct neuroinflammation and CNS injury. This is especially important for neuro-rheumatologic or paraneoplastic neurologic diseases, where systemic inflammation may override signals from the CNS. Without accurate markers for CNS-derived EVs, the development of peripheral biomarkers of neuroimmunologic diseases may be limited, hindering the ability of EV analysis to address the unmet needs discussed earlier. Second, the strong inflammatory environment and cross-talk between local cell types in the CNS may dilute the cell-specific signatures being sought in CNS-derived EVs. Third, many neuroimmunologic diseases consist of multi-phasic acute relapses, remissions, immunotherapy treatments, and progressive or chronic symptoms. This contrasts with neurodegenerative disease or traumatic brain injuries, which may have a more defined and expected trajectory and treatment course. This rapidly evolving environment and the rapid clearance of EVs in peripheral blood may make the specific timing of sample collection relative to symptom onset very important to consider. This may increase the variability in specific analyses as well as those obtained between studies. Without attention to these specifics in the study design, the field may provide conflicting data and have a more difficult path in identifying new biomarkers or treatments using EVs.

Summary

To improve care for neuroimmunologic diseases, we require new methods for diagnosis, treatment selection, and monitoring of these diseases, as well as an improved understanding of the underlying mechanisms of disease. The analysis of EVs may meet these needs. EVs have a vital role in intercellular communication between the CNS and periphery and between CNS cell types. In particular, research into CNS-derived EVs enriched from the blood presents the possibility of more precise assessments of current neuroinflammation without the use of invasive lumbar punctures or biopsies; this is vital for close and repeated monitoring of neuroinflammation during treatment. Current studies analyzing EVs have focused primarily on multiple sclerosis and related demyelinating diseases but show promise in identifying novel biomarkers for multiple neuroimmunologic diseases while providing insights regarding etiology and disease mechanisms. More work is necessary in nondemyelinating neuroimmunologic diseases such as autoimmune encephalitis, autoimmune ataxia, stiff person syndrome spectrum disorder, and neuro-rheumatologic diseases so we can develop an understanding of these diseases and the role of EVs in improving care for each. While challenges exist, the study of EVs has a high potential for filling many knowledge gaps in this field of neuroimmunology.

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