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Contents

Dear Readers, It is my pleasure to present the first issue of ***Archives of Clinical Neurology*** for 2025. As we embark on this new year, I extend my best wishes for continued success and professional growth in your respective areas of interest.

This issue features four papers, each deserving of special attention. I trust that you will find these contributions both insightful and stimulating.

Melanis and coauthors, in their review entitled "Contemporary Clinical Approach and Diagnostic Pitfalls in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)," emphasize the complexity of diagnosing CIDP, noting that over 15 diagnostic criteria have been proposed since 1970s. This underscores the inherent challenges in establishing a definitive diagnosis and differentiating CIDP from its mimics. The authors stress that an accurate diagnosis can be achieved through the integration of clinical presentation, electrophysiological findings, and ancillary investigations. Their discussion of the latest diagnostic criteria, alongside "red flags" and atypical features, offers a comprehensive and structured framework. This approach aims to streamline diagnosis and management, ensuring timely and effective interventions.

The clinical trials and subsequent FDA approval of monoclonal antibodies targeting amyloid aggregates for Alzheimer's disease (AD), as well as the pending approval by the European Medicines Agency (EMA), have generated both excitement and controversy. Numerous challenges continue to concern the broader scientific community, as well as various stakeholders, including public health administrators and the target population. Key issues include the uncertainty surrounding the prevalence of AD particularly in cases of mild cognitive impairment and early-stage disease. Defining the appropriate target population remains problematic, as does the burden on national healthcare systems to identify eligible individuals, which often requires invasive and/or costly diagnostic procedures. Additionally, there is a lack of easily accessible, approved biomarkers, while comorbidities and drug interactions impose further constraints. The need to monitor potential side effects adds another layer of complexity. Moreover, the surrogate endpoints used in clinical trials are not universally accepted, necessitating further validation studies. There is also a pressing need to establish consensus on the minimal clinically meaningful differences in therapeutic outcomes. These issues are highlighted in the narrative review by Athanasaki et al., which examines the key phase III clinical trials of disease-modifying anti-amyloid therapies. The review underscores the importance of addressing these challenges to optimize the clinical and societal impact of these novel treatments.

Idiopathic immune thrombocytopenia (ITP) has been suggested to occur with greater frequency in patients with multiple sclerosis (MS) compared to the general population. Furthermore, drug-induced ITP has also been reported in association with MS disease-modifying treatments, particularly with the use of alemtuzumab. Kyriakaki et al. describe two cases of MS patients who developed alemtuzumab-induced chronic ITP. Both patients were subsequently managed with ocrelizumab for the underlying MS exacerbations. Remarkably, treatment with ocrelizumab achieved remission of both MS and ITP, highlighting its potential dual therapeutic benefit in such cases.

Maili et al. report an uncommon case of prolonged amnestic syndrome lasting up to 24 hours, consistent with a diagnosis of transient global amnesia (TGA). This clinical syndrome, characterized by unclear pathophysiological mechanisms—ranging from vascular, migrainous, and epileptic hypotheses to psychogenic origins—highlights the challenges in establishing a differential diagnosis, particularly when considering mimics and chameleons. The discussion also considers findings from brain imaging, alongside of TGA's risk factors and triggers. Iatrogenic triggers are infrequently reported and deserve greater recognition, as healthcare professionals from various specialties are often involved in these cases.

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Άρθρα...

ΣΥΓΧΡΟΝΗ ΚΛΙΝΙΚΗ ΠΡΟΣΕΓΓΙΣΗ ΚΑΙ ΔΙΑΓΝΩΣΤΙΚΑ ΔΙΛΗΜΜΑΤΑ ΣΤΗ ΧΡΟΝΙΑ ΦΛΕΓΜΟΝΩΔΗ ΑΠΟΜΥΕΛΙΝΩΤΙΚΗ ΠΟΛΥΝΕΥΡΟΠΑΘΕΙΑ

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Περίληψη

Η Χρόνια Φλεγμονώδης Απομυελινωτική Πολυνευροπάθεια αποτελεί μια χρόνια, ανοσοδιαμεσολαβούμενη διαταραχή του περιφερικού νευρικού συστήματος. Παρά την πρόοδο στα διαγνωστικά κριτήρια, η CIDP παρουσιάζει σημαντικές προκλήσεις λόγω της κλινικής της ετερογένειας και της επικάλυψης με πολλές μιμητικές καταστάσεις, όπως οι αυτοάνοσες κομβοπάθειες, οι παραπρωτεϊναιμικές νευροπάθειες και οι κληρονομικές διαταραχές. Αυτή η συστηματική ανασκόπηση περιγράφει την κλινική προσέγγιση στη νόσο, με έμφαση στους διαφορετικούς της φαινοτύπους, τα διαγνωστικά κριτήρια, τις υποστηρικτικές εξετάσεις και τη διαφορική διάγνωση. Οι ηλεκτροφυσιολογικές μελέτες, η ανάλυση του εγκεφαλονωτιαίου υγρού, η απεικόνιση και οι αιματολικές εξετάσεις προσεγγίζονται στο πλαίσιο της διαγνωστικής τους αξίας και των περιορισμών τους. Δίνεται έμφαση στην αναγνώριση παγίδων, όπως η υπερβολική εξάρτηση από μη ειδικά ευρήματα και η λανθασμένη ερμηνεία αποτελεσμάτων. Μέσω της ολοκληρωμένης ανάλυσης κλινικών, ηλεκτροφυσιολογικών και υποστηρικτικών δεδομένων, οι κλινικοί γιατροί μπορούν να διακρίνουν με ακρίβεια τη νόσο από τους πιθανούς μιμητές και να διασφαλίσουν την έγκαιρη διάγνωση της . Αυτή η ανασκόπηση στοχεύει στην παροχή ενός δομημένου πλαισίου για τη βελτιστοποίηση της διάγνωσης και της προσέγγισης αυτής της περίπλοκης διαταραχής.

Λέξεις-κλειδιά: χρόνια φλεγμονώδης απομυελινωτική πολυνευροπάθεια, κλινικά κριτήρια, διαφορική διάγνωση, ηλεκτροφυσιολογικός έλεγχος, περιφερική νευροπάθεια

CONTEMPORARY CLINICAL APPROACH AND DIAGNOSTIC PITFALLS IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

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ABSTRACT

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is a chronic, immune-mediated disorder of the peripheral nervous system. Despite advancements in diagnostic criteria, CIDP presents significant challenges due to its clinical heterogeneity and overlap with numerous mimicking conditions, including autoimmune nodopathies, paraproteinemic neuropathies, and hereditary disorders. This review outlines the clinical approach to CIDP, focusing on its diverse phenotypes, diagnostic criteria, supportive investigations, and differential diagnosis. Electrodiagnostic studies, cerebrospinal fluid analysis, imaging, and serologic testing are discussed in the context of their diagnostic value and limitations. Emphasis is placed on identifying

pitfalls, such as overreliance on nonspecific findings and misinterpretation of test results. By integrating clinical, electrophysiological, and ancillary data, clinicians can accurately distinguish CIDP from mimics and ensure timely intervention. This review aims to provide a structured framework to optimise diagnosis and management in this complex condition.

Keywords: chronic inflammatory demyelinating polyneuropathy (CIDP), Clinical criteria, differential diagnosis, electrodiagnostic studies, peripheral neuropathy

INTRODUCTION

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is characterised as a rare, autoimmune-based peripheral nerve disorder that is amenable to treatment.[1] The reported incidence of CIDP is about 1 per 100,000 in general population and can ascend to 20% in patients older than 60 years of age.[2,3] Characterised by progressive or relapsing-remitting motor and sensory dysfunction, CIDP encompasses a broad spectrum of clinical manifestations and phenotypic variants, necessitating a nuanced diagnostic approach.[4] The underlying pathophysiology involves immune-mediated attacks on the myelin sheath, resulting in demyelination, axonal damage, and subsequent disability if left untreated.[5] Early diagnosis and intervention are critical to preventing irreversible nerve damage and functional decline.[6]

Since the original description of CIDP in the 1970s, over 15 sets of diagnostic criteria have been proposed.[7] The criteria published in 2021 by the European Academy of Neurology / Peripheral Nerve Society (EAN/PNS) were developed for use during routine clinical care and are available in the public domain.[6] These criteria provide clinicians with an invaluable resource by which the data collected during the evaluation of the patient with possible CIDP can be interpreted.[6] However, numerous mimics—ranging from autoimmune nodopathies and paraproteinemic neuropathies to genetic and systemic disorders—complicate the differentiation of CIDP from alternative diagnoses.[8] In addition, CIDP variants and atypical presentations further obscure the diagnostic landscape, underscoring the importance of an individualised and systematic approach.[9] This review provides a comprehensive exploration of the diagnostic framework for CIDP, including its clinical characteristics, electrodiagnostic features, and supportive investigations. Emphasis is placed on diagnostic pitfalls and the importance of distinguishing CIDP from its numerous mimics through a structured differential diagnosis. By synthesising current evidence, this review aims to offer clinicians practical insights into optimising diagnostic accuracy and ensuring appropriate management for patients with suspected CIDP.

CLINICAL PHENOTYPES

CIDP is a heterogeneous disorder with a wide spectrum of clinical presentations.[10] The most recent classification divides CIDP into three categories: typical CIDP, CIDP variants, and autoimmune nodopathies.[11]

Typical CIDP

Typical CIDP is characterised by a symmetrical, sensory, and motor polyradiculoneuropathy with combined proximal and distal weakness, areflexia, and minimal associated pain.[11,12] It accounts for 50% to 60% of all cases.[11,12] Distal motor deficits tend to be more pronounced, while sensory deficits predominantly involve large fibers due to their extensive myelination.[13,14] Cranial nerve and bulbar involvement are observed in approximately 10% to 20% of patients with CIDP.[15] These manifestations can contribute to significant functional impairment and complicate the clinical presentation.[15] Additionally, tremor has been identified as a prevalent symptom in multiple studies, further highlighting the variability in CIDP presentations and the importance of comprehensive neurological assessment.[16] Autonomic involvement in these patients is generally mild and localised, with symptoms such as constipation and urinary retention typically emerging only in more advanced stages of the disease.[17] The majority of patients with typical CIDP experience a **slowly progressive course**, although a **relapsing-remitting pattern** is observed in at least one-third of cases.[18] This relapsing-remitting presentation appears to be more common in younger individuals, underscoring the variability in disease progression across different age groups.[18] Symptoms that persist for more than eight weeks define the chronic nature of the condition.[19] Any presentation deviating from this pattern warrants consideration of alternative aetiologies or atypical forms of CIDP.[19] For instance, pure large-fibre sensory neuropathy with ataxia may indicate disease mimickers, distinct entities, or chronic immune sensory polyneuropathy (CISP).[19] Multifocal, asymmetric, or upper-limb-predominant involvement raises the suspicion of multifocal CIDP.[20] Typical CIDP rarely involves systemic symptoms such as fever, malaise, severe pain, or dysautonomia.[17] Patients with typical CIDP generally exhibit a favourable response to immunomodulatory therapies, including intravenous immunoglobulin (IVIG), subcutaneous immunoglobulin (SCIg), corticosteroids, and plasmapheresis.[21] However, individual responses

may vary, emphasising the importance of monitoring treatment outcomes and tailoring therapy to each patient's clinical course.

CIDP Variants

Pure Motor CIDP

Pure motor CIDP, which constitutes 4%-10% of cases mimics typical CIDP but with preserved sensation even on sensory conduction studies.[11] This preservation of sensation is a common clinical and electrophysiological feature in multifocal motor neuropathy (MMN). In MMN, however, conduction velocity away from the site of the block may remain normal, at least at the early stages.[21] Moreover, in the latter condition, weakness is typically focal in the distribution of individual nerves rather in the distribution of limbs.[22] The term motor-predominant CIDP is utilised, if sensory conduction studies show abnormalities.[23] While earlier reports suggested that some patients with CIDP might experience worsening symptoms with corticosteroid treatment, more recent studies have not substantiated these findings.[23] Current evidence indicates that most patients respond favourably to both intravenous immunoglobulin (**IVIG)** and **steroid therapy**, highlighting their effectiveness as key treatment modalities in CIDP management.[23]

Pure Sensory CIDP

Pure sensory CIDP accounts for about 35% of CIDP cases,[11,24] and is characterised by impaired vibration and joint position sense, along with gait ataxia, while muscle strength remains intact.[11,24] If motor conduction abnormalities are noted, the term sensory-predominant CIDP is applied.[6] Research suggests that sensory CIDP often represents a transient stage that precedes weakness in 70% of cases.[6] The condition primarily affects large myelinated fibers, which are responsible for proprioception and fine touch, while sparing the small unmyelinated fibers associated with pain and temperature sensation. As a result, patients with sensory CIDP typically do not experience pain or disturbances in thermal perception.[6] In sensory CIDP, the response to standard immunomodulatory treatments, such as IVIG and corticosteroids, is also favourable in most cases.[5,10] However, treatment efficacy may vary depending on the stage of the disease, particularly in cases where sensory dysfunction precedes motor involvement.[5,10]

Distal Acquired Demyelinating Symmetric (DADS) Neuropathy

DADS neuropathy involves distal sensory loss in all four limbs, often accompanied by gait disturbances.[4,11] Distal weakness may also occur, primarily in the lower limbs, but without proximal involvement.[25] It constitutes 2%–17% of all CIDP cases and typically progresses slowly, with high-amplitude, low-frequency tremors being a common feature.[26] Two-thirds of DADS cases are associated with immunoglobulin M (IgM) paraproteinemia, and within this subgroup, most individuals have anti-myelin-associated glycoprotein (MAG) antibodies.[27] This differentiation is particularly relevant when anti-MAG antibodies are present, as this subtype of DADS is generally recognised as a separate entity from CIDP.[13] Moreover, it demonstrates limited responsiveness to the standard immunomodulatory treatments commonly employed for CIDP and may exhibit favourable response to rituximab.[6]

Asymmetric sensorimotor (multifocal) CIDP

Asymmetric sensorimotor (multifocal) CIDP, which accounts for 6%–15% of cases, is also referred to as multifocal demyelinating neuropathy with persistent conduction block (Lewis-Sumner syndrome) or multifocal acquired demyelinating sensory and motor neuropathy (MADSAM).[19,24] Patients with multifocal CIDP typically present with a distinctly asymmetric and multifocal clinical picture that is often indistinguishable from other forms of mononeuropathy multiplex.[19,24] This pattern results in a combination of sensory and motor signs confined to the distributions of individual nerves.[6,28,29] Symptoms can originate in any nerve distribution, varying significantly among patients.[6,28,29] In addition to motor and sensory deficits, some individuals may experience autonomic symptoms, neuropathic pain, or cranial nerve involvement.[6,28,29] Rarely, multifocal CIDP presents as a **focal form**, where symptoms are restricted to a single limb or nerve.[6,28,29] These focal presentations pose a diagnostic challenge due to their limited distribution and overlap with other focal neuropathies.[6,28,29] Asymmetric sensorimotor CIDP typically responds well to IVIG, with some patients requiring adjunctive therapies like corticosteroids or plasmapheresis for adequate symptom control.

Focal CIDP

Focal CIDP, a rare form representing 1% of cases, affects the brachial or lumbosacral plexus or individual nerves.[11] It is often considered a localised form of MADSAM.[6] The majority of patients with **focal forms of CIDP** demonstrate a favourable response to **IVIG** therapy.[30]

Disorders not Classified as CIDP by European Academy of Neurology/Peripheral Nerve Society Task Force

Chronic Inflammatory Sensory Polyradiculopathy (CISP) and CISP plus

CISP constitutes 5%–12% of CIDP cases and is

regarded as a pure sensory form of CIDP, with preganglionic nerve root involvement.[6] This feature results in normal sensory conduction studies due to the integrity of postganglionic fibres.[6] Somatosensory evoked potentials (SSEPs) often reveal slowing of responses, particularly at N13 latencies or N9–N13 interpeak latencies.[6] If motor fibers are also affected at proximal sites, neurophysiology is expected to reveal conduction block at plexus and root level, absence of F-waves with normal motor conduction at distal and intermediate segments.[31] Elevated cerebrospinal fluid (CSF) protein is observed in 92% of cases, and MRI frequently shows spinal root enhancement.[30,32]

Autoimmune Nodopathies

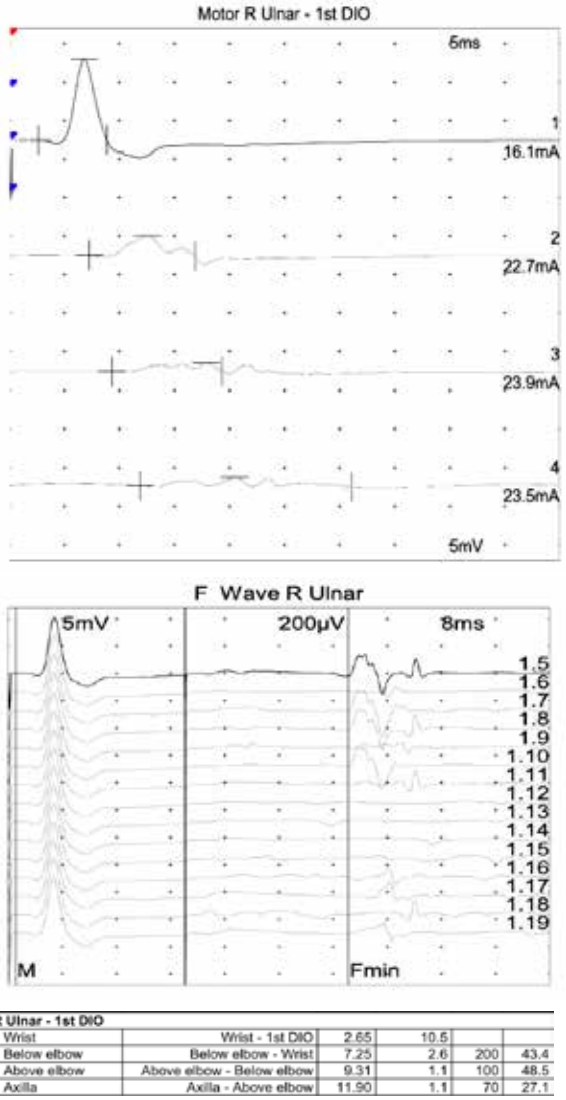
Autoimmune nodopathies are the most recently described CIDP mimics, involving autoantibodies targeting specific molecules within the nodes of Ranvier.[6] Identified antibodies include those against neurofascin 155 (NF155), neurofascin 186 (NF186), contactin 1 (CNTN1), and contactin-associated protein 1 (CASPR1).[6,33,34] These autoantibodies, predominantly immunoglobulin G4, do not activate complement or bind to immunoglobulin receptors, which may explain the poor response to IVIg emphasising the need for alternative therapeutic approaches (**Figure 2**).[5] Clinical features vary depending on the antibody subtype.[5] Anti-NF155 antibodies are associated with distal weakness and low-frequency, high-amplitude tremors, whereas anti-CNTN1 antibodies can present with acute to subacute severe weakness, tremors, and glomerulonephritis.[33,35–37] In contrast, anti-CASPR1 or anti-CNTN1/CASPR1 complex antibodies often resemble Guillain-Barré syndrome, with acute presentation and cranial nerve involvement.[38–40] Neuropathic pain is common across these conditions.[38–40] Physiologically, nodal and paranodal disorders may exhibit conduction changes similar to those observed in CIDP.[6] However, from a pathological perspective, **autoimmune nodopathies** are not definitively classified as demyelinating conditions.[6]

Diagnostic Criteria

The diagnosis of CIDP is established through a combination of clinical and electrodiagnostic criteria, as outlined in the 2021 European Academy of Neurology (EAN) and Peripheral Nerve Society (PNS) guidelines.[6]

Electrodiagnostic Criteria

Electrodiagnostic testing is a cornerstone in confirming the clinical diagnosis of CIDP, with the 2021 EAN/PNS guidelines emphasising motor nerve conduction findings as critical diagnostic markers.[6] Nerve conduction studies (NCS) are pivotal for identifying electrophysiological signs of peripheral nerve demyelination, including prolonged motor distal latencies, reduced motor conduction velocities, motor conduction block, temporal dispersion, and prolonged or absent F-waves (**Figure 1**).[6,41,42] Sensory responses are frequently diminished or entirely absent in both the upper and lower limbs, further aiding diagnosis.[6,41,42] However, accurately interpreting "demyelinating" findings on NCS can be challenging.[6,41,42] Electrodiagnostic guidelines are indispensable for addressing ambiguities encountered during routine



R Ulnar - 1st DIO					
Wrist	Wrist - 1st DIO	2.65	10.5		
Below elbow	Below elbow - Wrist	7.25	2.6	200	43.4
Above elbow	Above elbow - Below elbow	9.31	1.1	100	48.5
Axilla	Axilla - Above elbow	11.90	1.1	70	27.1

Figure 1. Motor conduction study of the right ulnar nerve in a 19-year-old female patient newly diagnosed with CIDP. The study revealed normal distal latency (2.65 ms) but showed evidence of conduction block in the Below Elbow–Wrist segment, indicated by a 75% drop in the amplitude of the CMAP and mild slowing of the motor conduction velocity (44m/sec). Additionally, significant slowing of motor conduction velocity was observed in the Axilla–Above Elbow segment (27m/sec). A prolonged minimal F-wave latency of 50.3 ms, consistent with demyelination, was also noted.
CIDP: chronic inflammatory demyelinating polyneuropathy; CMAP: compound muscle action potential.

evaluations.[6,41,42] If electrophysiological evidence of demyelination is absent, clinicians must explore alternative diagnoses.[6]

Several factors can complicate the interpretation of NCS in CIDP. Reduced compound muscle action potential amplitudes may lead to a loss of faster-conducting fibers, necessitating a significantly slower conduction velocity to confirm true demyelination.[43] Additionally, low limb temperatures (<30°C for lower limbs, <32°C for upper limbs) can artificially prolong distal latencies and slow conduction velocities, potentially mimicking demyelination.[6,41] However, distinguishing CIDP from conditions like POEMS syndrome can be particularly difficult, as their electrodiagnostic features often overlap.[44] This underscores the importance of integrating clinical, electrophysiological, and laboratory findings to ensure accurate diagnosis.

Supportive Criteria

Cerebrospinal Fluid

A hallmark finding in CIDP is **albuminocytologic dissociation**, characterised by elevated CSF protein levels alongside normal leukocyte counts (<10 cells/μL).[7] This finding has a sensitivity of 50%-77%.[7] Mild protein elevations may also occur in individuals with diabetes, and protein levels tend to increase with age, with a cutoff of 0.6 g/L applied for individuals over 50 years.[45] Leukocyte counts exceeding 50 cells/μL should prompt evaluation for alternative diagnoses, such as malignancy or infection.[46]

Serologic Testing

Comprehensive screening for serum monoclonal proteins using **serum protein electrophoresis** and **immunofixation** is recommended for all patients suspected of having CIDP.[6] Specific tests for **anti-MAG antibodies** and **nodal/paranodal antibodies** (e.g., anti-NF155, anti-CNTN1) provide both diagnostic clarity and prognostic insights.[47,48] Additionally, elevated levels of **vascular endothelial growth factor (VEGF)** can be indicative of Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes Syndrome. Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes **(POEMS) syndrome**, particularly in cases involving painful distal neuropathy, helping to differentiate it from CIDP.[49]

Nerve Biopsy

Nerve biopsy is reserved for instances where diagnostic uncertainty persists despite other evaluations.[6] To reduce the risk of complications, biopsies should be performed on severely affected nerves.[50] Histopathological hallmark findings include **thinly myelinated axons, small onion bulbs, demyelinated internodes,** and **perivascular macrophage clusters**, which are characteristic of CIDP.[50]

Imaging

Imaging studies can provide valuable insights into CIDP. Magnetic resonance imaging (MRI) often reveals nerve hypertrophy and gadolinium enhancement in the brachial or lumbosacral plexuses, aiding in the assessment of proximal nerve involvement.[6,51] MRI is typically reserved for **atypical cases**, particularly when clinical and electrophysiological findings suggest a focal pattern, such as in **multifocal CIDP**, or when alternative causes of neuropathy and infiltrative pathologies need to be excluded.[52] Studies employing various MRI techniques, most notably brachial plexus MRI, have reported nerve **enlargement or enhancement** in approximately 40% to 80% of patients with CIDP.[6,51,52] Ultrasound is a useful adjunct for evaluating diagnostic uncertainties.[6] However, findings such as nerve hypertrophy are not specific to CIDP and may also appear in conditions like hereditary neuropathies, lymphoma, sarcoidosis, or infections.[6,53]

Response to Treatment

Diagnostic confirmation can be supported by a significant therapeutic response to treatments like IVIg, plasmapheresis, or corticosteroids.[6,25] Improvements measured on scales such as the **Inflammatory Neuropathy Cause and Treatment (INCAT)** disability scale or the **Medical Research Council (MRC)** sum score lend additional evidence.[54] Patient-reported outcomes assessed through the **Inflammatory Rasch-Built Overall Disability Scale (I-RODS)** may further substantiate the diagnosis.[54] As showed in ICE study, assessing hand grip strength by dynamometer is a quick and sensitive estimate for monitoring CIDP patients.[55]

Additional Testing

Somatosensory evoked potentials (SSEPs) are particularly useful in diagnosing pure sensory CIDP, especially when standard electrodiagnostic criteria are not met.[6,56] Studies suggest that SSEPs can detect nerve root involvement in up to 100% of individuals with **chronic immune sensory polyradiculopathy (CISP)** who fail to meet conventional CIDP criteria.[6,56] These findings expand the diagnostic toolkit for evaluating atypical CIDP presentations.[6,56]

Diagnostic Pitfalls in CIDP

Despite the availability of established diagnostic criteria, the process for CIDP diagnosis is fraught with challenges that can lead to misdiagnosis.[6] Awareness of these obstacles is essential to avoid errors and ensure accurate identification of the condition.[6] A study by Allen et al highlighted this issue, reporting that nearly half (47%) of 59 patients referred with a presumptive diagnosis of CIDP ultimately failed to meet the clinical and electrodiagnostic (EDx) criteria.[57] The primary sources of diagnostic errors included

overinterpretation of minor nerve conduction abnormalities as demyelination, trivial elevations in CSF protein, and reliance on subjective reports of improvement following treatment rather than objective measures.[57]

CIDP is recognised as a syndrome encompassing a **"typical" phenotype** and multiple variants.[6] While motor and sensory deficits are the hallmark features across all forms of CIDP, other symptoms such as fatigue and distal extremity pain are frequently reported.[58,59] Fatigue often persists throughout all stages of the disease, even when it is no longer immunologically active.[58] Pain, commonly affecting one-third or more of patients, tends to be localised to the distal limbs.[59] Less commonly, tremor (affecting up to 50% of patients), mild autonomic dysfunction (25%), and cranial nerve involvement (5% to 20%, primarily involving the facial nerve) are observed.[15,17,60] While these symptoms are crucial for management, reliance on nonspecific features like pain or fatigue in the absence of characteristic patterns of numbness or weakness conforming to known CIDP variants may lead to misdiagnosis.[6]

The diagnostic complexity increases with **CIDP variants**. Typical CIDP, characterised by symmetric proximal and distal neuropathy progressing over at least two months, is generally easier to diagnose when supported by electrophysiological evidence of demyelination and the exclusion of other conditions such as paraproteinemia or genetic abnormalities.[56,61] In contrast, CIDP variants often mimic other disorders: **distal CIDP** may resemble length-dependent axonal neuropathies or genetic conditions, **multifocal CIDP** can be confused with mononeuropathy multiplex caused by inflammatory, traumatic, or genetic factors, **motor CIDP** may be mistaken for multifocal motor neuropathy or motor neuron diseases, and **sensory CIDP** may be misdiagnosed as various neuropathic or non-neuropathic disorders that affect skin sensation.[56,61]

Electrodiagnostic testing, a cornerstone of CIDP diagnosis, may also pose interpretive challenges.[22,41] Demyelinating features identified in **NCS** can be misinterpreted in several scenarios.[22,41] For example, amplitude-dependent slowing caused by the loss of fast-conducting fibers in axonal neuropathies, focal slowing at compressible sites, or amplitude-independent slowing in diabetic patients can mimic demyelination.[22,41] Clinicians should interpret prolonged distal latencies, reduced conduction velocities, or proximal amplitude reductions cautiously, particularly in cases with very low motor response amplitudes (<1 mV).[22,41] Fibular nerve recordings targeting the extensor digitorum brevis (EDB) muscle are especially prone to errors.[22,41] Additionally, failure to account for limb temperature—where lower limits are 30°C for lower limbs and 33°C for upper limbs—can artificially prolong distal latencies or slow conduction velocities, mimicking demyelination.[22,41] Overlooked anatomical variations, such as Martin-Gruber anastomoses, or improper stimulation techniques may further contribute to misinterpretations.[22,41]. To minimise these pitfalls, clinicians must thoroughly examine waveform quality and adhere to standardised procedural protocols, ensuring accurate and reliable diagnostic findings.[22,41] Therefore, the **EAN/PNS CIDP diagnostic guidelines** provide a comprehensive framework for differential diagnosis, which is essential for accurately distinguishing between CIDP and its variants (**Figure 2**).[6]

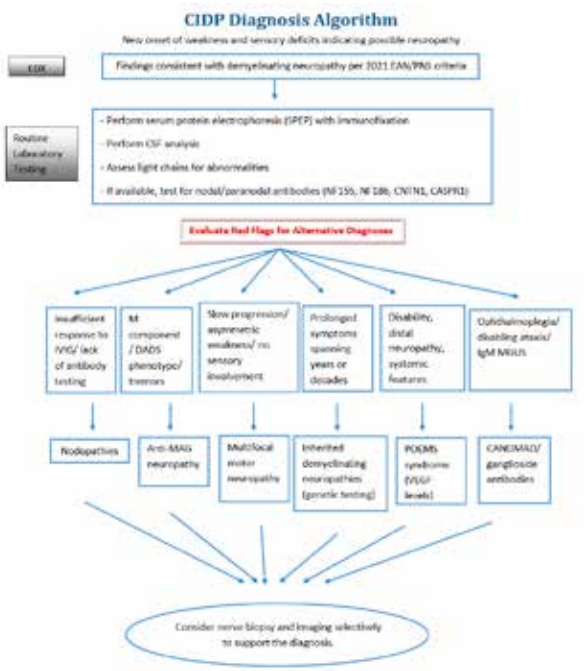


Figure 2. Diagnostic flowchart for chronic inflammatory demyelinating polyneuropathy (CIDP) diagnoses. **ab: antibody;** CANOMAD: chronic ataxic neuropathy with ophthalmoplegia: IgM paraprotein: cold agglutinins: and disialosyl antibodies; CASPR1: contactin-associated protein 1; CNTN1: contactin 1; DADS: distal acquired demyelinating symmetric neuropathy; EAN/PNS: European Academy of Neurology/Peripheral Nerve Society; EDX: electrodiagnostic studies; IgM: immunoglobulin M; IVIg: IV immunoglobulin; MAG: myelin-associated glycoprotein; MMN: multifocal motor neuropathy; MGUS: monoclonal gammopathy of undetermined significance; NF155: neurofascin 155; NF186: neurofascin 186; POEMS: polyneuropathy: organomegaly: endocrinopathy: monoclonal gammopathy: and skin changes; SPEP: serum protein electrophoresis; VEGF: vascular endothelial growth factor.

DIFFERENTIAL DIAGNOSIS IN CIDP

Acute Inflammatory Demyelinating Polyneuropathy (AIDP) and Related Conditions

CIDP is a chronic disorder characterised by progression beyond eight weeks.[11,62] When symptoms reach

their nadir within four weeks of onset, Guillain-Barré syndrome (GBS) should be considered.[63] However, distinguishing between CIDP and GBS can be complicated by treatment-related fluctuations in GBS, which may resemble CIDP.[63]

A specific diagnostic challenge arises with **acute-onset CIDP (A-CIDP)**, a form that begins acutely but continues to progress beyond four to eight weeks and is characterised by at least three relapses within nine weeks.[63] While A-CIDP is not considered phenotypically atypical in terms of clinical and EDx features, its rapid onset sets it apart.[63] Early recognition is critical, as A-CIDP requires ongoing immunotherapy. Key features distinguishing A-CIDP from GBS include its milder severity, rare cranial nerve involvement, and the absence of a need for mechanical ventilation.[63] Moreover, A-CIDP typically exhibits classic CIDP demyelinating features on EDx, which are not seen early in GBS.[63]

Less frequently, CIDP may present as **subacute inflammatory demyelinating polyneuropathy (SIDP)**, characterised by a monophasic course with symptoms peaking within four to eight weeks.[64] Patients presenting with subacute-onset neuropathy accompanied by tremor, ataxia, and distal weakness should be evaluated for CIDP variants, particularly **nodopathies.**[65] Lastly, it is important to differentiate **treatment-related worsening** in CIDP from treatment-refractory disease.[66] Worsening may result from the waning effects of therapy rather than true resistance to treatment, which could lead to misclassification as refractory CIDP.[66] Careful monitoring and re-evaluation of therapeutic response are essential to avoid such diagnostic errors.[66]

Demyelinating Neuropathies

Paraproteinemic Neuropathies

Paraproteinemic neuropathies represent a diverse group of disorders associated with the presence of monoclonal paraproteins in the serum.[67,68] These paraproteins, abnormal immunoglobulins produced by clonal plasma cells, can include heavy chains (e.g., IgA, IgM, IgG) or light chains (kappa or lambda).[67,68] They are often linked to hematologic conditions such as lymphoma, multiple myeloma, or primary amyloidosis but most commonly occur as **monoclonal gammopathy of undetermined significance (MGUS).**[27,67] MGUS, which becomes more prevalent with age, involves a single abnormal plasma cell clone in the bone marrow without malignant proliferation.[27,67] One subtype, **IgM paraproteinemic neuropathy** with a DADS phenotype, is a sensory-predominant condition marked by ataxia and gait instability (**Figure 2**).[26] Myelin-associated glycoprotein (MAG) antibodies are detectable in approximately 50% of individuals with IgM paraproteinemic neuropathy.[67,68]

Anti-MAG Neuropathy

Anti-MAG neuropathy is a slowly progressive condition that shares clinical similarities with DADS.[26,67,69] The disorder predominantly presents with distal sensory symptoms, while motor weakness is minimal or absent.[67,69] A distinguishing feature is the presence of tremors characterised by high amplitude and low frequency.[67,69]

Diagnosis is supported by the detection of **anti-MAG antibodies** alongside an **IgM paraprotein** in the serum (**Figure 2**).[67,69] In anti-MAG neuropathy, motor distal latencies are disproportionately prolonged relative to conduction velocity, creating distinct electrodiagnostic patterns.[67,69] Specifically, a reduced TLI (Terminal Latency Index) is particularly useful in distinguishing anti-MAG neuropathy from CIDP, as CIDP generally exhibits uniform demyelination throughout the nerve, resulting in less significant distal latency abnormalities compared to changes in conduction velocity. While the condition primarily affects distal nerves, cases involving proximal disease often respond favourably to **rituximab**, underscoring its role as a therapeutic option in selected patients.[67,69]

POEMS syndrome

POEMS syndrome is a multisystemic disorder associated with plasma cell proliferation, most commonly restricted to lambda light chains.[44,49] It is characterised by a severe, rapidly progressive subacute demyelinating neuropathy, often distal in nature, that can result in significant pain.[44,49] The monoclonal protein involved is predominantly a lambda light chain paired with either IgG or IgA heavy chains, distinguishing it from IgM-associated conditions such as MGUS and anti-MAG neuropathy.[67]

Diagnostic criteria for POEMS syndrome include the co-occurrence of demyelinating neuropathy and monoclonal gammopathy.[44,49] Elevated vascular endothelial growth factor (VEGF) levels, indicative of increased microvascular permeability, are a key feature and contribute to symptoms like papilledema and dependent lower-extremity oedema (**Figure 2**).[44,49] Osteosclerotic myeloma is frequently associated with POEMS syndrome and can be identified through imaging techniques such as X-ray skeletal surveys, low-dose total-body CT scans, or MRI.[44,49]

Additional minor criteria include endocrinopathies, though common conditions like diabetes and thyroid disorders are insufficient to qualify.[44,49] Distinctive skin changes, including hyperpigmentation, hypertrichosis, or haemangiomas, are often observed, along with hematologic abnormalities such as thrombocytosis or leucocytosis.[44,49] Organomegaly, particularly involving the liver or spleen, is another characteristic feature.[44,49]

EDx studies in POEMS syndrome typically show

uniform demyelination and axonal degeneration, more pronounced than in CIDP.[70] Nerve biopsies reveal axonal degeneration, neovascularisation, and fewer onion bulbs, alongside a degree of demyelination comparable to CIDP.[71]

Chronic Ataxic Neuropathy with Ophthalmoplegia, IgM Paraprotein, Cold Agglutinins, and Disialosyl Antibodies. Chronic ataxic neuropathy with ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies (CANOMAD)

CANOMAD is a rare neuropathy that closely resembles chronic Miller Fisher syndrome, with hallmark features of ataxia, areflexia, and ophthalmoplegia. The condition is often severely disabling due to profound ataxia. It is associated with specific antibodies, including anti-ganglioside, anti-GD1b, and anti-GQ1b.[5] The presence of IgM paraprotein and cold agglutinins further aids in diagnosis (**Figure 2**).[5]

Multifocal Motor Neuropathy

MMN is characterised by asymmetric weakness predominantly affecting the upper limbs and is classified as a pure motor mononeuropathy.[21,72] Unlike CIDP, MMN lacks sensory involvement, which helps differentiate the two conditions.[7,21,72] Muscle atrophy is often evident, even in the early stages, with approximately one-third of patients initially presenting with foot drop preceding upper limb involvement.[21,72] Men are more commonly affected, and the median age of onset is approximately 40 years, younger than the typical onset age for CIDP.[7,21,72] Other clinical features of MMN include cramps and fasciculations, which occur in about 40% of cases, with symptoms often exacerbated by cold exposure.[21,72] Electrodiagnostic studies reveal conduction block, a hallmark neurophysiological finding for MMN. Additional findings may include slightly slowed motor velocities, significantly reduced compound muscle action potential amplitudes, and fasciculations on needle electromyography (EMG).[7,21,72-73] Anti-GM1 antibodies are present in roughly 40% of cases (**Figure 2**).[21,72] The treatment of choice for MMN is IVIg, which is typically required on a long-term basis to manage the condition effectively.[21,72]

Axonal Polyneuropathies

Diabetes: Distinguishing between diabetes-related neuropathy and CIDP is a frequent clinical challenge, as both conditions can present with progressive peripheral neuropathy.[74,75] Diabetic neuropathy, most commonly diabetic sensorimotor polyneuropathy (DSPN), typically presents as a slowly progressive, length-dependent neuropathy. Symptoms often begin in the distal lower extremities, characterised by numbness, burning pain, and tingling. In advanced stages, the upper extremities may also be involved.[74,75] Autonomic symptoms, such as orthostatic hypotension, gastrointestinal dysmotility, or erectile dysfunction, are common in diabetes and can help differentiate it from CIDP.[76] In diabetic neuropathy, findings typically include axonal features such as reduced amplitudes of sensory and motor nerve action potentials and mild slowing of conduction velocities.[75] Diabetic neuropathy can occasionally show non-amplitude-dependent slowing of conduction velocities, which can make differentiation from CIDP challenging.[75] Multifocal or proximal findings strongly suggest CIDP.[75] It is important to note that diabetes and CIDP can coexist.[74-75] In such cases, the presence of clear demyelinating features on electrodiagnostic studies, proximal weakness, and response to immunotherapy support a diagnosis of CIDP.[74-75]

Sjögren's syndrome: It is an important differential diagnosis to consider in patients presenting with features suggestive of CIDP, particularly when there is prominent sensory involvement.[74-75] Peripheral neuropathies associated with Sjögren's syndrome can mimic CIDP in their presentation.[79] The most common phenotype is a sensory ganglionopathy (dorsal root ganglionopathy), which typically presents with marked sensory ataxia and asymmetrical sensory loss, predominantly involving large fibers.[77,78] This can create a clinical picture that overlaps with sensory-predominant CIDP and CISP. Unlike CIDP, however, motor involvement is often absent or minimal in Sjögren's-associated neuropathy.[77,78] Electrodiagnostic studies in Sjögren's syndrome-related neuropathy may show absent or severely reduced sensory nerve action potentials (SNAPs), reflecting the ganglionopathy, whereas motor nerve conduction studies are typically normal or only mildly affected.[77–79] In contrast, CIDP demonstrates widespread demyelinating features, including prolonged distal latencies, conduction block, and temporal dispersion.[77–79]

Amyloidosis: Among the paraproteinemic neuropathies, primary amyloidosis, particularly AL amyloidosis, is a significant differential diagnosis.[80,81] AL amyloidosis is caused by the deposition of misfolded immunoglobulin light chains (kappa or lambda) produced by a clonal plasma cell disorder.[80] The neuropathy in AL amyloidosis typically presents as a painful, length-dependent axonal polyneuropathy with prominent autonomic involvement, such as orthostatic hypotension, gastrointestinal dysmotility, and erectile dysfunction.[17,80] These features are less common in CIDP and can help differentiate AL amyloidosis.[80,81] Additionally, nerve biopsies in AL amyloidosis reveal amyloid deposition, which can be confirmed using Congo red staining.[80,81] Patients with AL amyloidosis may initially be misdiagnosed with CIDP, especially if

they present with weakness and sensory ataxia.[80,81] However, the presence of systemic symptoms (e.g., weight loss, nephrotic syndrome, or hepatomegaly) and resistance to standard CIDP therapies should prompt further evaluation for amyloidosis, including serum and urine electrophoresis with immunofixation, and biopsy of affected tissues.[80,81]

Genetic mimics

Charcot-Marie-Tooth (CMT) disease: This is the most common hereditary neuropathy and a significant mimic of CIDP.[82] Particularly, CMT1A, adult-onset CMT1B, CMT1X, and recessive forms such as CMT4 (e.g., CMT4C due to SH3TC2 genetic variants) can present with features suggestive of CIDP.[82,83] Electrodiagnostically, the majority of CMT subtypes are characterised by uniform demyelination and a lack of conduction block, which is consistent with their hereditary origin and linkage to specific genetic mutations.[83] The absence of conduction block serves as a crucial distinguishing factor between CMT and CID.[83] A careful family history and genetic testing, such as sequencing for peripheral myelin protein 22 (PMP22) gene duplications or deletions, can help confirm the diagnosis (**Figure 2**).[82,83]

Hereditary neuropathy with liability to pressure palsies (HNPP): This is another important genetic mimic of CIDP.[84,85] HNPP is characterised by susceptibility to focal neuropathies at compression sites, such as the ulnar or peroneal nerves.[84,85] Electrodiagnostic findings in HNPP reveal conduction slowing at entrapment sites, which may resemble electrophysiological findings seen in CIDP.[84,85] However, the clinical presentation of recurrent, transient focal neuropathies and the identification of PMP22 deletions help differentiate HNPP from CIDP (**Figure 2**).[84,85]

Transthyretin (TTR) familial amyloid polyneuropathy (FAP): It is a genetic condition caused by pathogenic variants in the TTR gene.[86,87] Although typically presenting as an axonal polyneuropathy, TTR-FAP can occasionally manifest with features of a demyelinating neuropathy that overlap with CIDP. Late-onset (>50 years) sporadic forms of TTR-FAP are particularly challenging to distinguish from CIDP.[86,87] Clinical clues include prominent pain, dysautonomia (e.g., orthostatic hypotension and gastrointestinal dysmotility), distal upper limb motor deficits, and an extension of small fibre sensory loss above the wrists.[86,87] The absence of ataxia and resistance to standard CIDP therapies may further suggest TTR-FAP.[86,87] Genetic testing for TTR mutations is essential for diagnosis, and the availability of targeted therapies, such as TTR stabilisers or gene-silencing agents, underscores the importance of accurate identification of this condition (**Figure 2**).[86,87]

CONCLUSIONS

CIDP is a complex condition with a wide range of clinical presentations, making the diagnostic process challenging.[9,23] Accurate diagnosis requires careful interpretation of clinical and diagnostic data to avoid misdiagnosis.[6,9,25] The extent of diagnostic evaluation should be tailored to each case. For typical CIDP, where no concerning features are present, minimal additional testing—such as screening for monoclonal proteins—may be sufficient.[6,9,25]

Several red flags can complicate the diagnosis and suggest alternative explanations for the symptoms.[6] These include dominant pain and fatigue rather than the characteristic numbness and weakness of CIDP; relentlessly progressive weakness with preserved or heightened reflexes, which is atypical.[6,58,59] Additional factors such as a family history of neuropathy, or clinical findings such as prominent distal atrophy or pes cavus may raise suspicion of a genetically determined neuropathy rather than CIDP.[6,83,88]

In cases with atypical features or diagnostic uncertainty, supportive testing may be useful but requires careful interpretation.[25] CSF analysis often reveals elevated protein levels with normal cell counts (albuminocytologic dissociation) in CIDP; however, mild elevations (<100 mg/dL) can also occur in diabetes, hereditary neuropathies, or with aging.[56] Overreliance on this finding should be avoided.[56] Imaging, particularly MRI, can show nerve hypertrophy or enhancement, but these findings are not specific to CIDP and may be seen in hereditary or infiltrative neuropathies.[6,51,52] Imaging is most appropriate in atypical cases to rule out other causes of neuropathy.[6,51,52] Nerve biopsy, while reserved for cases of diagnostic uncertainty, may show characteristic findings such as thinly myelinated axons, onion bulb formations, or perivascular inflammation.[50] However, these findings are not definitive for CIDP and must be interpreted within the broader clinical and electrophysiological context.[9] Improvements following immunomodulatory treatments like IVIg or corticosteroids should be measured objectively, as subjective responses can be misleading.[30,89]

The diagnostic process for CIDP requires a systematic approach that integrates clinical presentation, electrophysiological findings, and selectively applied diagnostic tools.[25] Overemphasis on nonspecific findings, such as modestly elevated CSF protein, ambiguous imaging results, or subjective treatment responses, can lead to diagnostic errors.[7] By carefully considering clinical features and utilising appropriate diagnostic tests, CIDP can be accurately distinguished from other neuropathies, ensuring proper management.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ΝΟΣΟΤΡΟΠΟΠΟΙΗΤΙΚΕΣ ΑΝΤΙ-ΑΜΥΛΟΕΙΔΙΚΕΣ ΘΕΡΑΠΕΙΕΣ ΓΙΑ ΤΗΝ ΗΠΙΑ ΝΟΗΤΙΚΗ ΔΙΑΤΑΡΑΧΗ Η/ΚΑΙ ΤΟ ΗΠΙΟ ΣΤΑΔΙΟ ΑΝΟΙΑΣ: ΑΡΘΡΟ ΑΝΑΣΚΟΠΗΣΗΣ ΤΩΝ ΚΥΡΙΑΡΧΩΝ ΚΛΙΝΙΚΩΝ ΜΕΛΕΤΩΝ ΦΑΣΗΣ ΙΙΙ

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ΠΕΡιΛΗΨΗ

Η νόσος Alzheimer είναι η πιο συχνή αιτία άνοιας, μια νευροεκφυλιστική διαταραχή η οποία προσβάλλει κατά βάση τους ηλικιωμένους και της οποίας ο επιπολασμός αυξάνει καθώς ο παγκόσμιος πληθυσμός γηράσκει. Η καθ' υπεροχήν εξασθένηση της πρόσφατης μνήμης είναι μια κυρίαρχη κλινική εκδήλωση της AD, στην αρχή τουλάχιστον, αν και υπάρχουν εξαιρέσεις, και η βασική παθολογία της νόσου αποτελείται από τη συσσώρευση πλακών β-αμυλοειδούς. Η συσσώρευση του β-αμυλοειδούς αντανακλάται και μέσω των βιοδεικτών (Αβ42, Αβ42/Αβ40), των οποίων τα επίπεδα μεταβάλλονται σχεδόν 19 με 15 χρόνια πριν από την έναρξη των συμπτωμάτων, σύμφωνα με την πορεία της νόσου η οποία αποτυπώνεται σε αρκετές μελέτες ακόμη και στις μέρες μας. Ως απόκριση στην παθολογική αναδίπλωση του β-αμυλοειδούς, έχουν δοκιμαστεί πολλές νέες θεραπείες με στόχο αυτό το παθολογοανατομικό υπόστρωμα, σε αντίθεση με τις αποδεκτές διαθέσιμες θεραπείες, από ετών, οι οποίες μπορούν να βελτιώσουν ορισμένα συμπτώματα μόνο, ενώ η ασθένεια εξελίσσεται αναπόφευκτα. Αυτό το κείμενο είναι ένα άρθρο ανασκόπησης των τριών μονοκλωνικών αντισωμάτων τα οποία έδειξαν μία κάποια αποτελεσματικότητα έναντι του β-αμυλοειδούς, του aducanumab, του lecanemab και του donanemab, και των σχετικών κλινικών δοκιμών φάσης III, ως προς το σχεδιασμό, τα κύρια χαρακτηριστικά, το προφίλ ασφάλειας και τα αποτελέσματα. Το τελευταίο μονοκλωνικό αντίσωμα έλαβε πρόσφατα έγκριση από τον Οργανισμό Τροφίμων και Φαρμάκων (FDA) και βρίσκεται υπό αξιολόγηση από τον Ευρωπαϊκό Οργανισμό Φαρμάκων (EMA), ενώ το aducanumab και το lecanemab έχουν ήδη εγκριθεί από τον FDA, και προσφάτως το lecanemab και από τον EMA. Υπογραμμίζουμε επίσης πολλά βασικά σημεία και κενά των συγκεκριμένων κλινικών μελετών και παρέχουμε πτυχές της συνεχιζόμενης έρευνας.

Λέξει-κλειδιά: νόσος Alzheimer, μονοκλωνικά αντισώματα, συσσώρευση β-αμυλοειδούς, κλινικές μελέτες

DISEASE MODIFYING ANTI-AMYLOID THERAPIES FOR MILD COGNITIVE IMPAIRMENT / MILD ALZHEIMER'S DISEASE: A NARRATIVE REVIEW OF THE KEY PHASE III CLINICAL TRIALS

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ABSTRACT

Alzheimer's disease is the most common cause of dementia, a neurodegenerative disorder of older adults primarily, which is rising as the world population ages. Selective memory impairment is a prominent clinical manifestation of AD, although there are exceptions, and the core disease pathology consists of

amyloid aggregation. The amyloid positivity is also reflected through the biomarkers ($A\beta_{42}$, $A\beta_{42}/A\beta_{40}$) that appear firstly changed, almost 19 to 15 years prior to symptoms, according to the disease trajectory which is confirmed by several studies even nowadays. In response to amyloidosis, plenty of novel therapies have been tried out and target the amyloid accumulation, contrary to the accepted available treatments which can improve some symptoms, while the disease inevitably progresses. This current article provides an overview of the three successful monoclonal antibodies against amyloid aggregates, aducanumab, lecanemab, and donanemab, and their relevant phase III clinical trials as for design, main characteristics, safety profile and outcomes. The latter one has been recently accepted by Food and Drug Administration (FDA) and is under evaluation of European Medicines Agency (EMA), though aducanumab and lecanemab have already been FDA approved, and only lecanemab has been recently EMA approved. We also underline several key points and gaps of current evidence and provide aspects of ongoing research.

Keywords: Alzheimer's disease, monoclonal antibodies, amyloid aggregations, clinical trials

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease, accounting for 60 – 70% of all dementia cases.[1] Usually, adults present with symptoms in mid to late life and apart from the common amnestic, different other clinical phenotypes have been recognised, including posterior cortical atrophy, logopenic variant primary progressive aphasia (PPA), corticobasal syndrome and frontal subtypes.[2] The pathophysiological hallmark of the disease is the extracellular aggregation of β-amyloid, in the form of amyloid plaques and the intracellular aggregation of hyperphosphorylated tau protein, in the form of neurofibrillary tangles.[3] In this biological context, the National Institute on Aging and Alzheimer's Association (NIA-AA) research framework, in 2018,[4] introduced a biological definition of the disease, through a classification scheme labelled AT(N), revised in 2024,[5] and since then AD is diagnosed and staged ***in vivo*** based on specific biomarker profiles in conjunction. Mounting evidence has already established the application of advanced neuroimaging techniques,[6] including amyloid and tau positron emission tomography (PET) and/or cerebrospinal fluid (CSF) biomarkers,[7] which are broadly used in clinical trials, whilst plasma biomarkers are expected to be validated and subsequently commonly used, according to the revised AD criteria.[5]

The current treatment scheme consists of therapies that offer partial symptomatic relief without halting the disease's progression and without targeting the underlying pathological burden or the neuroinflammation that has been already proved to contribute to AD pathogenesis.[8] Currently, many substances are being evaluated in clinical trials and, for instance, efforts are underway to study the efficacy of semaglutide in mild cognitive impairment (MCI) and/or mild AD, taking into consideration that glucose metabolism is associated with the pathogenetic mechanism of AD, as supported by recent studies.[9,10] Until recently, disease modifying treatments were not available. However, several recent developments of anti-amyloid monoclonal antibodies (mAbs), years in the pipeline, emerged although with variance in efficacy and adverse events. Bapineuzumab,[11] gantenerumab,[12] solanezumab,[13] and crenezumab[14] are examples of these mAbs that did not succeed in reducing cognitive decline, in comparison to others which showed statistically significant results in clinical trials. In June 2021, aducanumab was the first anti-amyloid antibody approved by FDA in the USA using the accelerated approval pathway, followed by lecanemab which has been fully FDA approved by the traditional pathway and also licensed by EMA, after re-assessment in November 2024. Donanemab is the third one that has been recently approved by the FDA. The present article summarises the key phase III clinical trials of the aforementioned approved monoclonal antibodies as for design, main characteristics, safety profile and outcomes. We also underline several crucial points and gaps of current evidence and provide aspects of ongoing research.

FUNCTIONS AND RATIONALE BEHIND THE IMMUNOTHERAPY DRUGS AGAINST AB

Alzheimer's disease is a complex neurodegenerative disease that has a prolonged preclinical phase of 10-30 years duration, during which the underlying biochemistry/pathology progresses but individuals remain cognitively unimpaired [15]. Multiple studies have demonstrated the continuum of disease pathology, identifying that CSF and plasma biomarkers, which reflect or are triggered by amyloidosis, were detected 15 to 19 years prior to symptom onset [16]. Amyloidosis is expressed through decreased plasma and CSF Aβ42, and Aβ42/Aβ40 or positive amyloid PET scan, whilst increased levels of CSF or plasma phosphorylated tau (p-tau) protein 181 or 217 are triggered by amyloidosis.[17] The three mAbs differ in the type and range of amyloid species targeted (Figure 1). More specifically, aducanumab addresses a broad range of amyloid species with a greater affinity of high molecular weight ones, and especially fibrils; lecanemab targets the soluble protofibrils;

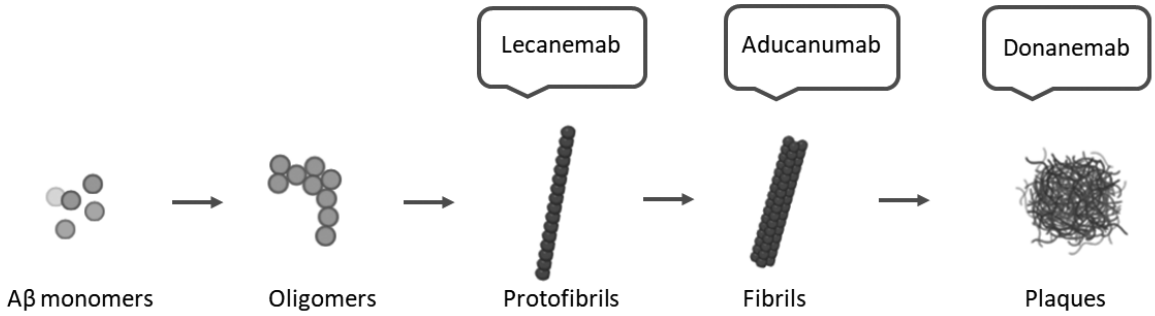

Figure 1: Monoclonal antibodies against specific targets of aggregated β-amyloid.

and donanemab is directed against insoluble plaques only.[18] All mAbs were implemented for MCI/mild AD and are immunoglobulins (Ig) G1 antibodies and their mechanism of action is the reduction of amyloid plaques through solubilization of Aβ and the activation of microglia with phagocytosis of Aβ fibrils via the endosomal / lysosomal system.[19] It is uncertain if these activated microglia can phagocytose both labelled and unlabelled protein aggregates, and if they could be directed to tau aggregates despite their intracellular location, because there is evidence that plasma ptau also responses to mAbs administration.[20] In addition to phagocytosis, complement activation promotes microglial uptake and surprisingly, there are other non-microglial mediated mechanisms for Aβ clearance. "Peripheral sink" activity has been described, for example, and refers to the action of mAbs through the peripheral blood inducing the efflux of Aβ aggregates via the blood brain barrier (BBB). Low density lipoprotein receptor-related protein 1 (LRP1) plays a major role in this mechanism.[21]

Aducanumab

Aducanumab is the first disease modifying therapy (DMT) for AD that received accelerated approval from the FDA on June 7, 2021.[22] Two phase 3 randomised double blind placebo-controlled trials, EMERGE and ENGAGE,[23] evaluated the efficacy and safety of aducanumab in patients with MCI or mild symptomatic AD. Participants of these two trials were 50-85 years old and were randomised 1:1:1 to aducanumab low dose, high dose, or placebo (Table 1) via intravenous infusion every 4 weeks. The major inclusion criteria were a Mini Mental State Examination (MMSE) score of 24 to 30 and the confirmation of amyloid pathology with amyloid PET (Table 2). The primary endpoint was the change in the Clinical Dementia Rating – Sum of Boxes (CDR-SB) from baseline until the week 78 and the secondary ones were other commonly used neuropsychological scales (Table 2) accompanied by the mean change of the cortical composite standardised uptake value ratio (SUVR) in the amyloid PET. The primary endpoint was not met in

Study	Antibody	Company	Dose		Sample size			Age	Dosage protocol / Duration
Haeberlein et al. 2022 (EMERGE)	aducanumab	Biogen, Neurimmune	3 mg/kg or 6 mg/kg	10 mg/kg	543	547	548	50 - 85	Every 4 weeks iv / 76 weeks
Haeberlein et al. 2022 (ENGAGE)	aducanumab	Biogen, Neurimmune	3 mg/kg or 6 mg/kg	10 mg/kg	547	555	545	50 - 85	Every 4 weeks iv / 76 weeks
van Dyck et al. 2023 (CLARITY AD)	lecanemab	Eisai, BioArktic, Biogen	10 mg/kg		859	875		50 - 90	Every 2 weeks iv / 18 months
Sims et al. 2023 (TRAILBLAZER – ALZ 2)	donanemab	Lilly	700 mg for the first 3 doses and 1400 mg thereafter		860	876		60 - 85	Every 4 weeks iv / 76 weeks

Table 1. Phase III trials features and baseline characteristics of participants.
The participants in EMERGE and ENGAGE trials were randomised (1:1:1) to receive low-dose aducanumab, high-dose aducanumab, or placebo. The three columns of sample size concerning these studies correspond to low dose, high dose, and placebo group respectively.
iv: intravenously.

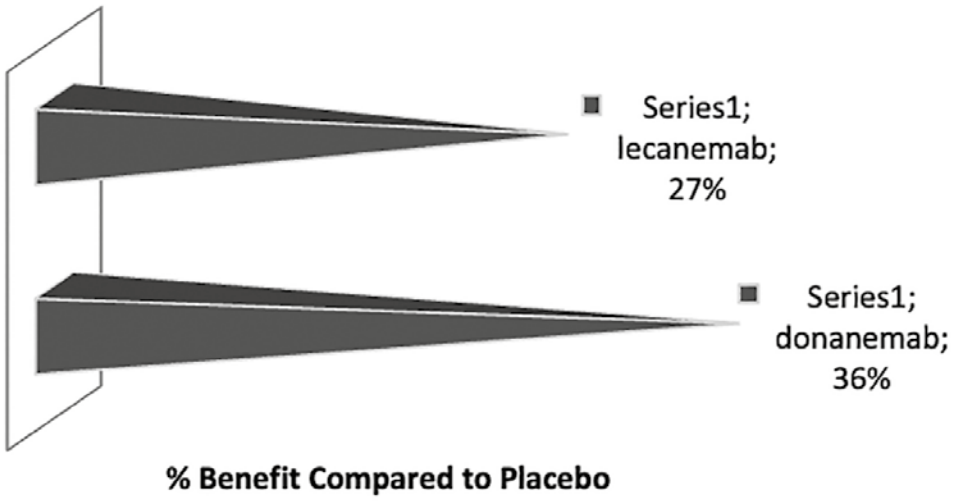

Figure 2: % Benefit of mAbs lecanemab and donanemab compared to placebo in CDR-SB, based on CLARITY-AD and TRAILBLAZER-ALZ 2, respectively.
CDR-SB: Clinical Dementia Rating - Sum of Boxes

ENGAGE trial while the high dose group in EMERGE experienced less worsening in mean CDR – SB than the placebo group (Table 3), without even reaching the clinically important threshold for CDR-SB change. [24] However, even in the unsuccessful ENGAGE trial, post hoc analysis data – limited to subjects exposed to the 14 sets of infusions- revealed also an interesting impact on CDR-SB in the high dose ENGAGE arm.[25] As for safety issues, Amyloid Related Imaging Abnormalities (ARIA) refers to radiological findings accounted to vasogenic oedema (ARIA-E) and/or haemorrhagic lesions, acute or chronic, (ARIA-H). [26] Of particular note, APOE ε4 carriers and participants of high dose group were mainly susceptible to ARIA but in the great majority of almost all cases symptoms were manageable and resolved within 4 months (83%). These symptoms are not identical and include predominantly headache, dizziness, nausea, and confusion.[27]

On January 31, 2024, it was announced by the corresponding company (Biogen) that aducanumab 100 mg/mL injection for intravenous use would not be at disposal anymore and this decision was not associated to any safety concern.[28]

Lecanemab

Consequently, lecanemab, initially approved through the accelerated approval pathway by the FDA, is the first mAb against Aβ aggregates, which was granted traditional approval, on July 6, 2023,[29] following the deliberation of the CLARITY AD study. [20] Almost one year later, on 14 November 2024, EMA issued the consent of lecanemab's marketing authorisation, after re-examination, suggesting that the benefit could overwhelm the risk of the adverse events, and especially ARIA, for individuals with one or no copy of ApoE4.[30] CLARITY AD, the aforementioned confirmatory trial, was an 18-month, multicentre, double-blind, placebo-controlled, parallel-group trial in patients aged 50 to 90 years with either MCI or mild AD (Table 1). Eligible subjects were assigned in a 1:1 ratio to receive lecanemab, 10mg/kg intravenously every 2 weeks, or placebo, and they scored over 22 in MMSE, while amyloid positivity was obtained through amyloid PET or CSF $A\beta_{42}$ (Table 2). An effort was made to broaden the study population, including, for example, non-White participants (20%) and patients under anticoagulation therapy if the dose was stable at least 4 weeks before screening. The mean change of CDR-SB was the primary end point. Secondary end points included a new scale that is called Alzheimer's Disease Composite Score (ADCOMS).[31] This score consists of several items of other already used scales, and in particular of Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), MMSE, and CDR-SB (Table 4) and it has been proposed as an outcome measure of prodromal AD with increased sensitivity.[31] Even though a clinically meaningful effect in the mean CDR-SB score was not observed, lecanemab accomplished statistically significant changes in CDR-SB, resulting in a 27% delay of disease progression (Figure 2). This result is consistent with the efficacy in reducing the amyloid burden on PET, about 55.5 in centiloid scale, and it has an effect of 4 to 6 months on slowing disease progression when added to existing therapy,[32] raising question as to whether is meaningful or not.[30]

During the study period, the safety results included infusion reactions (>10%) and ARIA-H and ARIA-E (Table 3), but the overall percentages were lower than those observed in aducanumab trials, again

Study	Clinical eligibility criteria	Radiological eligibility criteria	Primary endpoint	Key Secondary endpoint
Haeberlein et al. 2022 (EMERGE)	CDR 0.5 MMSE ≥ 24 RBANS ≤ 85	Positive amyloid PET scan, brain MRI with ≤ 4 microbleeds, ≤ 1 lacunar infarct, without any prior ICH cortical infarct, severe white matter disease or superficial siderosis	CDR - SB	MMSE, ADAS-Cog13 and ADCS-ADL-MCI
Haeberlein et al. 2022 (ENGAGE)	CDR 0.5 MMSE ≥ 24 RBANS ≤ 85	Positive amyloid PET scan, brain MRI with ≤ 4 microbleeds, ≤ 1 lacunar infarct, without any prior ICH, cortical infarct, severe white matter disease or superficial siderosis	CDR - SB	MMSE, ADAS-Cog13 and ADCS-ADL-MCI
van Dyck et al. 2023 (CLARITY AD)	CDR 0.5 1 standard deviation below age-adjusted mean in the WMS-IV LMII MMSE ≥ 22	Positive amyloid PET scan#, brain MRI with ≤ 4 microbleeds, ≤ 1 lacunar infarct, without any prior ICH, stroke involving a major vascular territory, severe white matter disease or superficial siderosis	CDR - SB	PET – SUVR, ADCOMS, ADAS-Cog14
Sims et al. 2023 (TRAILBLAZER – ALZ 2)	20 < MMSE < 28	florbetapir F18 PET, flortaucipir F18 PET, brain MRI with ≤ 4 microbleeds, > 1 area of superficial siderosis, without any prior ICH or severe white matter disease	iADRS	ADAS-Cog13, ADCS-iADL, CDR-SB and MMSE

Table 2. Main characteristics of trials' design and endpoints.

CDR: Clinical Dementia Rating; MMSE: Mini Mental State Examination; RBANS: Repeatable Brief Assessment of Neuropsychological Status; WMS-IV LMII: Wechsler Memory Scale IV-Logical Memory (subscale) II; PET: Positron Emission Tomography; MRI: Magnetic Resonance Imaging; ICH: intracerebral haemorrhage; SB: Sum of Boxes; ADAS-Cog13: Alzheimer's Disease Assessment Scale–Cognitive Subscale 13 items; ADCS-ADL-MCI: The Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale for use in Mild Cognitive Impairment; iADRS: The Integrated Alzheimer's Disease (AD) Rating Scale; SUVR: standard uptake value ratio; ADCOMS: The Alzheimer's Disease Composite Score.

#Amyloid positivity could also be determined through CSF measurement of $A\beta_{1-42}$.

with higher frequency in ApoE ***ε4*** homozygous participants. Within the lecanemab group, the symptomatic subjects with ARIA-E were 2.8% and with ARIA-H were 0.7%. During this core study, there were 6 deaths in lecanemab arm, unrelated to the treatment without surpassing placebo, but, during the open-label extension (OLE) study (18-48 months), 4 deaths were attributed to lecanemab and two of them occurred due to intracerebral haemorrhage (ICH).[33]

Donanemab

The third anti-amyloid antibody which was recently fully approved by the FDA, on 2nd July 2024 (34), through the promising results of TRAILBLAIZER-ALZ2 (35), is the donanemab and targets the insoluble amyloid plaques in the brain (Figure 1). The main trial design and duration is similar to CLARITY AD but there are major distinguishing features. The participants, aged 60 to 85 years, with mild dementia or MCI, scored between 20 to 28 on MMSE and were further subdivided into groups according to tau PET scan, low/medium or high tau. Therefore, it was en-

Study	Adjusted mean difference from placebo in CDR-SB in 18 months		Adjusted mean change from baseline in amyloid PET (centiloid scale)		ARIA - H	ARIA - E
Haeberlein et al. 2022 (EMERGE)	-0.39 (-22%)#		-71%#		44%#	35%#
Haeberlein et al. 2022 (ENGAGE)	0.03 (2%)#		-59%#		42%#	36%#
van Dyck et al. 2023 (CLARITY AD)	- 0.45		- 55.48		17.3%	12.6%
Sims et al. 2023 (TRAILBLAZER – ALZ 2)	-0.67¥	-0.70§	-88¥	-87§	31.4%	24%

Table 3. Phase III trials outcomes.
Negative percentage means less progression (CDR-SB) in the treated arm and decrease in centiloid scale.
CDR-SB: Clinical Dementia Rating - Sum of Boxes; PET: Positron Emission Tomography; ARIA: Amyloid Related Imaging Abnormalities; -H: haemorrhage; -E: oedema/effusion.
#high dose aducanumab; ¥in the low/medium tau population; §in the combined population.

sured an accurate diagnosis of AD, beyond amyloid positivity appropriately for the diagnostic criteria of the disease.[4,5] Another differentiating point is the primary outcome (Table 2) of this trial which is the integrated Alzheimer's Disease Rating Scale (iADRS), a sensitive instrument in capturing treatment group differences in trials. This combines ADAS-Cog14 and ADCS-iADL, as a composite score of both cognition and functional status (36,37), as shown below:

iADRS = [-1 ADAS-Cog14 + 90] + ADCS-iADL

At 18 months, amyloid centiloid scale decreased by 88 in the low/medium tau population and it is noteworthy that almost 50% of the participants met the completion criteria of the study as for amyloid clearance (centiloids < 11), and discontinued the treatment. The slowing of clinical progression reached 36% for CDR-SB in the low/medium tau population (Figure 2) and 28.9% in the combined population, a clinically meaningful result regardless of statistical model. These percentages reflect a delay in cognitive decline by 7.53 months in the low/medium tau population and 5.44 months in the combined population.[38] Furthermore, as a downstream effect of amyloid plaque clearance, the examined plasma biomarkers were markedly decreased, especially plasma p-tau 217, instead of p-tau 181 used in CLARITY AD. This effect was not equivalent to tau SUVR which didn't show any significant difference during the 76 weeks. As expected, ARIA-H and ARIA-E were unavoidable (Table 3) but independent to antithrombotic use with at least half of cases (57.9%) occurring within the first three infusions of donanemab.

CRITICAL CONSIDERATIONS

The use of anti-amyloid monoclonal antibodies has attracted worldwide attention but requires careful consideration, taking into account the following special concerns. Initially, strict extrapolation of clinical trial criteria to real-world populations may limit the patients which could be benefited, since participants were free of some of the most common comorbidities (eg stroke or seizures within 12 months before randomisation) whilst even the concomitant use of specific medication could be an obstacle of their eligibility. Furthermore, the proportion of Black or Hispanic participants was unequivocally lower than White patients (approximately 91.5%). Actually, there are certain subgroups of AD patients who are excluded by DMTs' administration, such as patients with mixed pathologies, significant visual problems (posterior cortical atrophy (PCA)), behavioural and other atypical presentations, younger age, and inherited AD. The latter category also encompasses Down syndrome population which represents a genetic form of AD with complete penetrance of AD pathology by the age of 30 years and dementia by 45 to 50 years.[39,40]

A meaningful consideration is about the subsequent handling of these patients in regard to ARIA, beyond the examined 18 months duration of these clinical trials. It has to be clarified the complete reversibility of ARIA and this is critical, mainly, because lots of cerebrovascular events are not unusual in real-world aging population and the emergent therapies may be harmful. This is the unfortunate example of one patient, being on the lecanemab arm of CLARITY AD, who died from intracerebral haemorrhage following tissue plasminogen activator due to ischemic stroke and the autopsy revealed cerebral amyloid angiopathy (CAA).[41] Another important point that poses a question is the feasibility of amyloid clearance preservation and the duration of this outcome. As for the amyloid clearance, it is crucial to reconsider the physiological functions of amyloid and realise if the more beneficial effects of donanemab in CDR-SB

Scale	Item Name
ADAS-Cog	Delayed word recall
	Orientation
	Word recognition
	Word-finding difficulty
MMSE	Orientation to time
	Drawing
CDR-SB	Personal care
	Community affairs
	Home and hobbies
	Judgment and problem solving
	Memory
	Orientation

Table 4. Alzheimer's Disease Composite Score (ADCOMS)
ADAS-Cog: Alzheimer's Disease Assessment Scale–Cognitive Subscale; MMSE: Mini Mental State Examination; CDR-SB: Clinical Dementia Rating-Sum of Boxes.

are due to treatment interruption in case of massive decrease of amyloid plaques in order to avoid the excess removal of the soluble Aβ species. In addition, it is required careful study to discover any association between the amyloid removal and the whole brain volume loss that was noticed by these trials.[42]

Regarding the unsuccessful studies of several mAbs and the intended CDR-SB reduction over 30%, it is debatable if this magnitude of response reflects a clinical meaningful change.[43] The magnitude of the acceptable drug-placebo difference is dependent also on the cognitive scoring tool used, so there are thresholds for ADAS-Cog, MMSE etc, accordingly. The FDA has stated the minimal clinically important difference (MCID) which is a clinician anchored threshold and has not been met in any scale involved in these three key clinical trials.[44] First of all, this estimate differs between mild AD and MCI, with lower sensitivity of change of CDR-SB in the latter one, explaining partially smaller effects of trials containing higher number of participants with MCI.[45] The families, patients, and clinical doctors do not perceive the positive outcome, >30% decrease of CDR-SB, because of the lack of improvement above baseline.[42] In fact, this degree is equivalent to a prolongation of the MCI phase by approximately 7.5 months. It is expected that upcoming mAbs may increase the difference between treatment and no treatment arm. Finally, except the clinical, there is also the biological threshold of achievement and is based on β-amyloid clearance, expressed through centiloids in amyloid PET, and this cut off value is established in 25 centiloids. Levels of β-amyloid above 25 centiloids. Remaining levels of β-amyloid above 25 centiloids foreshadow unsuccessful results in clinical progression, irrespective of total amount of amyloid clearance achieved.[42]

The cornerstone of the limitation of the clinical use of these mAbs is the cost, which has already been of great concern in the research community.[46] Indicative parameters of the aforementioned limitation are the cost of detecting the eligible patients, the nosocomial dependence for the intravenous infusion, the strategic stuffing of these healthcare facilities and the multiple follow-up magnetic resonance imaging (MRI). Accordingly, the pricing policy of lecanemab,[46] for example, hasn't been determined in Europe and it is remarkably difficult to estimate the pharmaceutical expenditure, especially since the estimate of the number of targeted population cannot be accurate in some countries without well-established registries. Furthermore, the current cost, may be unsustainable for the economy of the European Union[46] and the potential extrapolation to reimbursement models, resembling Medicare and Veterans Health Administration USA, could raise concerns for inequality in public health access which is discordant to the standards of at least some of the European countries.

Moreover, in the light of the urgency of early detection of affected individuals, with less invasive and less costly techniques, plasma biomarkers have emerged as useful tools in AD diagnosis and following progression or treatment response. Among these, ptau 217 has gained a place in diagnostic criteria[5] since it has been suggested to have a decent diagnostic accuracy.[47,48]

CONCLUSIONS

In general, there have been tested several mAbs and plenty of them did not succeed in reaching the curative effect on functional and cognitive symptoms of AD patients,[49] and at the same time, many efforts have failed with anti-tau monoclonal antibodies.[50] However, there are many encouraging results that are anticipated by ongoing clinical trials, such as subcutaneous formulation of lecanemab and Trailblazer-ALZ 3, a trial with innovative design targeting cognitively unimpaired participants.[51] Additional evidence is needed in order to provide the appropriate therapy to our patients, with realistic expectation, safety and convenience. Nevertheless, anti-amyloid mAbs have revolutionised therapeutic development, leading to a new era of AD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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POST-ALEMTUZUMAB CHRONIC IMMUNE THROMBOCYTOPENIA REMISSION AFTER SWITCH TO OCRELIZUMAB

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ABSTRACT
CD52 depletion with the monoclonal antibody alemtuzumab is a very effective treatment for multiple sclerosis (MS) but unfortunately is also commonly associated with autoimmune manifestations. Usually these affect thyroid function and can be mild or even subclinical; the rarer, however, immune thrombocytopenia (ITP) can be severe, have a delayed onset and requires acute intervention; therefore, prolonged vigilance is needed. Herein, we report two patients with MS treated with alemtuzumab, who developed chronic ITP. Both cases suffered multiple relapses and proved refractory to conventional and non-immunological, second-line ITP management. Interestingly, B-cell depletion therapy administrated for the management of MS activity that had reappeared after alemtuzumab treatment resulted in sustained ITP remission. This observation suggests that B-cell depletion therapy can have a beneficial effect on immune deregulation, not only by eliminating MS activity but also secondary autoimmunity such as ITP; and consequently, that the mechanism of post-alemtuzumab ITP is B cell-mediated.

Keywords: Multiple sclerosis, alemtuzumab, immune thrombocytopenia, secondary autoimmunity, ocrelizumab

ΥΦΕΣΗ ΧΡΟΝΙΑΣ ΙΔΙΟΠΑΘΟΥΣ ΘΡΟΜΒΟΠΕΝΙΚΗΣ ΠΟΡΦΥΡΑΣ ΠΟΥ ΑΝΑΠΤΥΧΘΗΚΕ ΜΕΤΑ ΑΠΟ ΑΛΕΜΤΟΥΖΟΥΜΑΜΠΗ ΜΕΤΑ ΑΠΟ ΑΛΛΑΓΗ ΣΕ ΟΚΡΕΛΙΖΟΥΜΑΜΠΗ

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ΠΕΡΙΛΗΨΗ
Η εξάλειψη των CD52+ κυττάρων με το μονοκλωνικό αντίσωμα alemtuzumab αποτελεί πολύ αποτελεσματική θεραπεία της πολλαπλής σκλήρυνσης (ΠΣ), αλλά δυστυχώς συνοδεύεται συχνά από δευτεροπαθείς αυτοάνοσες εκδηλώσεις. Συνήθως αυτές αφορούν το θυρεοειδή και μπορούν να είναι ήπιες ή και υποκλινικές. Η πιο σπάνια ωστόσο εκδήλωση ιδιοπαθούς θρομβοπενικής πορφύρας (ΙΤΡ) μπορεί να είναι τόσο όψιμη όσο και σοβαρή, κατά συνέπεια να απαιτεί εγρήγορση αλλά και άμεση θεραπευτική παρέμβαση. Στην παρούσα αναφορά περιγράφουμε δυο περιπτώσεις ασθενών με ΠΣ που έλαβαν alemtuzumab και ανέπτυξαν χρόνια ΙΤΡ. Και στις 2 περιπτώσεις υπήρξαν πολλαπλές υποτροπές και ανθεκτικότητα της ΙΤΡ στις μη ανοσολογικές θεραπείες 1ης και 2ης γραμμής. Κατά ενδιαφέροντα τρόπο, η θεραπεία εξάλειψης των Β λεμφοκυττάρων, η οποία ετέθη λόγω ακτινολογικής ή και κλινικής ενεργότητας της ΠΣ, οδήγησε σε εμμένουσα ύφεση της ΙΤΡ. Η παρατήρηση αυτή μας οδηγεί στο να συμπεράνουμε πως η θεραπευτική εξάλειψη των Β λεμφοκυττάρων μπορεί να έχει ευεργετικές επιδράσεις στην ανοσολογική εκτροπή, όχι μόνο εξαλείφοντας τη δραστηριότητα της πολλαπλής σκλήρυνσης αλλά και φαινόμενα δευτεροπαθούς αυτοανοσίας όπως την ΙΤΡ, η οποία κατά συνέπεια φαίνεται να είναι διαμεσολαβούμενη από Β λεμφοκύτταρα.

Λέξεις κλειδιά: Πολλαπλή σκλήρυνση, alemtuzumab, ιδιοπαθής θρομβοπενική πορφύρα, δευτεροπαθής αυτοανοσία, ocrelizumab

INTRODUCTION

Alemtuzumab is a humanised anti-CD52 monoclonal antibody that targets circulating T and B lymphocytes, as well as NK cells; it is approved for the treatment of relapsing-remitting multiple sclerosis (RRMS).[1] Albeit its efficacy in limiting RRMS disease activity is high (in 60% of patients no evidence of disease activity was noted during a 6 year-follow-up period), secondary autoimmune manifestations have limited its application.[2] These secondary autoimmune adverse events commonly include thyroid disorders, which in some cohorts occurring in up to 55% of patients,[3] and more rarely immune thrombocytopenia (ITP) and autoimmune nephropathies, occurring in 2.8% and 0.2% of patients, respectively[2]; very rare hematologic anomalies such as post-alemtuzumab autoimmune haemolytic anaemia have also been reported.[4] Relative quantitative imbalance of B and T cells with an overshooting of B cells in the absence / reduced presence of T cells, and especially prevention of secondary autoimmune phenomena by low-dose rituximab have led to the hypothesis that these secondary autoimmunities are primarily B cell-mediated.[5,6]

ITP is characterised by low platelet count in the absence of systemic disease and be divided into three phases: newly diagnosed (0-3 months), persistent (3-12 months) and chronic (>12 months).[7] In addition, ITP can be considered primary or secondary, caused by e.g. drugs, infections, autoimmune diseases or lymphoproliferative neoplasms. The pathogenetic mechanism in many-but not all- cases involves autoantibodies against platelet transmembrane receptor GPIIb/IIIa.[8] Treatment includes high-dose corticosteroids, commonly followed by po tapering, and intravenous immunoglobulin (IVIG) as first-line/initial agents, whereas second-line therapies include the anti-CD20 monoclonal antibody (mAb) rituximab, thrombopoietin receptor agonists (TPO-RAs) and splenectomy.[9] Post-alemtuzumab ITP is marked by delayed onset, overall good responsiveness to first-line as well as second-line therapies, and sustained remission after treatment.[10] Here, we present two cases of relapsing, chronic post-alemtuzumab ITP, where the anti-CD20 mAb ocrelizumab was applied due to MS activity breakthrough, but also affected an increase in platelet count and stabilisation of ITP.

CASE REPORTS

Case one

A 39-year-old man was diagnosed with multiple sclerosis (MS) in February 2017 after developing right hand and leg numbness and weakness. After another relapse and an increase in lesion load over a 2-month period, alemtuzumab was administered in July 2017 and August 2018. His past medical and family history was unremarkable for autoimmune diseases, allergies, or haematological diseases. In December 2020, the patient presented with a haemorrhagic episode, low platelet count (PLT: 6.000/μL) and after a thorough investigation, ITP was diagnosed. Treatment with prednisone was initiated (80 mg/day po) and resulted in rapid platelet count improvement. Prednisone was gradually tapered off with simultaneous initiation of the po TPO-RA eltrombopag, under which the platelet count remained stable until October 2021, when it was discontinued. One year after the initial insult, a relapse with symptomatic thrombocytopenia occurred and was successfully treated with dexamethasone (40mg/day for 4 days iv). The third relapse of ITP occurred 2 months later, when the patient presented again symptomatic thrombocytopenia (PLT: 7.000/μL). Treatment comprised of dexamethasone (24mg/day for 4 days) and eltrombopag (75mg/day) and three days after dexamethasone initiation the platelet count was back to normal (Figure 1). However, due to the repeated relapses eltrombopag was continued as maintenance therapy.

After a new sensory MS relapse and a corresponding new C7 T2-weighted lesion in February 2023, infusions with ocrelizumab (600 mg IV every 6 months) were initiated in September 2023. Interestingly, the platelet count improved after each ocrelizumab administration (Figure 1) and eltrombopag was reduced and eventually stopped one year after ocrelizumab initiation. The platelet count remained within normal values until May 2024 (when these lines were written), while no haemorrhagic events or evidence of MS activity were noted.

Case two

A 48-year-old man with a past history of resolved ITP 30 years ago was diagnosed with RRMS in 2014, following an episode of left-side numbness and urinary retention. Treatment with glatiramer acetate (GA) was started without delay, however two relapses occurred, EDSS score increased to 4, and multiple new T2-weighted lesions were located with MRI. Relapses and associated disability worsening occurred more than six months after initiation of GA and new T2 lesions were detected in comparisons with a re-baseline MRI performed more than six months after the initiation of GA. Therefore, in April 2018 treatment was escalated to alemtuzumab, with the second cycle being administered in May 2019. In August 2019 the patient was admitted to the hospital following a haemorrhagic episode and a platelet count of 7.000/μL. After haematological and immunological workup, ITP was diagnosed and combined treatment with ivIg, corticosteroids and a platelet transfusion was administered, leading to

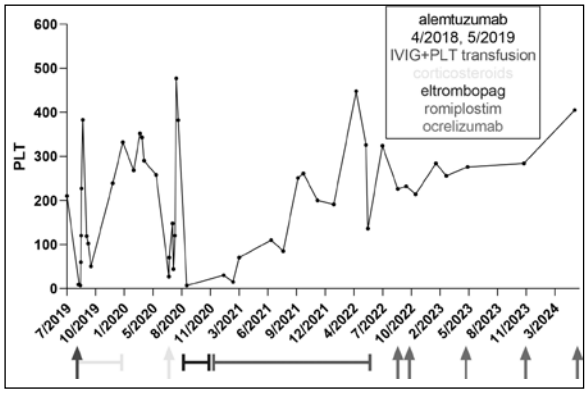

Figure 1: Platelet count is depicted as a function of time for patient 1, while coloured arrows and bar along the y axis represent different immune thrombocytopenia (ITP) therapies as indicated in the insert

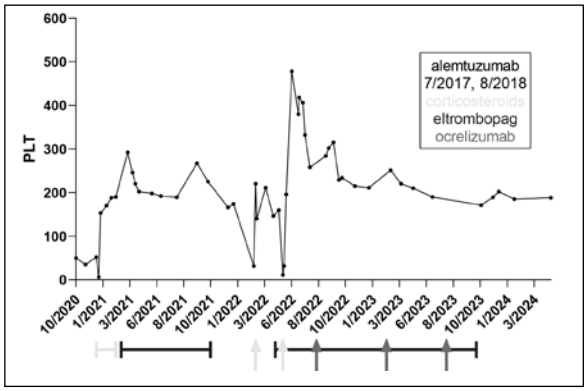

Figure 2: Platelet count is depicted as a function of time for patient 2, while coloured arrows and bar along the y axis represent different immune thrombocytopenia (ITP) therapies as indicated in the insert.

remission (Figure 2). In May 2020 however an ITP relapse occurred (PLTs: 27.000/μL), for which first corticosteroids, then eltrombopag were administered. Due to insufficient response, a switch to romiplostim (a thrombopoietin analog) was necessary and resulted in the patient achieving a platelet count of approximately 200.000/μL and being weaned off of romiplostim by June 2022 (Figure 2). In July 2022, new lesions were noted on routine follow-up MRI, and ocrelizumab was initiated in September 2022. Ocrelizumab administration every six months was associated with further improvement in platelet levels. Until May 2024 (when these lines were written) the patient fulfilled No Evidence of (MS) Disease Activity (NEDA-3) criteria, and the platelet count constantly improved with repeat ocrelizumab infusions in parallel absence of haemorrhagic symptoms.

DISCUSSION

We describe two patients with MS who received alemtuzumab, followingly developed chronic ITP with multiple relapses as a secondary autoimmune phenomenon, and achieved increased platelet counts and sustained ITP remission after repeated ocrelizumab infusions for the management of MS activity. In the first case, ocrelizumab likely enabled TPO-RA withdrawal and in the second case, ocrelizumab likely contributed to sustained remission and platelet count increase. The efficacy of the anti-CD20 monoclonal antibody rituximab as a second-line treatment in ITP and alemtuzumab-related ITP is well-established.[9,10] Here, we report similar or perhaps better efficacy of ocrelizumab, another anti-CD20 mAb that has been, in contrast to rituximab, approved for the treatment of MS.[11] Ocrelizumab has been shown to be 2 to 5 times more efficient than rituximab in mobilising antibody-dependent cell-mediated cytotoxicity (ADCC), whereas mobilisation of complement-dependent cytotoxicity (CDC) was 3 to 5 times less efficient.[12] Further, ocrelizumab was a bit more effective than rituximab in suppressing MS relapses, as shown in a recent multicentre cohort study.[13] These differences notwithstanding, our results are in line with those reported from the clinical development program of alemtuzumab[10] and build upon past experience to convey the message that CD20+ B cell depletion with ocrelizumab can effectively target post-alemtuzumab ITP. Although the natural course of ITP and post-alemtuzumab ITP is sustained remission after acute therapy, multiple ITP relapses and their cessation after CD20+ B cell depletion in the absence of other symptomatic therapy in both patients presented support its beneficial effect.

In addition to ITP, CD20+ B cell depletion has led to the remission of various secondary autoimmune phenomena following alemtuzumab treatment: Grave's disease with or without orbitopathy, acquired haemophilia A, autoimmune encephalitis, as well as haemolytic anaemia.[4,14–16] This implies that B cell activity could be the common denominator of secondary autoimmunity following alemtuzumab therapy. This aberrant B cell activity could be connected to earlier B cell repopulation compared to CD4+ T cells, slight overshooting of B cell levels in relation to their baseline, absence of T cell regulation, or qualitative B cells defects. Moreover, in both patients described here ocrelizumab was applied after the first signs of MS activity, either clinical or radiological. One could however consider that earlier application of CD20 depletion, prior to MS disease activity reappearance, might be of additional benefit. Specifically, low-dose rituximab has been applied post-alemtuzumab whenever B cells reach 50% of their baseline levels, resulting in a remarkable prevention of secondary autoimmune phenomena.[6]

FUNDING

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ETHICS APPROVAL

The study has been approved by the institutional IRB.

AUTHORSHIP CONTRIBUTION STATEMENT

PS conceived the idea of the manuscript. GK, DT, JT, CK, and PS treated the patients. GK drafted the manuscript and created the figures, and DT, JT, CK, and PS edited it.

DECLARATION OF COMPETING INTERESTS

The authors have no relevant competing interests to disclose. There are no prior publications or submissions of this article with any overlapping information, including original studies and patients.

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DATA AVAILABILITY

The data supporting the findings of this study are available upon reasonable request.

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ΑΣΥΝΗΘΙΣΤΗ ΕΚΔΗΛΩΣΗ ΠΑΡΟΔΙΚΗΣ ΣΦΑΙΡΙΚΗΣ ΑΜΝΗΣΙΑΣ ΜΕΤΑ ΑΠΟ ΕΝΔΟΣΚΟΠΙΚΗ ΕΞΕΤΑΣΗ ΤΟΥ ΓΑΣΤΡΕΝΤΕΡΙΚΟΥ

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Περίληψη

Εισαγωγή: Η παροδική σφαιρική αμνησία αποτελεί ένα κλινικό σύνδρομο, άγνωστου υποκείμενου αιτιοπαθογενετικού μηχανισμού, το οποίο χαρακτηρίζεται από αιφνίδιας εγκατάστασης διαταραχή της εμπροσθόδρομης και σε μικρότερο βαθμό της οπισθόδρομης μνήμης, χωρίς εγκατάσταση μόνιμης γνωσιακής βλάβης. Συνήθως συνοδεύεται από αλλοίωση μικρής διαμέτρου, με περιορισμό της διάχυσης στην ακολουθία μοριακής διάχυσης στην μαγνητική τομογραφία εγκεφάλου, στην περιοχή του κροταφικού λοβού και χαρακτηριστικά στην περιοχή CA1 του ιπποκάμπου. Οι κλινικές εκδηλώσεις της παροδικής σφαιρικής αμνησίας είναι συνήθως μικρής διάρκειας, έως και 24 ωρών. Παρόλα αυτά, επεισόδια μεγαλύτερης διάρκειας με άτυπα χαρακτηριστικά έχουν περιγραφεί στη βιβλιογραφία. **Μέθοδοι**: Στην παρούσα εργασία παρουσιάζουμε ένα περιστατικό με παρατεταμένο αμνησικό επεισόδιο, διάρκειας 24 ωρών, μετά από ενδοσκοπική εξέταση του γαστρεντερικού. Στην ασθενή είχε προηγηθεί χορήγηση γενικής αναισθησίας. **Παρουσίαση Περιστατικού:** Ασθενής 70 ετών προσήλθε στο Τμήμα Επειγόντων Περιστατικών, με κυρίαρχη εμπροσθόδρομη και συνυπάρχουσα ηπιότερη οπισθόδρομη αμνησία, μετά από λήψη γενικής αναισθησίας στα πλαίσια διενέργειας ενδοσκοπικής εξέτασης του γαστρεντερικού. Εκτενής διαγνωστικός έλεγχος απέκλεισε άλλα πιθανά αίτια της αμνησίας. Μαγνητική τομογραφία εγκεφάλου διενεργήθηκε 24 ώρες μετά την εκδήλωση των συμπτωμάτων, αποκαλύπτοντας στικτή βλάβη με περιορισμό της διάχυσης εντός του δεξιού ιπποκάμπου, συμβατή με οξεία ισχαιμία. Η ασθενής διαγνώστηκε με παροδική σφαιρική αμνησία, σχετιζόμενη με την προηγηθείσα ιατρική πράξη. **Συμπεράσματα:** Η κλινική εικόνα και τα απεικονιστικά ευρήματα της ασθενούς μας ήταν συμβατά με την διάγνωση της παροδικής σφαιρικής αμνησίας. Η παρουσίαση αυτού του περιστατικού υπογραμμίζει την σημασία της έγκαιρης και σωστής αναγνώρισης των επεισοδίων παροδικής σφαιρικής αμνησίας, ακόμα και όταν οι κλινικές εκδηλώσεις ή η διάρκεια των συμπτωμάτων δεν είναι τα πλέον τυπικά. Πολύ σημαντικό επίσης είναι να αποκλειστούν άλλες πιθανές διαγνώσεις που μπορεί να απαιτούν άμεση θεραπεία και αντιμετώπιση.

Λέξεις-κλειδιά: παροδική σφαιρική αμνησία, ενδοσκόπηση γαστρεντερικού συστήματος, μαγνητική τομογραφία εγκεφάλου, αναισθησία

AN ATYPICAL FORM OF TRANSIENT GLOBAL AMNESIA AFTER GASTROINTESTINAL ENDOSCOPY. A COMPLICATED DIAGNOSIS

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ABSTRACT

Background: Transient global amnesia (TGA) is a clinical syndrome of unknown physiology characterised by a sudden onset of anterograde amnesia and a milder reduction of retrograde episodic long-term memory, without compromise of other neurologic functions. It is usually accompanied by vanishing

punctate magnetic resonance imaging (MRI) diffusion-weighted imaging (DWI) lesions in hippocampal CA1 area. Episodes of TGA are of brief duration, usually lasting up to 24h. However, episodes with atypical characteristics have been also described. **Methods**: We report a case of prolonged amnestic syndrome, lasting up to 24 hours, following gastrointestinal (GI) endoscopy and previous sedation with general anaesthetics. **Results:** A 70-year-old female was admitted to the Emergency Department, with profound anterograde amnesia and variable retrograde amnesia, after recovery from sedation due to GI endoscopy, a few hours earlier. A thorough diagnostic workup excluded alternative causes of amnesia. The Brain MRI performed 24h following symptoms onset, revealed hyperintense DWI punctate signal within the lateral part of the right hippocampus, consistent with acute hippocampal ischemia. She was ultimately diagnosed with TGA related to a medical procedure. **Conclusion:** Our patient's clinical and imaging features were consistent with the diagnosis of TGA. This case highlights that clinical neurologists should not be deterred by atypical amnestic symptoms lasting >24-hours, if the patient's clinical/radiologic presentation is consistent with TGA. However, they should carefully rule out other conditions that need immediate treatment.

Keywords: transient global amnesia, gastrointestinal endoscopy, MRI, sedation

INTRODUCTION

Transient global amnesia (TGA) occurs usually in middle-aged or elderly individuals and is characterised by the abrupt onset of anterograde amnesia, accompanied by repetitive questioning.[1,2] Apart from the amnesia, there are no focal neurological deficits. Attacks last for minutes or hours and the ability to lay down new memories is gradually recovered, leaving only a dense amnestic gap for the duration of the episode and often the hours leading up to it. Guyotat and Courjon[1] first described these amnestic episodes and in 1964 Fisher and Adams[2] reported attacks coined the term 'TGA'.

Emotional stress (ie, triggered by gastric endoscopy, birth/death announcement, and difficult/exhausting workday), physical effort (ie, gardening, house work, sawing wood, sexual intercourse, weight lifting), and water contact/temperature change (ie, hot bath/shower and cold swim) are described most frequently immediately before an attack and are considered "close events".[3] Interest was centreed on the phenomenology of the attacks and their aetiology, as this form of amnesia is sometimes difficult to differentiate from other amnestic syndromes (psychogenic, post-traumatic, epileptic, stroke, encephalopathy, and toxin/drug ingestion).[4]

In 1990, Hodges and Warlow[5] suggested that the etiological uncertainty of TGA mainly resulted from the lack of both clear diagnostic criteria and well-documented epidemiological studies. They attempted to address this problem by conducting a study of 153 cases, some of them fulfilling strict diagnostic criteria. They showed that while clinical features were not particularly relevant for separating 'pure TGA' patients from other amnestic patients, meeting the criteria was a significant predictor for a good outcome, as they designated a group of patients with a good prognosis and no higher prevalence of vascular risk factors than in other forms of transient amnesia. Amnestic patients who did not fulfil the TGA criteria had a significantly worse outcome. After that, many case reports and group studies have been published, but no comprehensive survey has been carried out to characterize the clinical features of this syndrome more accurately.

As mentioned earlier, medical procedures represent a precipitating factor. Gastrointestinal (GI) endoscopies are frequently used as diagnostic tool to identify abnormalities within the GI tract. Endoscopic procedures are invasive and may cause pain and discomfort. Therefore, combination of sedatives and analgesic agents is given to increase a patient's tolerance and cooperation.[6] Commonly used drug combinations in GI endoscopic procedures are drugs with a hypnotic effect such as midazolam, propofol in combination with an opioid such as fentanyl. With the use of various neurocognitive test, researchers have shown an association between the drugs used in and in sort term reversible decline in cognitive function.[7] In addition, case reports of TGA have been reported in the literature, following GI endoscopy.

A rare, acute-onset anterograde amnestic syndrome occurring in the setting of opioid use, closely linked to fentanyl, is of special interest.[8] This opioid-associated amnestic syndrome (OAS) is characterized by diffuse lesions of the hippocampus bilaterally on diffusion-weighted Magnetic Resonance Imaging (MRI), because of excitotoxic effect in this anatomic area.[9] Reports indicate that OAS lasts for weeks to months and in some instances, a year or longer. Opioid-associated amnestic syndrome can be easily distinguished from TGA when there is an impaired level of consciousness or sufficient follow-up observation. However, OAS cases may present with similar features to those of TGA, including frequent repetition, and absence of altered levels of consciousness. Moreover, the possibility of "transient" OAS cases of

shorter duration (and potentially attributed to TGA) could be considered.

Herein, we describe an atypical case, prompting questions about our current diagnostic criteria and the underlying pathophysiological mechanisms that contribute to TGA.

CASE DESCRIPTION

A 70-year-old female with history of weight loss in the last months, presented to the emergency department (ED) accompanied by anaesthesiologist, with sudden onset confusion and memory loss following gastrointestinal endoscopy a few hours earlier. According to the gastroenterologist's referral note, the patient had received standard doses of midazolam, fentanyl, and propofol, but was unreasonably slow to recover despite the administration of naloxone and flumazenil, and after regaining consciousness she was disoriented in space and time. The patient did not have any past medical history, did not report similar episodes of memory loss, and she did not receive regularly any medication.

In the ED, the patient had normal vital signs and she was alert, with profound anterograde amnesia and mild retrograde amnesia. The clinical examination revealed no focal neurological signs. A thorough diagnostic workup (Brain Computed Tomography, CT-Angiography, Doppler ultrasound of the cervical/cerebral arteries, laboratory testing) excluded alternative causes of amnesia. The electroencephalogram (EEG) was performed within 24 h from symptom onset, showing no epileptic evidence.

Initial brain MRI was performed 24h after the symptom onset, revealing increased signal within the lateral part of the right hippocampus on the diffusion-weighted imaging (Figure 1A), associated with a corresponding reduction in the apparent diffusion coefficient (Figure 1B), consistent with acute hippocampal ischemia.

Within 24 hours of her hospitalisation, the patient remained confused and worried. She had complete amnesia of the event that occurred around the introspection and could not engrave any new information. She kept repeating "how did I get here", "what happened to me", and forgetting any new information within seconds. Secondary stroke prevention with antiplatelet agents was administered. Within 24-48 hours of hospitalisation, the patient fully recovered without any acute reperfusion treatment. After that, she was able to engrave new information while she had complete amnesia of the event.

The clinical picture and diagnostic workup are compatible with an episode of atypical transient global amnesia (TGA). Although rare, this has been described in the literature as an episode of TGA following GI endoscopy. The patient was discharged in stable condition, without any residual neurological dysfunction, with instructions for re-evaluation in the Outpatient Stroke Clinic. Follow-up brain MRI, performed 1 month later, did not reveal any abnormal findings (Figure 1C) and provided evidence for the reversibility of diffusion restriction in the right hippocampus.

DISCUSSION

We consider, after excluding other pathological conditions, that the clinical picture of our patient, with the prolonged duration of amnesia and the lesion with diffusion restriction within the lateral part of the right hippocampus, refers to an atypical form of iatrogenic induced TGA, although it does not absolutely comply with the established clinical criteria.[10] Possible explanations might include the emotional stress of instrumentation, associated pain, autonomic activation from passing the scope and medication use (although TGA is also recorded fol-

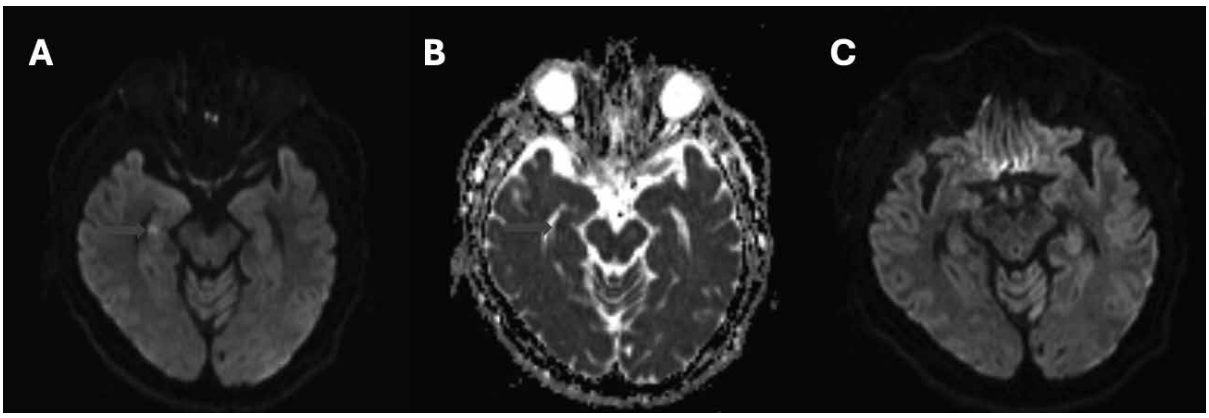

Figure: Neuroimaging findings
Figure Legend: Diffusion-weighted imaging showing a punctate area of diffusion restriction in the medial right temporal lobe 24 hours after the episode (Panel A; red arrow), with a corresponding reduction in the apparent diffusion coefficient (Panel B; red arrow) consistent with acute hippocampal ischemia. Follow-up brain Magnetic Resonance Imaging 1 month after the episode, revealing no abnormal lesions (Panel C).

lowing endoscopy without medication).

The diagnosis of TGA is based on patient's history, as well as on neurological and bedside neuropsychological examination and the exclusion of possible differential diagnoses. The diagnosis usually can be established primarily clinically in the acute stage based on the criteria of Caplan and Hodges and Warlow[5]:

- Acute onset and pronounced new memory impairment.
- Duration of at least 1 h, regression within 24 h.
- No focal neurological symptoms/deficits and no additional cognitive deficits.
- Absence of impaired consciousness or disorientation to person.
- No previous trauma or epilepsy.

Clinical symptoms beyond isolated memory impairment with antero- and retrograde amnesia, including somnolence, severe headache, vomiting, confusion, fever etc., or incomplete recovery after more than 24 h argue against TGA and require rapid differential workup to rule out other potential underlying aetiologies.

Characteristic DWI lesions are most likely to appear 24–72 h following symptom onset, especially in the CA1 region (about 30% of lesions) of the hippocampus, most of which are accompanied by T2-weighted hyperintensity and are still detectable 10–14 days after episode.[6,7] Detection of these DWI lesions support the TGA diagnosis and could be found in up to 75% of all patients. However, absence of DWI lesions does not exclude TGA.[11,12]

Nevertheless, the role of sedative medication and its potential effect on event's duration could be discussed. Various studies focus on the effect of drugs, as monotherapy or in combination, and on the duration of their effects on cognitive functions. Surveillance data from ED visits in Massachusetts between January 2019 and June 2023 do not suggest that opioid use is a risk factor for TGA. Proposed mechanistic differences between OAS and TGA might begin to offer insight into this observation. Although OAS is thought to result primarily from an excitotoxic effect of opioids on the hippocampus, the leading underlying mechanisms of TGA are vascular or migrainous in nature, including ischemia and cortical spreading depression, respectively. Additionally, patients with OAS commonly present with altered consciousness due to respiratory depression, whereas those with TGA do not.[13,14]

Two clinical cases with prolonged TGA, reported in the literature, describe a 12-year-old boy who developed prolonged retrograde amnesia following sedation with propofol[15] and a 66-year-old female with prolonged TGA, persisted for 72 h, with no clear emotional or psychological stressor.[10]

In conclusion, this case highlights a patient diagnosed eventually with an atypical presentation of TGA, because of the prolonged duration and the administered medications, that made the diagnosis controversial. Although TGA represents a rare complication of medical procedures, clinical neurologists and gastroenterologists should be aware of its possible occurrence and the potential atypical manifestations. It is difficult to distinguish whether a prolonged course of amnesia points towards a different pathophysiological mechanism of TGA or other clinical entity. Thus, it is very important to rule out other entities, mimicking transient amnestic episodes and probably requiring immediate intervention so that no valuable time will be lost.

To the best of our knowledge, this case is one of the few reported cases with prolonged, iatrogenic induced TGA, associated with MRI evidence of transient unilateral hippocampal ischemia, most probably due to a transient reduction in regional hippocampal blood flow.

CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest.

FUNDING INFORMATION

No funding was received for the present study.

ETHICAL APPROVAL

The approval for the study protocol was not necessary because our institutional review board does not require approval for case reports.

INFORMED CONSENT

Informed consent was obtained from the patient in the study.

DATA AVAILABILITY

All data needed to evaluate the conclusions in the paper are present in the paper. Additional data related to this paper may be requested from the corresponding author, upon reasonable request.

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