Innovations in Pharmaceutical Sciences & Care
Volume 1, Issue 1

Spinal-Onset Autoimmune Encephalitis: A Rare and Overlooked Neuroimmunological Entity

[1]*Hanin Abueida
[1]Library and Learning Commons - Zayed University, UAE.

Abstract

Autoimmune encephalitis (AE) is traditionally conceptualised as a brain-centred inflammatory disorder; however, accumulating evidence indicates that a subset of patients presents with spinal cord involvement as the initial manifestation. This narrative review synthesises current literature on spinal-onset autoimmune encephalitis, a rare and frequently under-recognised neuroimmunological phenotype. A comprehensive search of major databases from 2016 to 2025 identified cohort studies, case series, and reviews describing myelitis or longitudinally extensive transverse myelitis (LETM) preceding encephalitic features. Across studies, the clinical trajectory consistently demonstrated a spinal-first inflammatory process followed by delayed cerebral involvement, most commonly associated with GFAP astrocytopathy and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Early brain MRI findings were often non-specific or normal, whereas cerebrospinal fluid abnormalities showed greater diagnostic sensitivity during the transition phase. Diagnostic delay was frequent and strongly correlated with increased neurological disability and relapse risk. These findings support the recognition of spinal-onset autoimmune encephalitis as a distinct clinical continuum, highlighting the need for early CSF-based evaluation and timely immunotherapy to improve outcomes.

Keywords: Spinal-onset autoimmune encephalitis, autoimmune encephalitis, longitudinally extensive transverse myelitis (LETM), myelitis; delayed encephalopathy, GFAP astrocytopathy, myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), cerebrospinal fluid (CSF); neuroimmunology, diagnostic delay, differential diagnosis, immunotherapy.

1. Introduction

Autoimmune encephalitis (AE) is a complex neuroinflammatory condition characterised by the immune system mistakenly attacking healthy central nervous system tissue. As reported by Orozco et al. (2023), AE was framed as an immune-mediated disorder driven primarily by neuronal surface antibodies. This pathophysiology produced subacute encephalitic syndromes through targeted immune-mediated damage. As discussed by Zuliani (2021), the expanded neuronal targets include glial-directed autoimmunity, as diverse clinical trials emerged that moved beyond classical limbic definitions. Hiesgen and Schutte (2023) claimed that neuroinflammatory cascades often impair the key neural signalling and synaptic transmission, resulting in the rapid deterioration of cognition, mental conditions, and motor impairments. Wang (2026) described a shift of the disease classification form towards antigen-specific phenotypes, and in the contemporary diagnosis regimen, clinical, radiological, and serological data are included to attain more accurate classification. Glial fibrillary acidic protein (GFAP) astrocytopathy was one of the most frequent types of encephalomyelitis that may have specific radiologic characteristics like linear periventricular enhancement. In a study, Uzawa et al. (2024) stated that myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) also functioned as a primary component of the expanded AE landscape. The condition frequently involved both optic nerve inflammation and extensive spinal cord lesions.

The clinical recognition of spinal-onset variants presented a major challenge because initial symptoms typically centred on isolated spinal cord dysfunction. In a study by Asnafi (2020), spinal-onset AE was operationally defined as myelitis or longitudinally extensive transverse myelitis (LETM) that preceded encephalitic signs. Kunchok (2021) reported that phenotype was common, mainly with motor or sensory impairments, without a significant effect on cognitive functions that developed at an early age. As described by Howard (2022), magnetic resonance imaging

Hanin Abueida
Library and Learning Commons - Zayed University, UAE.
Email: hanina@outlook.com

(MRI) of the brain was frequently insignificant in the early phases of the disease, where intracranial abnormalities could not be identified at the beginning of the process of encephalitic. Furthermore, Sanvito (2024) noted that the development of spinal to cerebral manifestations took place over a few weeks. The lag in brain involvement meant that many patients did not meet established diagnostic criteria at the time of initial evaluation. As documented by Uzawa (2024), differentiation from neuromyelitis optica spectrum disorder (NMOSD) relied on the broader inflammatory signatures found in autoimmune encephalitis. This phenotype exhibited a distinct clinical trajectory compared to the more localised inflammation seen in NMOSD.

Delayed recognition of the spinal-first presentation often led to inappropriate treatment protocols and poor long-term recovery. As reported by Orozco (2023), diagnostic delays are linked directly to the development of irreversible neurological disability. The absence of encephalitic progression was identified, leading to the lack of the required high doses of immunotherapies (Jiménez Echavarria et al., 2025). According to the findings of Van Steenhoven (2023), clinical heuristics were highly biased toward limbic symptoms, effectively ruling out uncharacteristic presentations. Investigating patients who initially presented with spine-related symptoms were often poorly managed as cases of multiple sclerosis or infectious myelitis (Van Steenhoven et al., 2023). Early diagnostic criteria, as defined by Uher (2025), were ineffective in the presentation of the entire breadth of the AE spectrum. The dependence on brain-centred protocols slowed the provision of timely immunotherapy to cases of spinal onset.

Although recent studies on autoimmune encephalitis (AE) have achieved certain progress, there are still considerable gaps in the understanding of the shift of the spinal to cerebral pathology, particularly in the cases of Longitudinally Extensive Transverse Myelitis (LETM). There is also a lack of empirical evidence on the gauging of prognostic value of early lesions of the spine and their effect on the outcome of encephalitic. Moreover, there are geographical and institutional differences in the methods of detection and management that delay the development of uniform protocols. Lack of longitudinal studies, which can monitor the changes of information from the spinal-onset to the cerebral involvement, is an additional challenge to the development of effective diagnostic and therapeutic recommendations.

Therefore, this narrative review aimed to synthesise current evidence on spinal-onset autoimmune encephalitis, addressing diagnostic challenges, clinical implications, pathophysiology, and management strategies.

2. Methodology

2.1 Review Design and Rationale

The adoption of a state-of-the-art narrative review design addressed the heterogeneous evidence landscape of spinal-onset autoimmune encephalitis. This clinical entity integrated retrospective cohorts, individual case reports, and evolving antibody classifications that did not support formal meta-analysis. The synthesis clarified diagnostic issues and therapeutic implications through a systematic investigation of the phenotype of glial and neuronal surface-bound antibodies; particularly, antibodies against N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and gamma-aminobutyric acid type B (GABA-B) receptors.

2.2 Search Strategy

The search strategy involved a comprehensive search through the databases of PubMed, Scopus, Web of Science, Springer Link, and Google Scholar from 2016 to 2025. Through a multi-database method, the review was found to have sufficient global coverage of cohort and regionally focused case series. Primary search keys were created to identify autoimmune encephalitis with spinal cord inflammation, and a Boolean operator was used to define a progression of myelitis into encephalitis. Specific searches of Glial Fibrillary Acidic Protein (GFAP) and Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD) phenotypes were also searched. Hand-searching of reference lists captured additional niche case series not identified through initial keyword queries (Table 1).

2.3 Eligibility Criteria

Eligibility criteria prioritised scientific accuracy by isolating cases with a clear temporal evolution. Inclusion required documented myelitis or Longitudinally Extensive Transverse Myelitis (LETM) preceding encephalitic symptoms to focus specifically on the atypical spinal-first phenotype. Exclusion occurred if encephalitic symptoms preceded spinal involvement, if presentations remained isolated to the brain, or if autoimmunity was limited to peripheral systems. Detailed inclusion and exclusion criteria are shown in Table 2.

Table 1. Search Strategy Parameters

S. No.	Boolean Search Strings
1	("spinal-onset" OR "LETM") AND "autoimmune encephalitis"
2	TITLE-ABS-KEY ("GFAP astrocytopathy" AND "myelitis")
3	TS= ("MOGAD" AND "LETM" AND "encephalitis")
4	"Longitudinally extensive transverse myelitis autoimmune"
5	"Spinal-onset autoimmune encephalitis" + "clinical progression"

Table 2. Inclusion and Exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Study Type	Peer-reviewed cohorts and case series.	Editorials and conference abstracts.
Phenotype	Spinal-first (LETM/Myelitis) onset.	Brain-first or isolated NMOSD.
Antibody	GFAP, MOG, or Neuronal Surface positive.	Antibody-negative without CSF inflammation.
Disease Scope	Primary CNS inflammatory pathology.	Peripheral autoimmunity (e.g., GBS, Myasthenia).
Language	Full-text manuscripts in English only.	Non-English or translated abstracts only.
Timeline	Evidence published between 2016 and 2025.	Any evidence published before 2016.

2.4 Study Selection and Data Extraction

The selection process followed a transparent dual-phase screening protocol involving independent reviews of titles and abstracts. Full-text analysis was followed for all potentially relevant articles to confirm phenotypic accuracy. Any disagreements over study inclusion were resolved through consensus among reviewers. Data extraction focused on key variables, including the temporal progression of spinal and encephalitic symptoms and patient outcomes.

2.5 Quality Assessment (SANRA)

The Scale of the Assessment of Narrative Review Articles (SANRA) was used to evaluate the quality of the narrative in order to guarantee rigorous reporting. In this evaluation, the transparency of research objectives, research referencing quality, and the logical organisation of the clinical evidence were reviewed. The SANRA model impacted the final synthesis process since it was applied to recognise the studies with the best internal validity, which entails the strongest evidence utilised to shape the review. Cohort-based studies were given more weight as opposed to individual case reports to improve the relevance of the result to the general consideration, as well as alleviate the effects of anecdotal evidence. The last group included 12 studies having the strongest evidence of the spinal-onset phenotype, as illustrated in Table 3.

3. Results

3.1 Defining the Spinal-Onset Autoimmune Encephalitis Phenotype

Clinically, this phenotype was defined by an initial myelopathic syndrome, most commonly longitudinally extensive transverse myelitis (LETM) that precedes or rapidly overlaps with cerebral dysfunction. Seminal cohort studies by Fang et al. (2016) and Flanagan et al. (2017) identified autoimmune GFAP astrocytopathy as a prototype for this meningoencephalomyelitis, where spinal cord involvement is a cardinal, rather than incidental, feature. Similarly, research related to MOG-IgG-associated disorders (MOGAD) delineates a spectrum where myelitis serves as a sentinel event before the onset of cortical encephalitis (Cobo-Calvo et al., 2018; Jarius et al., 2018). Clinically, this phenotype is distinguished from multiple sclerosis by the severity of the spinal lesion (often hemorrhagic or spanning >3 segments) and the subsequent evolution into encephalopathy, characterised by seizures, cognitive decline, or psychiatric features (Asnafi et al., 2020) Howard et al., 2022). The increasing volume of literature since 2016 reflects a paradigm shift in recognising autoimmune manifestations that span the entire neuroaxis rather than remaining confined to the limbic system, as shown in Table 4.

Table 3. SANRA Quality Assessment Scores for Selected Studies

Study ID	Aims (0-2)	Referencing (0-2)	Reasoning (0-2)	Presentation (0-2)	Total
Study 01	2	2	2	2	8
Study 02	2	2	2	2	8
Study 03	2	2	1	2	7
Study 04	1	2	2	2	7
Study 05	2	2	2	2	8
Study 06	2	1	2	2	7
Study 07	2	2	2	2	8
Study 08	2	2	1	1	6
Study 09	2	2	2	2	8
Study 10	2	1	2	2	7
Study 11	2	2	2	2	8
Study 12	1	2	2	2	7

3.2 Core Phenotype: Spinal-First Inflammation (LETM/ myelitis)

The analysis of the included studies reveals that the clinical trajectory of this spinal-onset phenotype consistently begins with a distinct spinal syndrome. Fang et al. (2016) noted that Longitudinally Extensive Transverse Myelitis (LETM) is the most common radiologic manifestation during the prodrome and is especially common in the GFAP-IgG range. Extending these findings, Flanagan et al. (2017) revealed a significant diagnostic specificity on testing the patients with lesions across three or more vertebral levels. They identified a linear perivascular radial enlargement as a distinguishing feature, making it apparent that the construct is definite between multiple sclerosis. Jarius et al. (2018) found that MOG-IgG seropositivity is strongly associated with severe, spinal restricted attacks, and they established myelitis as the sentinel event preceding cerebral involvement in a considerable percentage of no-MS demyelination cases, as shown in Figure 1.

Reports across regions suggest this phenotype is observed internationally. Uawithya et al. (2026) determined that the prevalent expression of subacute myelitis in time-varying cohorts can contribute to misdiagnosis with an infectious or vascular myelopathy. Cheng et al. (2023) observed that even in cases characterised as “overlapping encephalitis,” the spinal cord remains the primary site of initial inflammatory attack. Regarding symptomatology, Gao et al. (2022) indicated that the profound neuropathic pain and sensory disturbances seen in these patients result from complex neuro-immune crosstalk rather than purely structural mechanical injury. Gklinos et al. (2024) further noted that these sensory deficits frequently present as the sole initial complaint before motor involvement, suggesting a specific vulnerability of sensory tracts in the early inflammatory cascade.

3.3 Transition Phase: Emergence of Encephalitis

following the initial spinal manifestations, data synthesis shows that approaching the critical transition phase is characterised by cephalad movement of pathology. Howard et al. (2022) report that delayed encephalopathy often occurs in patients who initially present with isolated myelitis, presenting clinically in the following forms: new-onset seizures, acute confusion, or specific neuropsychiatric changes weeks after the spinal onset. Morris et al. (2024) demonstrated that this clinical deterioration often occurs paradoxically, evolving despite the apparent stabilisation or improvement of spinal symptoms, which suggests a distinct, sequential migratory inflammatory mechanism rather than a simultaneous neuraxis strike. The literature indicates that this transition is often misinterpreted as a complication of steroid treatment or infection rather than disease progression.

A crucial finding regarding diagnostic sensitivity during this window was the discrepancy between clinical signs and radiological evidence. Sanvito et al. (2024) found that early brain MRI scans often remained normal or showed only non-specific white matter changes during the onset of psychiatric symptoms, which frequently delayed the diagnosis of encephalitis. According to Sanvito et al.

Table 4. Characteristics of Included Studies Defining Spinal-Onset Autoimmune Encephalitis

Author(s)	Year	Study Design	Autoantibody Profile	Initial Spinal Phenotype	Encephalitic Evolution	Key Outcomes
(Fang et al., 2016)	2016	Retrospective cohort	GFAP-IgG	LETM, myelitis	Encephalopathy, seizures	Immunotherapy-responsive; relapse reported
(Flanagan et al., 2017)	2017	Multicentre cohort	GFAP-IgG	LETM, meningo-myelitis	Cognitive and psychiatric features	Favourable outcomes with early treatment
(Jarius et al., 2018)	2018	Consensus review	MOG-IgG	LETM, acute myelitis	Cortical encephalitis	Relapsing course in the subset
(Cobo-Calvo et al., 2018)	2018	Cohort study	MOG-IgG	LETM	Encephalopathy, seizures	Prognosis is dependent on early immunotherapy
(Asnafi et al., 2020)	2020	Population-based study	Seronegative/ MS-mimic	LETM	Delayed encephalitic features	High misdiagnosis rate
(Dubey et al., 2018)	2018	Epidemiological cohort	Neuronal surface Abs	Myelitis	Encephalitis	Worse outcomes with diagnostic delay
(Howard et al., 2022)	2022	Case report + review	Seronegative	Hemorrhagic LETM	Acute encephalopathy	Severe disability
(Cheng et al., 2023)	2023	Case report	GFAP-IgG	Myelitis	Cortical encephalitis	Post-infectious trigger identified
(Uzawa et al., 2024)	2024	Narrative review	MOG-IgG / AQP4-IgG	LETM	Variable cerebral involvement	Spectrum overlap highlighted
(Zuliani et al., 2021)	2021	Review	Neuronal surface Abs	Myelitis	Limbic and diffuse encephalitis	Diagnostic expansion advocated
(Kunchok et al., 2021)	2021	Cohort study	MOG-IgG + neuronal Abs	LETM	Encephalopathy	Antibody overlap common
(Acewicz et al., 2021)	2021	Case report	Systemic autoimmunity	Myelitis	Encephalomyelitis	Autoimmune overlap syndrome

(2024), inflammatory markers in the cerebrospinal fluid (CSF), specifically pleocytosis and oligoclonal bands, were far more sensitive during this transition, appearing abnormal significantly earlier than the emergence of cortical T2-hyperintensities. These findings support the results reported by Howard et al. (2022), emphasising that the absence of structural brain lesions on standard imaging does not preclude the diagnosis of ascending autoimmune encephalitis. Consequently, the results suggest that the "spinal-first" phenotype represents a continuum where the clinical focus shifts from the cord to the cortex, necessitating lumbar puncture over repeat neuroimaging when behavioural changes emerge in myelitis patients.

3.4 Disease Course and Outcomes

The longitudinal analysis of the included studies revealed that the spinal-onset phenotype follows a distinct trajectory often characterised by relapse and chronicity. According to Silva et al. (2025), in contrast to monophasic viral myelitis, autoimmune etiologies often show a multiphasic course, in which a spinal attack is succeeded by cerebral relapse unless treated. Dubey et al.

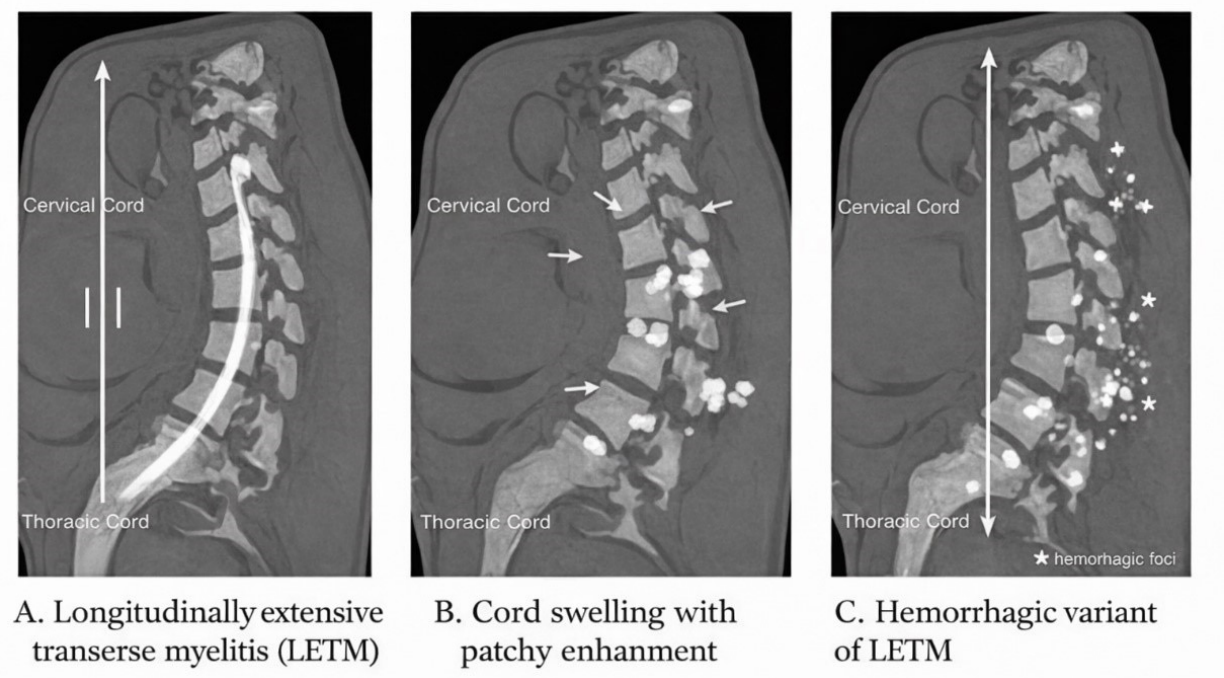

Figure 1. SchematicRepresentative spinal MRI patterns (LETM distribution; cord swelling/hemorrhagic variants)
**(Source: Author)*

(2018) revealed a remarkable escalation of the permanent disability scores in patients in whom corticosteroids were used initially to control LETM without the use of maintenance immunosuppression. Wang et al. (2026) observed that immunotherapy dependence was a defining feature of this cohort, with a substantial number of patients requiring long-term B-cell depletion to prevent encephalitic recurrence.

Furthermore, Van Steenhoven et al. (2023) discovered that existing clinical definitions of autoimmune encephalitis are less sensitive when applied to patients with predominant myelopathy, which leads to a watch-and-wait strategy that allows the disease to progress. According to Uher et al. (2025), there is the highest rate of misdiagnosis during the transition period when mild signs of psychiatry are misaligned to physical disease-related psychological pressure and not as organic brain disease. The results support the conclusions of Silva et al. (2025), who argued that early diagnosis of the spinal phenotype can be regarded as the most relevant changeable factor in avoiding long-term cognitive and motor impairments.

3.5 Immunological Complexity and Overlap Syndromes

The synthesis of serological data highlights that spinal-onset autoimmune encephalitis is not an existing entity but represents a larger impairment of immune tolerance. Kunchok et al. (2021) demonstrated that the co-existence of antibodies specifically MOG-IgG1, combined with neuronal surface antibodies like anti-NMDAR, is significantly more common in this phenotype than in classic encephalitis. Acewicz et al. (2021) reported that this entity frequently manifests in patients with pre-existing systemic autoimmune disorders, such as rheumatoid arthritis, complicating the attribution of neurological symptoms. Molazadeh et al. (2022) noted that these overlap syndromes have a hybrid clinical presentation where systemic inflammation can mask the initial indicators of autoimmunity in the central nervous system.

Moreover, according to the literature, this complexity is driven by genetic and post-infectious factors. Gilligan et al. (2025) identified a strong association between specific HLA haplotypes and the susceptibility to developing concurrent spinal and cerebral autoimmunity. In addition to intrinsic autoimmunity, Ndondo et al. (2022) reported that a specific category of cases occurs in sequence after the virus infections CNS, signifying a secondary autoimmune cascade. Wurdack et al. (2024) theorised that such post-infection evolution is driven by molecular mimicry, in which the immune response to some viral stimulus unintentionally reacts with the spinal antigens. In accordance with the results of Kunchok et al. (2021), these reports support the idea of defining spinal-onset

AE as a spectrum disorder that requires a wide-ranging serological screening to reveal persisting immunological intersections. Collectively, the included studies identify spinal-onset autoimmune encephalitis as a reproducible clinical trajectory characterised by early myelitis, delayed encephalopathy, diagnostic delay, and improved outcomes with early immunotherapy. GFAP astrocytopathy and MOGAD emerge as the most frequently implicated antibody-defined syndromes. Delayed recognition is consistently associated with higher disability and relapse risk.

Discussion

A consistent pattern has emerged within the literature regarding autoimmune encephalitis: spinal cord involvement frequently heralds the development of subsequent brain inflammation. Specifically, longitudinally extensive transverse myelitis (LETM) often precedes (meningo) encephalitis, a sequence most often seen in patients with MOGAD or GFAP astrocytopathy (Cobo-Calvo et al., 2018; Fang et al., 2016). The reproducibility of these findings across independent global centers reinforces the validity of this temporal phenotype (Gklinos et al., 2024; Uawithya et al., 2026).

The presence of certain biomarkers, such as GFAP-IgG, MOG-IgG, and neuronal surface antibodies offer a necessary biological plausibility and diagnostic framework to spinal-onset AE. Molazadeh et al. (2022) discussed in a study that GFAP antibodies and MOG antibodies, respectively, describe the pathophysiology of primary astrocytic injury and LETM before cortical demyelination. Furthermore, Wang et al. (2022) and Gilligan et al. (2025) have identified neuronal surface antibodies as key drivers of severe encephalitic progression following initial spinal manifestations. Recent academic syntheses, such as Kurkowska-Jastrzębska et al. (2025), now categorize these antibody-mediated clinical patterns as fundamental components of the broader autoimmune encephalitis (AE) spectrum, rather than viewing them as isolated or atypical phenomena.

4.2 Pathophysiology: Integrated, Evidence-Based Mechanisms

Autoimmune GFAP astrocytopathy exemplifies the downstream consequences of primary astrocytic immune injury. The dysfunction of the astrocytes in this model causes a significant breach of the blood–CNS barrier, thereby facilitating to secondary neuronal engagement. A diffuse, perivascular meningoencephalomyelitis occurs consistently instead of a focal disease, as shown by pathological and CSF studies, explaining the spontaneous switch of spinal to cranial symptoms (Fang et al., 2016; Flanagan et al., 2017). Contemporary clinicopathological reviews further support this astrocyte-associated inflammatory pattern (Gklinos et al., 2024). Alongside this, MOGAD contributes a complementary antigen-density–driven demyelinating process. Although the study conducted by Jarius et al. (2018) showed that immune response is generally directed at the optic nerves and spinal cord, long spinal tracts can be targeted; cortical vulnerability, coupled with a predilection toward long tracts, forms a specific pathological substrate of the observed clinical process.

Furthermore, experimental and clinical evidence support a model of mutual signalling between immune cells, glia and neurons along the neuraxis to aid the propagation between the spinal cord and the cranium. Stimulated microglia and astrocytes enhance local inflammation, sending the signal outside the index spinal lesion (Gao et al., 2022). Importantly, the CSF-mediated transport of antibodies and inflammatory cytokines can occur without hematogenous dissemination in case of dysfunction of the blood-brain barrier (Ramanathan et al., 2023; Wang et al., 2022). This neuro-immune crosstalk concept offers a unified mechanistic explanation of how a spinal-dominant onset can develop into diffuse encephalitis via direct anatomical continuity and CSF pathways without referring to hypothetical systemic pathways.

Moreover, according to Cheng (2023), spinal-onset AE usually has precipitating events with viral and systemic immune triggers. The presence of viral encephalitis has been shown to transition into secondary autoimmune disease (Wurdack et al., 2024), which is consistent with the rest of the world's understanding of post-infectious CNS autoimmunity (Ndondo et al., 2022). These results are consistent with existing theory on immune priming: an initial infectious invasion should enhance future autoimmune assaults on spinal and cerebral foci.

4.3 Diagnostic Challenges and Mimics: Clinical Consequences

The current diagnostic framework, specifically the widely utilised 2016 clinical criteria for autoimmune encephalitis (AE), heavily emphasises the rapid onset of encephalopathy and corresponding brain MRI abnormalities. This craniocentric focus inadvertently

leads to the significant under-recognition of spinal-first presentations, as these patients often lack initial cerebral manifestations (Orozco et al., 2023). Van Steenhoven et al. demonstrated that validation studies examining these criteria have confirmed a markedly reduced sensitivity when applied to early-stage or atypical disease phenotypes, particularly those beginning in the spinal cord (Van Steenhoven et al., 2023). Consequently, patients presenting with isolated myelitis frequently fail to meet the strict thresholds for "possible AE" during the initial therapeutic window. This diagnostic gap creates a critical delay in recognition, leaving patients vulnerable during the phase when immunomodulatory intervention would be most effective.

Sanvito et al. (2024) observed that the dependence on conventional paraclinical markers also makes it even more difficult to diagnose this entity as early as possible. Although essential in the advanced stage of the disease, brain MRI is often normal and portrays non-specific changes in the initial phase of the spinal disease, with limited diagnostic value (Sanvito et al., 2024). According to Flanagan (2017) and Zuliani et al. (2021), the time-sensitive nature of clinical decision-making is often compromised by the lengthy testing periods required to identify specific antibodies, such as those for GFAP and neuronal surface antigens. In a study by Morris et al. (2024), it was observed that although the electroencephalography (EEG) is capable of aiding a diagnosis of subclinical evolution of encephalitis, patterns in clinical practice indicate that the technique is often underused on patients with symptoms that are referred by the spinal tract, creating a missed opportunity to ensure that the cerebral involvement is confirmed (Morris et al., 2024).

As reported by Asnafi et al. (2020), the hallmark feature of longitudinally extensive transverse myelitis (LETM) presents a substantial differential challenge. Clinicians must differentiate spinal AE from multiple sclerosis, in which LETM is rare but documented (Asnafi et al., 2020), and from NMOSD and MOGAD (Uzawa et al., 2024). Consistent with the findings of Acewicz et al. (2021) and Jimenez Echavarria et al. (2025), this variation is also expanded by an extensive list of systemic autoimmune, infectious, metabolic and neoplastic conditions which may imitate this picture (Acewicz et al., 2021); Jimenez Echavarria 2025). Misclassification between these entities is likely to delay initiation of appropriate immunotherapy, thus exacerbating neurological outcomes in the long term.

4.4 Management Strategies and Evidence Gaps

Effective management of spinal-onset AE hinges on a proactive diagnostic strategy that prioritises early lumbar puncture. A systematic cerebrospinal fluid (CSF) is necessary not only to exclude infectious etiologies in a rigorous way but also to perform a broad-spectrum antibody (Patel et al., 2022). Zuliani et al. (2021) cautioned that serum-only testing presents a substantial likelihood of the occurrence of false-negative outcomes, and this risk particularly exists when a patient has intrathecal antibody production. The results provided by Patel et al. (2022) and Wang et al. (2022) prove the point that, due to the high risk of irreversible morbidity caused by untreated spinal-encephalitic progression, it is increasingly becoming recommended to introduce early empiric immunotherapy in the case of high clinical suspicion, but not to wait until such cases are confirmed by exact serological evidence.

Furthermore, it was also demonstrated by Wang et al. (2022) that the acute phase of a patient with a severe disease or those with first-line steroid and intravenous immunoglobulin refractory to treatment require immediate second-line immunosuppression, such as rituximab, cyclophosphamide, or any other biologic treatment to prevent the progression of the disease. According to the observation of Cobo-Calvo et al. (2018), the use of long-term maintenance therapy is especially relevant to avoid recurrence in patients diagnosed with relapsing phenotypes, including MOGAD and autoimmune GFAP astrocytopathy. As highlighted by Dubey et al. (2018), despite these emerging strategies, the field remains limited by a complete absence of randomised controlled trials specific to spinal-onset AE. The existing management guidelines are mainly based on small, retrospective groups, which are prone to referral and severity bias, reducing the importance of prospective studies in future.

4.5 Clinical Implications and Prognosis

The clinical evolution of spinal-onset autoimmune encephalitis (AE) is a disease paradigm that is time-sensitive. There is empirical evidence suggesting that the severity of the primary longitudinally extensive transverse myelitis (LETM) and therapeutic intervention delay are highly predictive of long-term disability and death (Silva et al., 2025). As a result, early diagnosis of this spinal-to-cranial progression provides a brief treatment period; early diagnosis would allow clinicians to administer treatment before the inflammatory cascade causes irreversible atrophy of the spinal cord or extensive encephalitic damage

to the brain, thus significantly determining the functional clinical outlook of the patient.

Kammeyer et al. (2024) reported that beyond physical disability, predicting neurological recovery requires a nuanced evaluation. The growing availability of biomarkers of glial and neuronal structural damage have potential to enhance prognostication and enable more personalised management (Kammeyer et al., 2024). Ginanneschi et al. (2024) highlighted that the possible implications of the brain require careful monitoring of cognitive health. Although most screening tools were originally developed for neurodegenerative disorders, their application here underscores the critical importance of early neuropsychological assessment. Such instruments are essential for identifying subtle cognitive impairments associated with inflammatory CNS diseases, thereby ensuring that cognitive and behavioral sequelae are not overlooked during rehabilitation.

4.6 Position Statement

The accumulated evidence supports the conclusion that spinal-onset autoimmune encephalitis is a clinically meaningful and biologically grounded presentation, rather than a mere diagnostic curiosity. Failure to identify this characteristic pattern is a major contributor to the cause of late immunotherapy, preventable permanent neurological damage and common misdiagnosis with atypical multiple sclerosis or cryptogenic myelitis. Thus, existing diagnostics should change to accommodate inflammatory presentations of the spine directly. Such a shift in the paradigm necessitates a reduced threshold to initiate early comprehensive CSF analysis and provide timely immunosuppression to stop the progression of the disease. Through acknowledgement of this entity, the medical community is able to streamline clinical practice closer to the neurobiology of such disorders.

5. Conclusion

This narrative review highlights spinal-onset autoimmune encephalitis as a distinct yet under-recognised neuroimmunological phenotype. The evidence consistently demonstrates a spinal-first inflammatory course, most commonly presenting as longitudinally extensive transverse myelitis (LETM), followed by delayed encephalopathy. This pattern is particularly evident in GFAP astrocytopathy and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Diagnostic delays are common and are strongly associated with worse neurological outcomes, emphasising the importance of early cerebrospinal fluid evaluation and timely initiation of immunotherapy.

6. Strengths and Limitations

This narrative review provides a comprehensive synthesis of spinal-onset autoimmune encephalitis by integrating evidence from cohort studies, case series, and contemporary immunological classifications, thereby highlighting a clinically meaningful but under-recognised disease phenotype. A key strength lies in the structured appraisal of antibody-defined syndromes and their spinal-first trajectories, offering clinically actionable insights into diagnostic and therapeutic decision-making. The use of SANRA-based quality assessment further strengthens the internal validity of the synthesis.

However, several limitations should be acknowledged. The narrative design precludes quantitative meta-analysis and limits the ability to generate mutual estimates of incidence, treatment efficacy, or prognosis. Much of the available evidence is derived from retrospective studies and severe antibody-positive cases, introducing referral, severity, and publication bias. Inconsistencies in diagnostic criteria, antibody testing methodologies, and follow-up duration also complicate cross-study comparisons.

References

Acewicz, A., Wierzba-Bobrowicz, T., Michałowski, Ł., Pęcak, M., Tarka, S., Chutorański, D., Stępień, T., Felczak, P., Sklinda, K., & Nasierowska-Guttmejer, A. (2021). Encephalomyelitis associated with rheumatoid arthritis: a case report. Folia Neuropathologica, 59(1), 91-97.

Asnafi, S., Morris, P. P., Sechi, E., Pittock, S. J., Weinshenker, B. G., Palace, J., Messina, S., & Flanagan, E. P. (2020). The frequency of longitudinally extensive transverse myelitis in MS: a population-based study. Multiple sclerosis and related disorders, 37, 101487.

Cheng, P., Huang, W., Yang, M., Chen, Z., Geng, Y., Zhang, X., & Chen, W. (2023). Autoimmune GFAP astrocytopathy after viral encephalitis: a case report of bimodal overlapping encephalitis. Frontiers in Immunology, 14, 1258048.

Cobo-Calvo, A., Ruiz, A., Maillart, E., Audoin, B., Zephir, H., Bourre, B., Ciron, J., Collongues, N., Brassat, D., & Cotton, F. (2018). Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults: the MOGADOR study. Neurology, 90(21), e1858-e1869.

Dubey, D., Pittock, S. J., Kelly, C. R., McKeon, A., Lopez-Chiriboga, A. S., Lennon, V. A., Gadoth, A., Smith, C. Y., Bryant, S. C., & Klein, C. J. (2018). Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. Annals of neurology, 83(1), 166-177.

Fang, B., McKeon, A., Hinson, S. R., Kryzer, T. J., Pittock, S. J., Aksamit, A. J., & Lennon, V. A. (2016). Autoimmune glial fibrillary acidic protein astrocytopathy: a novel meningoencephalomyelitis. JAMA neurology, 73(11), 1297-1307.

Flanagan, E. P., Hinson, S. R., Lennon, V. A., Fang, B., Aksamit, A. J., Morris, P. P., Basal, E., Honorat, J. A., Alfugham, N. B., & Linnoila, J. J. (2017). Glial fibrillary acidic protein immunoglobulin G as biomarker of autoimmune astrocytopathy: analysis of 102 patients. Annals of neurology, 81(2), 298-309.

Gao, Y., Mei, C., Chen, P., & Chen, X. (2022). The contribution of neuro-immune crosstalk to pain in the peripheral nervous system and the spinal cord. International immunopharmacology, 107, 108700.

Gklinos, P., Athanasopoulos, F., Giatrakou, V., Arkoudis, N.-A., Pournara, D., Giagkou, E., Tountopoulou, A., Vassilopoulou, S., & Mitsikostas, D.-D. (2024). Unveiling GFAP astrocytopathy: insights from case studies and a comprehensive review of the literature. Antibodies, 13(4), 79.

Howard, C. W., Racosta, J. M., & Robinson, D. B. (2022). Acute hemorrhagic longitudinally extensive transverse myelitis–A case report and review of the literature. Neuroimmunology Reports, 2, 100051.

Jarius, S., Paul, F., Aktas, O., Asgari, N., Dale, R. C., De Seze, J., Franciotta, D., Fujihara, K., Jacob, A., & Kim, H. (2018). MOG encephalomyelitis: international recommendations on diagnosis and antibody testing. Journal of neuroinflammation, 15(1), 134.

Jiménez Echavarria, A. M., Escobar Jaramillo, S., & Gloria Escobar, J. M. (2025). Longitudinal extensive transverse myelitis as the initial manifestation of the acquired immunodeficiency syndrome. Acta Neurológica Colombiana, 41(3).

Kammeyer, R., Chapman, K., Furniss, A., Hsieh, E., Fuhlbrigge, R., Ogbu, E. A., Boackle, S., Zell, J., Nair, K. V., & Borko, T. L. (2024). Blood-based biomarkers of neuronal and glial injury in active major neuropsychiatric systemic lupus erythematosus. Lupus, 33(10), 1116-1129.

Kunchok, A., Flanagan, E. P., Krecke, K. N., Chen, J. J., Caceres, J. A., Dominick, J., Ferguson, I., Kinkel, R., Probasco, J. C., & Ruvalcaba, M. (2021). MOG-IgG1 and co-existence of neuronal autoantibodies. Multiple Sclerosis Journal, 27(8), 1175-1186.

Morris, H., Kaplan, P. W., & Kane, N. (2024). Electroencephalography in encephalopathy and encephalitis. Practical Neurology, 24(1), 2-10.

Ndondo, A. P., Eley, B., Wilmshurst, J. M., Kakooza-Mwesige, A., Giannoccaro, M. P., Willison, H. J., Cruz, P. M. R., Heckmann, J. M., Bateman, K., & Vincent, A. (2022). Post-infectious autoimmunity in the central (CNS) and peripheral (PNS) nervous systems: an African perspective. Frontiers in Immunology, 13, 833548.

Orozco, E., Valencia-Sanchez, C., Britton, J., Dubey, D., Flanagan, E. P., Lopez-Chiriboga, A. S., Zalewski, N., Zekeridou, A., Pittock, S. J., & McKeon, A. (2023). Autoimmune encephalitis criteria in clinical practice. Neurology: Clinical Practice, 13(3), e200151.

Patel, A., Meng, Y., Najjar, A., Lado, F., & Najjar, S. (2022). Autoimmune encephalitis: a physician's guide to the clinical spectrum diagnosis and management. Brain sciences, 12(9), 1130.

Ramanathan, S., Brilot, F., Irani, S. R., & Dale, R. C. (2023). Origins and immunopathogenesis of autoimmune central nervous system disorders. Nature Reviews Neurology, 19(3), 172-190.

Sanvito, F., Pichiecchio, A., Paoletti, M., Rebella, G., Resaz, M., Benedetti, L., Massa, F., Morbelli, S., Caverzasi, E., & Asteggiano, C. (2024). Autoimmune encephalitis: what the radiologist needs to know. Neuroradiology, 66(5), 653-675.

Silva, P. B. R., Pereira, S. L. A., Aguiar, G., Terrim, S., Marques Filho, F. V., Silva, G. D., Neto, H., Boaventura, M., Adoni, T., & Sato, D. K. (2025). Longitudinally extensive transverse myelitis: Impact on functional prognosis and mortality in a 10-year follow-up cohort. Multiple sclerosis and related disorders, 94, 106279.

Uawithya, E., Siriphiphatcharoen, P., Benjapibal, B., Kittipadakul, S., & Siritho, S. (2026). Clinical, Imaging, and Immunological Features of GFAP Astrocytopathy: A Systematic Review with Regional Comparison. Multiple sclerosis and related disorders, 107019.

Uzawa, A., Oertel, F. C., Mori, M., Paul, F., & Kuwabara, S. (2024). NMOSD and MOGAD: an evolving disease spectrum. Nature Reviews Neurology, 20(10), 602-619.

Van Steenhoven, R. W., de Vries, J. M., Bruijstens, A. L., Paunovic, M., Nagtzaam, M. M., Franken, S. C., Bastiaansen, A. E., De Bruijn, M. A., Van Sonderen, A., & Schreurs, M. W. (2023). Mimics of autoimmune encephalitis: validation of the 2016 clinical autoimmune encephalitis criteria. Neurology: Neuroimmunology & Neuroinflammation, 10(6), e200148.

Wang, B., Wang, C., Feng, J., Hao, M., & Guo, S. (2022). Clinical features, treatment, and prognostic factors in neuronal surface antibody-mediated severe autoimmune encephalitis. Frontiers in Immunology, 13, 890656.

Wurdack, K., Prüss, H., & Finke, C. (2024). Evolution from viral encephalitis to autoimmune encephalitis to multiple sclerosis: a case report. Journal of neurology, 271(10), 7035-7038.

Zuliani, L., Marangoni, S., De Gaspari, P., Rosellini, I., Nosadini, M., Fleming, J. M., De Riva, V., Galloni, E., Perini, F., & Frigo, A. C. (2021). Epidemiology of neuronal surface antibody-mediated autoimmune encephalitis and antibody-based diagnostics. Journal of Neuroimmunology, 357, 577598.